Review TRENDS in Cognitive Sciences Vol.9 No.2 February 2005

Mapping brain maturation and cognitive development during adolescence

Tomáš Paus[1,2]

[1]Brain and Body Centre, University of Nottingham, Nottingham, UK
[2]Montreal Neurological Institute, McGill University, Montreal, Canada

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 genome 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 *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).

Corresponding author: Paus, T. (tomas.paus@nottingham.ac.uk).
Available online 6 January 2005

 1364-6613/$ - see front matter doi:10.1016/j.tics.2004.12.008

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].

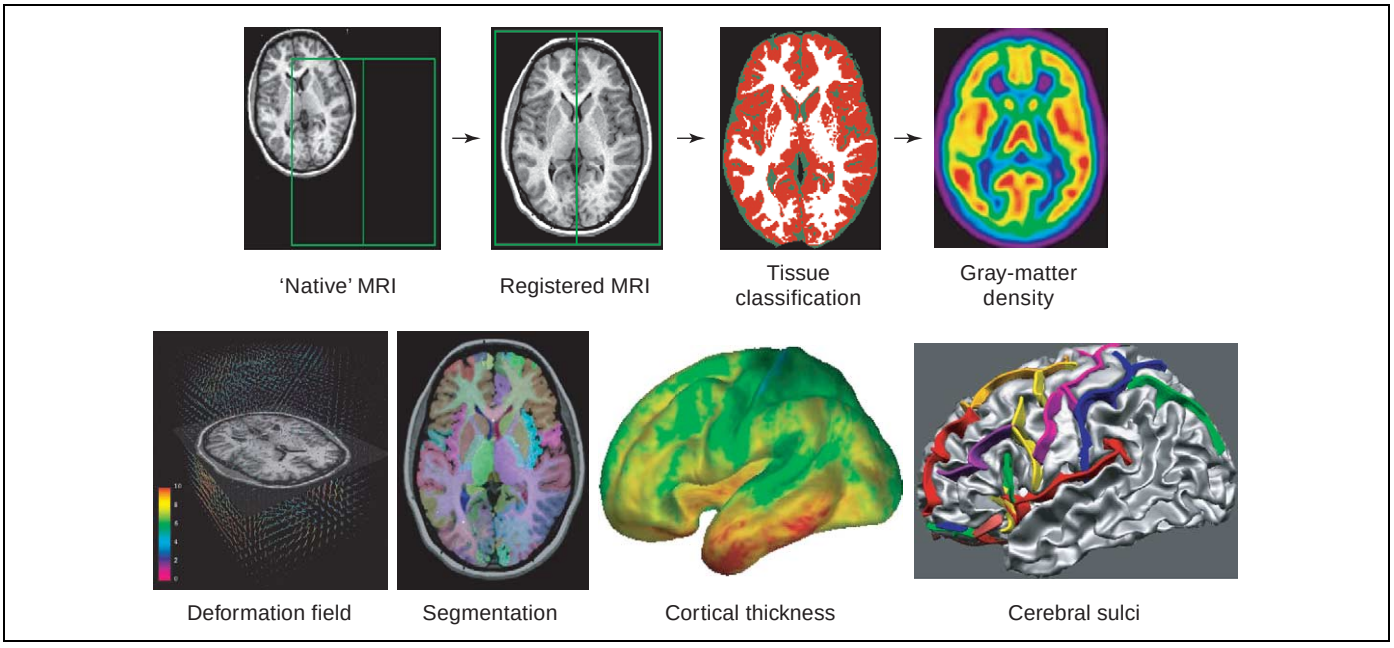

Figure 1. Image-processing pipeline. **Top row**: A typical image-processing pipeline begins with a transformation of a magnetic-resonance (MR) image from the acquisition ('native') to standardized stereotaxic space; this process generates an image that is 'registered' with the template brain. The next 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 myelination 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).

data [8]. In this cohort, Giedd and colleagues observed a steady increase in the overall volume of white matter (WM) throughout the studied age-range of 4 to 21 years [13]. This finding is consistent with previous observations ([14]; n=88, 1–30 years; [15]; n=85, 5–17 years). In a subsample of the NIMH cohort (n=111), Paus *et al.* have documented an increase in WM density in the internal capsule and the left arcuate fasciculus, the latter containing fibres presumably connecting the anterior (Broca) and posterior (Wernicke) speech regions (Figure 2; [16]). Another example of regional variation in WM maturation is a region-specific growth of the corpus callosum; both cross-sectional and longitudinal analyses revealed continuous age-related changes in the posterior but not the anterior section [17–19]. In a recent study, Blanton *et al.* [20] documented significant gender differences in WM of the left inferior frontal gyrus, a region comprising the pars opercularis, triangularis and orbitalis and, presumably, containing speech-related areas: boys (n=25, 6–17 years) but not girls (n=21, 6–15 years) showed a linear age-related increase in the WM volume in this region.

Overall, functional consequences of such gains in WM volume are clear: faster and more efficient sharing of information within, for example, various fronto-cortical circuits, as well as smooth communication between the frontal cortex and other cortical and subcortical regions.

Developmental findings: grey matter

Linearity of the developmental changes in brain maturation observed for white matter does not appear to hold in the case of grey matter (GM). In the NIMH sample, Giedd *et al.* [13] reported increases in the GM volume of the frontal and parietal lobes, which peaked at about the age of 10 and 12 years in girls and boys, respectively. Following these maxima, there was a subtle but significant decrease in the GM volumes in these two lobes. The temporal and occipital GM did not show this pattern. Other investigators found similar age-related changes in the frontal and parietal lobes. Thus, Sowell *et al.* [21] described a 'loss' of GM density over the dorsal and parietal lobes between childhood (7–11 years, n=14) and adolescence (12–16 years, n=11), which was accelerated further – but only in the frontal cortex – from adolescence to adulthood (23–30 years, n=10); it is of interest that the loss of GM density was correlated inversely with local brain growth. Using longitudinal data (13 subjects, 3 or more scans per subject for a total of 52 scans, age 4–21 years), Gogtay *et al.* [22] confirmed such a loss of GM density. It appears to start around puberty in the sensorimotor areas and spreads rostrally over the frontal cortex and caudally over the parietal and then temporal cortex (Figure 3). The dorsolateral prefrontal cortex and the posterior part of the superior temporal gyrus appear to 'lose' grey matter the last [22]. Overall, there is an agreement across the above studies in that cortical GM volumes change in a non-linear fashion across different regions throughout childhood and adolescence. The most striking finding is the apparent 'loss' of grey matter during late adolescence, perhaps after the onset of puberty. But is it really a loss of grey matter or a gain of intra-cortical white matter? (see Box 3).

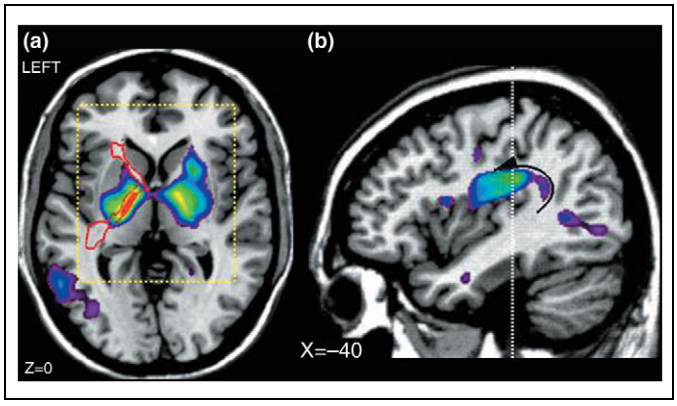

Figure 2. Age-related changes in white-matter density in **(a)** the internal capsule, and **(b)** the left arcuate fasciculus. Thresholded maps of t-statistic values are superimposed on axial (capsule) and sagittal (arcuate) sections through the MR image of a single subject. The images depict the exact 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

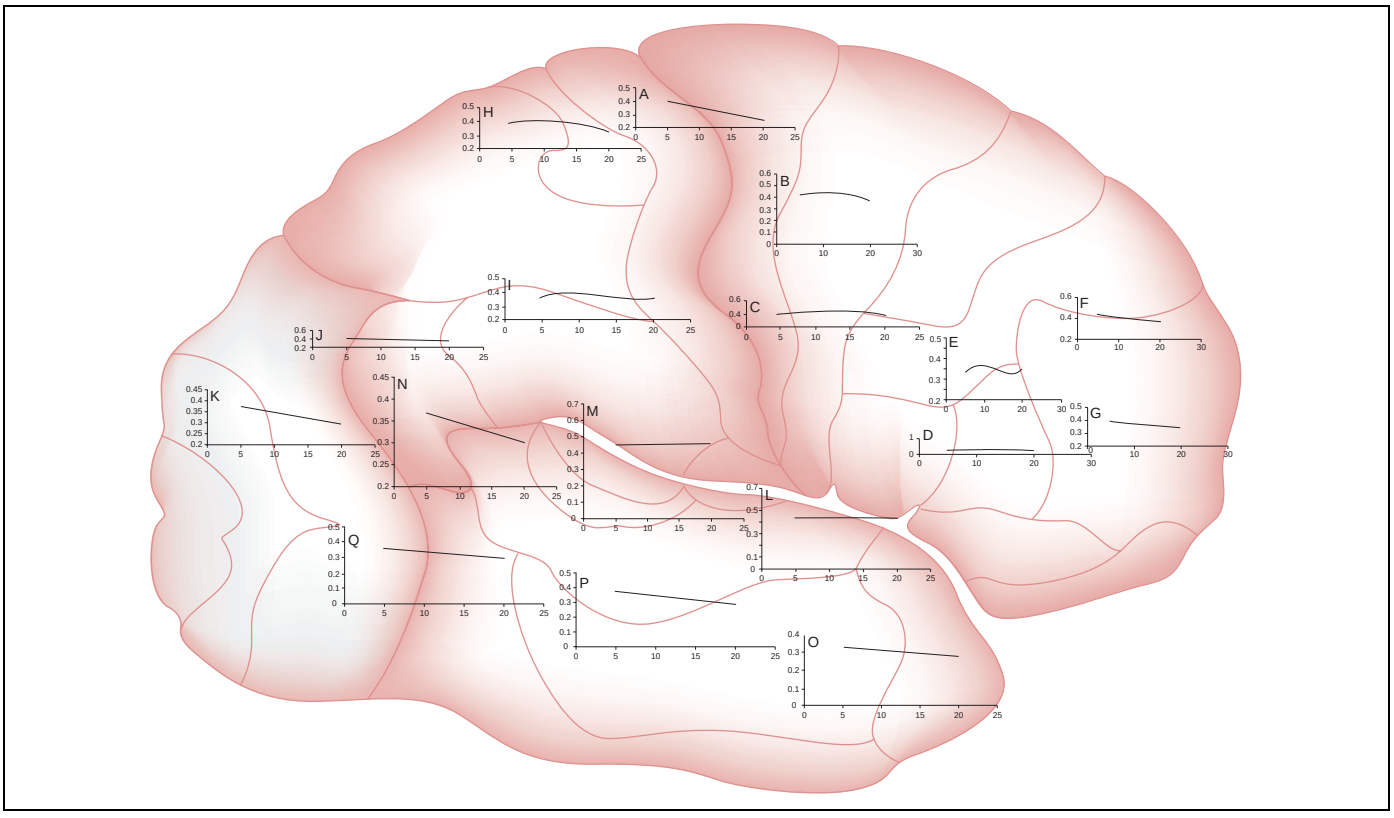

Figure 3. Age-related changes in cortical grey matter. Mixed-model regression plots (grey-matter vs. age) at the following regions of interest: A, precentral gyrus and primary motor cortex; B, superior frontal gyrus, posterior end near central sulcus; C, inferior frontal gyrus, posterior end; D, inferior 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 postcentral gyrus; 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.

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

occur. The relationship between the fMRI signal and brain activity is not straightforward, however. Changes in local haemodynamics most probably reflect the sum of excitatory postsynaptic inputs in the sample of scanned tissue [29]. The firing rate of 'output' neurons may also be related to local blood flow [30,31] but only inasmuch as it is linked in linear fashion to excitatory postsynaptic input. Further, inhibitory neurotransmission could lead to decreases in cerebral blood flow indirectly, through its presynaptic effects on postsynaptic excitation [32]. Interpretation of the BOLD signal aside, the use of fMRI in studies of children and adolescents presents many specific challenges of both technical (e.g. head motion and its correction) and conceptual (e.g. age vs. performance) nature [33].

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

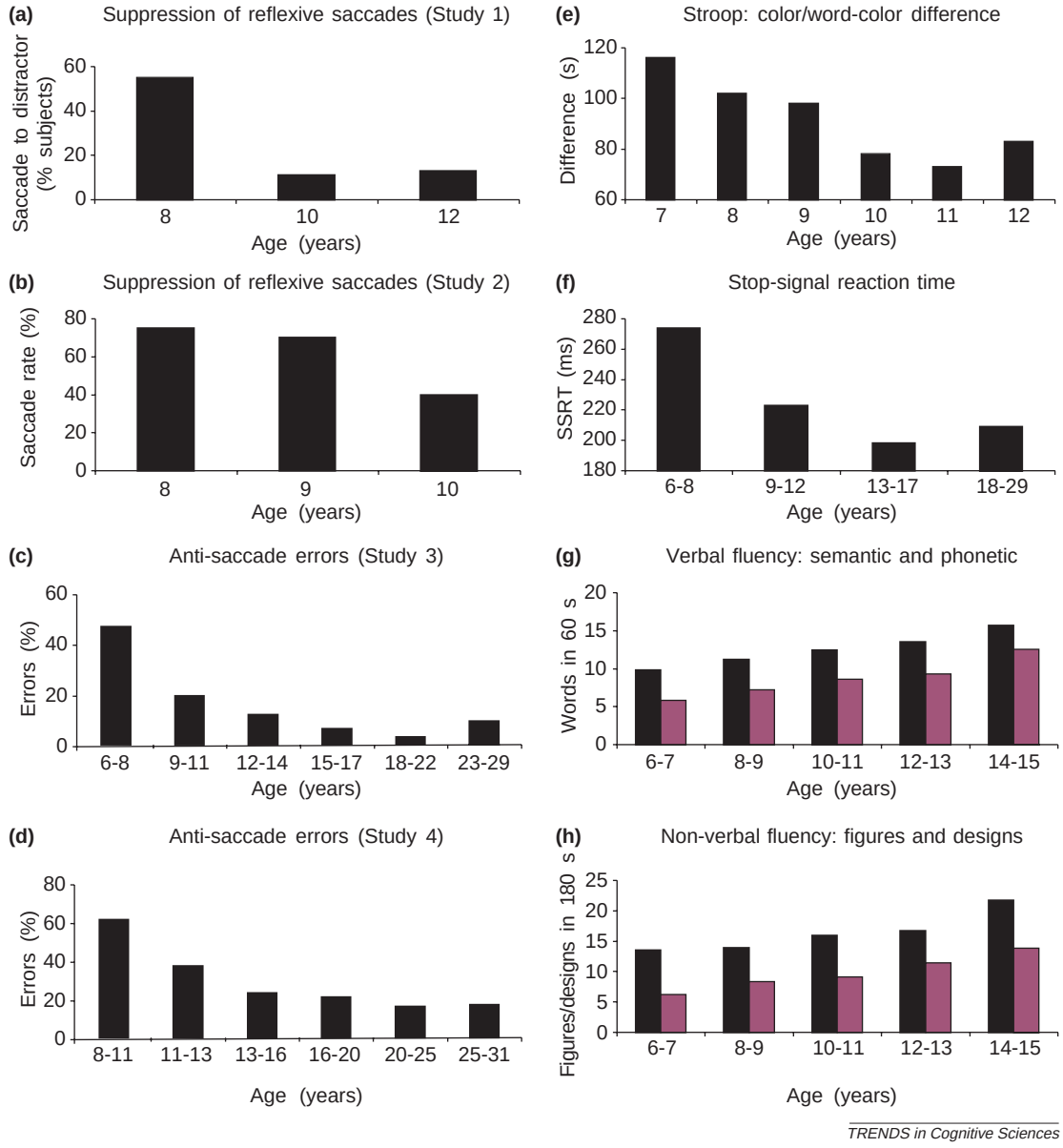

Figure 4. Age-related changes in executive functions. **(a–d)** Results of four studies of response inhibition assessed in the oculomotor domain. **(a)** An unexpected visual stimulus was flashed in the periphery while children were moving their eyes along a dimly illuminated arc; shown is the percentage of 8-, 10-, and 12-yr-old children (24–26 subjects per age group) who were unable to suppress reflexive saccades to the peripheral stimulus [81]. **(b)** Children were instructed to maintain fixation in the centre of the computer screen while unexpected visual stimuli were flashed in the periphery; shown is the percentage of unsuppressed eye movements made by 8-, 9-, and 10-yr-old children (15–18 subjects per age group) [82]. **(c)** Subjects (12–22 subjects per age group) were asked to gaze at the fixation point and, after the appearance of a peripheral target, look to the opposite side; shown is the percentage of eye movements directed incorrectly towards the actual target ('anti-saccade errors'). In this version of the task, the fixation point remained lit while the peripheral target appeared [83]. **(d)** The same anti-saccade task as **(c)** but here the fixation point disappeared 200 ms before the presentation of the peripheral target, making the task more difficult (19–43 subjects per age group) [84]. **(e,f)** Developmental trends in two other tasks of inhibitory control. In the Stroop task, children (12–33 subjects per age group) were asked to name the ink colour of either 100 patches of the colours red, blue and green or 100 colour names printed in a discrepant ink colour; shown is the difference in the time required to complete the two tasks (colour-words minus colour-patches) [85]. In the Stop-signal task (f), children (29–55 subjects per age group) were told to stop responding with button presses to a visual stimulus (letter X or O) when hearing a tone ('stop' signal); shown is the minimum delay between the onset of stimulus and tone necessary to stop the response, the so called stop-signal reaction time (SSRT) [86]. **(g,h)** Developmental trends in verbal and non-verbal fluency [87]. In the two verbal-fluency tasks (g), children (18–51 subjects per age group) were asked to name fruits (semantic fluency; black bars) or as many words starting with 'm' (phonetic fluency; purple bars) as they could in 60 s. In the two non-verbal fluency tasks, the same groups of children were asked to draw, as fast as possible, different meaningful designs (semantic; black bars) or linear geometric figures (non-semantic; purple bars) as they could in 180 s.

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).

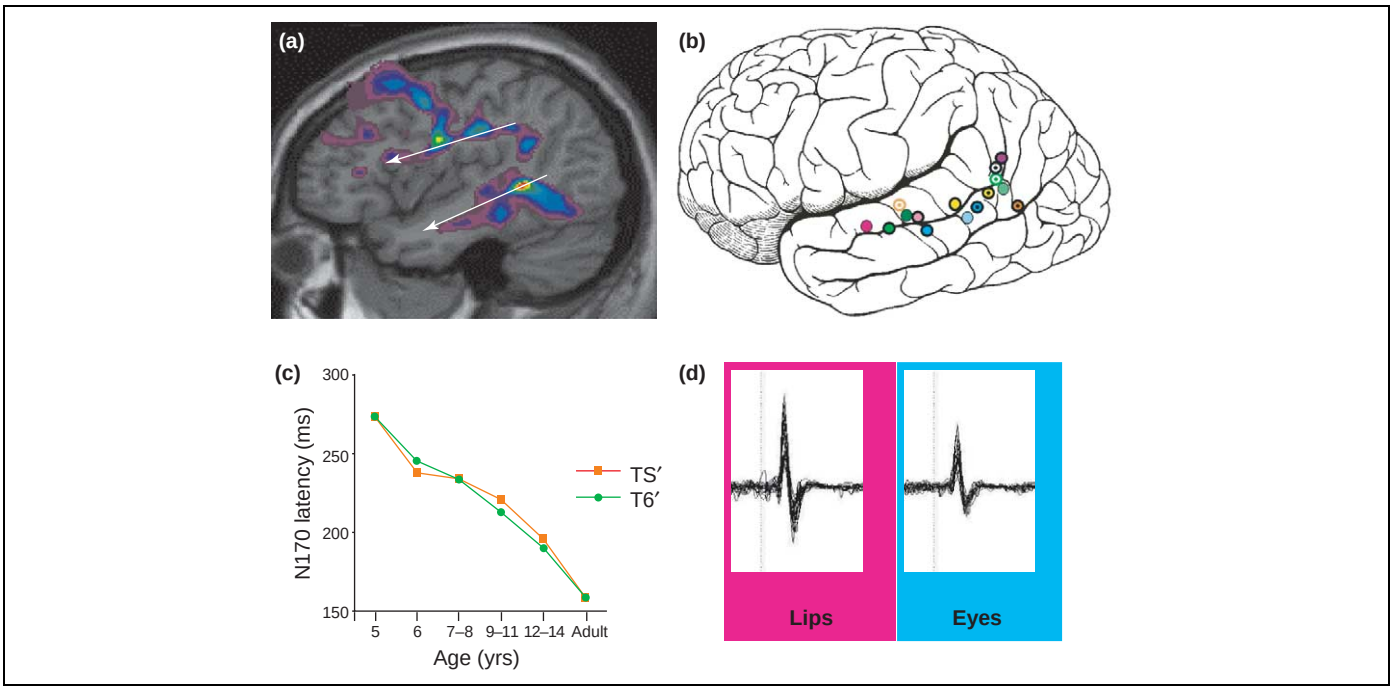

Figure 5. Brain and social cognition. **(a)** Age-related changes in white-matter density along the putative fronto-temporal (top arrow) and the occipito-temporal (bottom arrow) pathways [48]; 36 children and adolescents, aged 10–19 years, were scanned at least twice (average interval of 3.5 yrs). Note that the changes in the fronto-temporal pathway replicate the original cross-sectional data [16] whereas those in the occipito-temporal pathway suggest maturation of a system involved in processing of biological motion. **(b)** Activation of regions along the left superior temporal sulcus during the perception of biological motion by adult subjects [55]. **(c)** Developmental changes in the latency, recorded with electroencephalography, of the cortical response to the presentation of black-and-white photographs of faces (9–14 subjects per age group) [59]. **(d)** Modulation of motor excitability during observation of speech-related movements of the lips in adults; a higher amplitude of muscle evoked potentials is elicited with transcranial magnetic stimulation when the subject watches someone else speak (left) rather than move their eyes (right) [88].

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.

Acknowledgements

The work and ideas expressed in this article arose over many years through interactions with my colleagues at the Brain Imaging Center of the Montreal Neurological Institute (Drs. Collins, Evans, Pike, Worsley and Zijdenbos), the MNI Cognitive Neuroscience Unit (Drs. Leonard, Milner, Petrides and Zatorre), the Child Psychiatry Branch of the National Institute of Mental Health (Drs. Giedd and Rapoport) and, most importantly, students and fellows in my laboratory. I would like to thank in particular those colleagues who have contributed to the design of our studies of adolescence, namely Drs. Barrett, Grosbras, Leonard, Pike, Poulsen, and Watkins, and Ms. Aleong. The author's research is supported by the Canadian Institutes of Health Research, Canadian Foundation for Innovation, National Science and Engineering Research Council of Canada, and the Santa Fe Institute Consortium.

References

1 Bogin, B. (1999) Evolutionary perspective on human growth. *Annu. Rev. Anthropol.* 28, 109–153
2 Dean, C. *et al*. (2001) Growth processes in teeth distinguish modern humans from Homo erectus and earlier hominins. *Nature* 414, 628–631
3 Minugh-Purvis, N. and McNamara, K.J., eds (2002) *Human Evolution through Developmental Change*, Johns Hopkins University Press
4 Steinberg, L. (2005) Cognitive and affective development in adolescence. *Trends Cogn. Sci.* (in press)
5 Mountcastle, V.B. (1997) The columnar organization of the neocortex. *Brain* 120, 701–722
6 Toga, A.W. and Thompson, P.M. (2002) New approaches in brain morphometry. *Am. J. Geriatr. Psychiatry* 10, 13–23
7 Paus, T. *et al*. (2001) Maturation of white matter in the human brain: a review of magnetic-resonance studies. *Brain Res. Bull.* 54, 255–266
8 Giedd, J.N. (2004) Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci.* 1021, 77–85
9 Durston, S. *et al*. (2001) Anatomical MRI of the developing human brain: what have we learned? *J. Am. Acad. Child Adolesc. Psychiatry* 40, 1012–1020
10 Yakovlev, P.I. and Lecours, A.R. (1967) In *Regional Development of the Brain in Early Life* (Minkowski, A. ed.), pp. 3–70, Blackwell Scientific
11 Brody, B.A. *et al*. (1987) Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J. Neuropathol. Exp. Neurol.* 46, 283–301
12 Benes, F.M. *et al*. (1994) Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Arch. Gen. Psychiatry* 51, 477–484
13 Giedd, J.N. *et al*. (1999) Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* 2, 861–863
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
15 Reiss, A.L. *et al*. (1996) Brain development, gender and IQ in children. A volumetric imaging study. *Brain* 119, 1763–1774
16 Paus, T. *et al*. (1999) Structural maturation of neural pathways in children and adolescents: *in vivo* study. *Science* 283, 1908–1911
17 Giedd, J.N. *et al*. (1996) A quantitative MRI study of the corpus callosum in children and adolescents. *Brain Res. Dev. Brain Res.* 91, 274–280
18 Giedd, J.N. *et al.* (1999) Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 23, 571–588
19 Pujol, J. *et al*. (1993) When does human brain development end? Evidence of corpus callosum growth up to adulthood. *Ann. Neurol.* 34, 71–75
20 Blanton, R.E. *et al*. (2004) Gender differences in the left inferior frontal gyrus in normal children. *Neuroimage* 22, 626–636
21 Sowell, E.R. *et al*. (2001) Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during post-adolescent brain maturation. *J. Neurosci.* 21, 8819–8829
22 Gogtay, N. *et al*. (2004) Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U. S. A.* 101, 8174–8179
23 Anderson, S.W. *et al*. (1999) Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat. Neurosci.* 2, 1032–1037
24 Golestani, N. *et al*. (2002) Anatomical correlates of learning novel speech sounds. *Neuron* 35, 997–1010
25 Pujol, J. *et al*. (2002) Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. *Neuroimage* 15, 847–855
26 Schlaug, G. *et al*. (1995) Increased corpus callosum size in musicians. *Neuropsychologia* 33, 1047–1055
27 Isaacs *et al*. (2001) Calculation difficulties in children of very low birthweight: a neural correlate. *Brain* 124, 1701–1707
28 Draganski, B. *et al*. (2004) Neuroplasticity: changes in grey matter induced by training. *Nature* 427, 311–312
29 Logothetis, N.K. *et al*. (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150–157
30 Heeger, D.J. *et al*. (2000) Spikes versus BOLD: what does neuroimaging tell us about neuronal activity? *Nat. Neurosci.* 3, 631–633
31 Rees, G. *et al*. (2000) A direct quantitative relationship between the functional properties of human and macaque V5. *Nat. Neurosci.* 3, 716–723
32 Mathiesen, C. *et al*. (1998) Modification of activity-dependent increases of cerebral blood flow by excitatory synaptic activity and spikes in rat cerebellar cortex. *J. Physiol.* 512, 555–566
33 Davidson, M.C. *et al*. (2003) Imaging the developing brain with fMRI. *Ment. Retard. Dev. Disabil. Res. Rev.* 9, 161–167
34 Casey, B.J. *et al*. (1995) Activation of prefrontal cortex in children during a nonspatial working memory task with functional MRI. *Neuroimage* 2, 221–229
35 Thomas, K.M. *et al*. (1999) A developmental functional MRI study of spatial working memory. *Neuroimage* 10, 327–338
36 Casey, B.J. *et al*. (2002) Dissociating striatal and hippocampal function developmentally with a stimulus-response compatibility task. *J. Neurosci.* 22, 8647–8652
37 Kwon, H. *et al*. (2002) Neural basis of protracted developmental changes in visuo-spatial working memory. *Proc. Natl. Acad. Sci. U. S. A.* 99, 13336–13341
38 Adleman, N.E. *et al*. (2002) A developmental fMRI study of the Stroop color-word task. *Neuroimage* 16, 61–75
39 Luna, B. *et al*. (2001) Maturation of widely distributed brain function subserves cognitive development. *Neuroimage* 13, 786–793
40 Rubia, K. *et al*. (2000) Functional frontalisation with age: Mapping neurodevelopmental trajectories with fMRI. *Neurosci. Biobehav. Rev.* 24, 13–19
41 Tamm, L. *et al*. (2002) Maturation of brain function associated with response inhibition. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 1231–1238
42 Bunge, S.A. (2002) Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron* 33, 301–311
43 Petersen, S.E. (1990) Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* 249, 1041–1044
44 Schlaggar, B.L. *et al*. (2002) Functional neuroanatomical differences between adults and school-age children in the processing of single words. *Science* 296, 1476–1479
45 Brown, T.T. *et al*. (2004) Developmental changes in human cerebral functional organization for word generation. *Cereb Cortex*. (in press)
46 Gardner, M. and Steinberg, L. Peer influence on risk-taking, risk preference, and risky decision-making in adolescence and adulthood: An experimental study. *Dev. Psychol*. (in press)
47 Benes, F.M. (1989) Myelination of cortical–hippocampal relays during late adolescence. Schizophr. Bull. 15, 585–593

48 Watkins, K.E. *et al*. (2002) Maturation of white matter tracts during adolescence: A longitudinal MRI study. *Neuroimage* 16 (Suppl.) 1718–1719
49 Puce, A. *et al*. (1998) Temporal cortex activation in humans viewing eye and mouth movements. *J Neurosci.* 18, 2188–2199
50 Decety, J. *et al*. (1997) Brain activity during observation of actions. Influence of action content and subject's strategy. *Brain* 120, 1763–1777
51 Grezes, J. *et al*. (1999) The effects of learning and intention on the neural network involved in the perception of meaningless actions. *Brain* 122, 1875–1887
52 Beauchamp, M.S. *et al*. (2002) Parallel visual motion processing streams for manipulable objects and human movements. *Neuron* 34, 149–159
53 Bonda, E. *et al*. (1996) Specific involvement of human parietal systems and the amygdala in the perception of biological motion. *J. Neurosci.* 16, 3737–3744
54 Allison, T. *et al*. (2002) Category-sensitive excitatory and inhibitory processes in human extrastriate cortex. *J. Neurophysiol* 88, 2864–2868
55 Allison, T. *et al*. (2000) Social perception from visual cues: role of the STS region. *Trends Cogn. Sci.* 4, 267–278
56 Kilts, C.D. (2003) Dissociable neural pathways are involved in the recognition of emotion in static and dynamic facial expressions. *Neuroimage* 18, 156–168
57 Goren, C.C. (1975) Visual following and pattern discrimination of face-like stimuli by newborn infants. *Pediatrics* 56, 544–549
58 Carey, S. (1992) Becoming a face expert. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 335, 95–102
59 Taylor, M.J. *et al*. (1999) ERP evidence of developmental changes in processing of faces. *Clin. Neurophysiol.* 110, 910–915
60 McGivern, R.F. (2002) Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. *Brain Cogn.* 50, 73–89
61 Yang, T.T. *et al*. (2003) Amygdalar activation associated with happy facial expressions in adolescents: a 3-T functional MRI study. *J. Am. Acad. Child Adolesc. Psychiatry* 42, 979–985
62 Baird, A.A. *et al*. (1999) Functional magnetic resonance imaging of facial affect recognition in children and adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 38, 195–199
63 Thomas, K.M. *et al*. (2001) Amygdala response to facial expressions in children and adults. *Biol. Psychiatry* 49, 309–316
64 Gallese, V. *et al*. (2004) A unifying view of the basis of social cognition. *Trends Cogn. Sci.* 8, 396–403
65 Jackson, P.L. and Decety, J. (2004) Motor cognition: a new paradigm to study self-other interactions. *Curr. Opin. Neurobiol.* 14, 259–263
66 Evans, A.C. *et al*. (1993) '3D statistical neuroanatomical models from 305 MRI volumes'. In *Proc. IEEE Nuclear Science Symposium and Medical Imaging Conference*, pp. 1813–1817, IEEE
67 Collins, D.L. *et al*. (1994) Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18, 192–205
68 Talairach, J. and Tournoux, P. (1988) *Co-Planar Stereotaxic Atlas of the Human Brain*, Thieme Medical Publishers, New York
69 Zijdenbos, A.P. *et al*. (2002) Automatic 'pipeline' analysis of 3D MRI data for clinical trials. *Application to multiple sclerosis IEEE Trans Med Imag* 21, 1280–1291
70 Cocosco, C.A. *et al*. (2003) A fully automatic and robust MRI tissue classification method. *Med Image Anal* 7, 513–527
71 Ashburner, J. and Friston, K.J. (2000) Voxel-based morphometry–the methods. *Neuroimage* 11, 805–821
72 Collins, D.L. *et al*. (1995) Automatic 3D model-based neuroanatomical segmentation. *Hum. Brain Mapp.* 3, 190–208
73 MacDonald, D. *et al*. (2000) Automated extraction of inner and outer surfaces of cerebral cortex from MRI. *Neuroimage* 11, 564–574
74 Lerch, J. and Evans, A.C. (2004) Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage* (in press)
75 Le Goualher, G. *et al*. (1999) Automated extraction and variability analysis of sulcal neuroanatomy. *IEEE Trans. Med. Imaging* 18, 206–217
76 Braitenberg, V. (2001) Brain size and number of neurons: an exercise in synthetic neuroanatomy. *J. Comput. Neurosci.* 10, 71–77
77 Braitenberg, V. and Schüz, A. (1998) *Cortex: Statistics and Geometry of Neuronal Connectivity*, Springer-Verlag
78 Huttenlocher, P.R. (1979) Synaptic density in human frontal cortex: Developmental changes and effects of aging. *Brain Res.* 163, 195–205
79 Flechsig, P. (1901) Developmental (myelogenetic) localisation of the cerebral cortex in the human subjects. *Lancet* 2, 1027–1029
80 Kaes T. (1907) *Die Grosshirnrinde des Menschen in ihren Massen und in ihrem Fasergehalt*, Fischer, Jena
81 Paus, T. (1989) The development of sustained attention in children might be related to the maturation of frontal cortical functions. *Acta Neurobiol. Exp.* 49, 51–55
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
83 Munoz, D.P. *et al*. (1998) Age-related performance of human subjects on saccadic eye movement tasks. *Exp. Brain Res.* 121, 391–400
84 Fischer, B. *et al*. (1997) On the development of voluntary and reflexive components in human saccade generation. *Brain Res.* 754, 285–297
85 Armengol, C.G. (2002) Stroop test in Spanish: children's norms. *Clin. Neuropsychol.* 16, 67–80
86 Williams, B.R. *et al*. (1999) Development of inhibitory control across the life span. *Dev. Psychol.* 35, 205–213
87 Matute, E. *et al*. (2004) Verbal and nonverbal fluency in Spanish-speaking children. *Dev. Neuropsychol.* 26, 647–660
88 Watkins, K.E. *et al*. (2003) Seeing and hearing speech excites the motor system involved in speech production. *Neuropsychologia* 41, 989–994