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Imaging the developing brain: what have we learned about cognitive development?

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The human brain undergoes significant changes in both its structural architecture and functional organization across the life span. Advances in neuroimaging techniques over the past decade have allowed us to track these changes safely in the human *in vivo*. We review the imaging literature on the neurobiology of cognitive development, focusing specifically on cognitive task-dependent changes observed in brain physiology and anatomy across childhood and adolescence. The findings suggest that cortical function becomes fine-tuned with development. Brain regions associated with more basic functions such as sensory and motor processes mature first, followed by association areas involved in top-down control of behavior.

Introduction

The year 2005 marks a decade since the first application of fMRI to developmental questions [1]. It is well established that brain development and cognitive maturation occur concurrently during childhood and adolescence [2–4], but much less is known about the direct relationship between neural and cognitive development. This review highlights what we have learned about the biological substrates of cognitive development over the past decade, advances and limitations of the methods, and the relevance of these studies to understanding and developing interventions for individuals with atypical development. Emphasis is placed on studies that inform how cognitive development and learning map onto changes in brain anatomy, connectivity and physiology across childhood and adolescence.

Contemporary non-invasive neuroimaging methods have provided developmental scientists with the opportunity to track safely cognitive and neural processes underlying human development (see Box 1). These methods have advanced the field of developmental neuroscience by providing evidence of changes in structural architecture and functional organization in the developing brain *in vivo*. However, these measures provide only an indirect measure of brain structure and function. Changes in the volume of a structure or amount of activity as measured by MR methods lack the resolution to characterize the mechanism of change definitively. Histological evidence suggests that brain development is a dynamic process of regressive and progressive changes (see Box 2). As such, MRI-based cortical changes observed with development may be a combination of myelination, dendritic pruning and changes in the vascular, neuronal and glial density. Nonetheless, the methodologies provide information about regional development that, in conjunction with histological studies, could tease these processes apart. Furthermore, because these tools permit not only scanning of children but also repeated scanning of the same individual over time, they can provide measurement of general neuroanatomical changes with both learning and development. This review highlights MR-based measures of change in neuroanatomy, cortical connectivity and cortical function with learning and development.

Neuroanatomical development of the human brain

Several structural imaging studies have mapped the neuroanatomical course of human brain development [5]. The findings parallel many of the post-mortem histological findings, providing validity for *in vivo* imaging measures, and also parallel behavioral and cognitive development. Claims of causality between coincidental changes in brain and behavioral development is a common trap into which one could fall by simply assuming linear changes across systems and direct associations between these changes. Nonetheless, the synchrony in time course of the changes reported in MRI-based anatomical studies and cognitive development have driven more direct tests of these associations in functional imaging studies. For this reason, MRI-morphometric studies of change in structural architecture are highlighted.

The most compelling reports of structural changes with development over the period of childhood and adolescence have come from recent longitudinal MRI studies [6,7]. In general, the sequence in which the cortex matures parallels cognitive milestones in human development [6–9]. First, regions subserving primary functions, such as motor and sensory systems, mature earliest, with

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Box 1. Magnetic resonance methods

Magnetic resonance technologies have introduced a new set of tools for capturing features of brain development in living, developing humans. The three most common MR methods used in the study of human development and learning are illustrated in Figure I. These imaging methods became especially important to cognitive and developmental scientists when the functional capabilities were discovered. The functional methodology measures changes in blood oxygenation in the brain that are assumed to reflect changes in neural activity [55,56], and eliminates the need for exogenous contrast agents, including radioactive isotopes [57,58]. DTI is a relatively new MR technique that can detect changes in white matter microstructure based on properties of diffusion [59,60]. Diffusion of water in white matter tracts is affected by myelin and the orientation and regularity of fibers and provides an index of brain connectivity. Because all three of these MR techniques are non-invasive, development and learning can be tracked more precisely within individuals with repeat scans over short or long intervals of time (days to years).

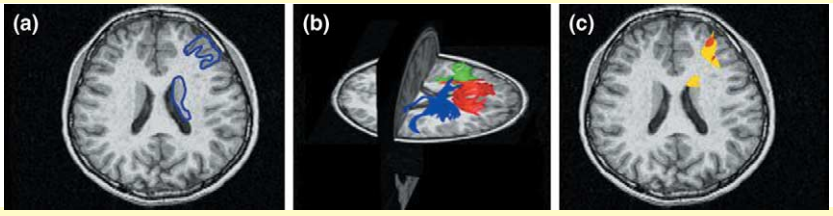

Figure I. (a) Structural MRI produces structural images of the brain that are useful for anatomical and morphometric studies; **(b)** DTI measures connectivity of fiber tracts between anatomical structures; and **(c)** functional MRI measures patterns of brain activity within those structures.

temporal and parietal association cortices associated with basic language skills and spatial attention maturing next. Higher-order association areas, such as the prefrontal and lateral temporal cortices, which integrate primary sensorimotor processes and modulate basic attention and language processes, seem to mature last [6,7]. Specifically, MRI-based measures showed that cortical gray matter loss occurred earliest in the primary sensorimotor areas

Box 2. Structural architecture of the developing brain

The human brain undergoes dramatic changes in both its structural architecture and functional organization that reflect a dynamic interplay of simultaneously occurring progressive and regressive events. Although the total brain size is about 90% of adult size by age 6 years, the brain continues to undergo dynamic changes throughout adolescence and well into young adulthood [61]. Figure I illustrates some of these developmental changes, including proliferation and migration of cells mostly during fetal development [62,63], regional changes in synaptic density during postnatal development [11,12,64], and protracted development of myelination well into adulthood [65]. Current non-invasive neuroimaging methods do not have the resolution to delineate which of these processes underlies observed developmental changes beyond gray and white matter subcomponents.

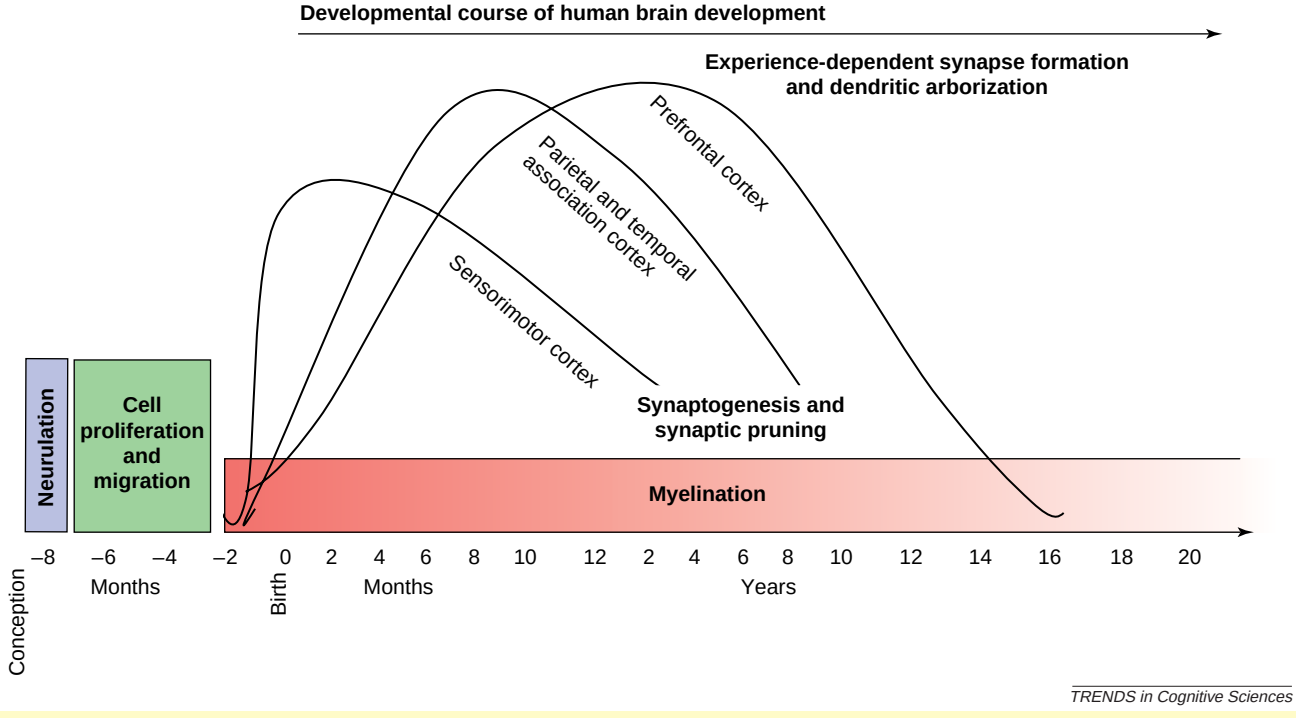

Figure I. See text for details. Adapted with permission from Ref. [66].

and latest in the dorsolateral prefrontal cortex [6,10]. These findings are consistent with non-human and human primate postmortem studies showing that the prefrontal cortex matures at a more protracted rate than sensorimotor cortex in synaptic density [11,12]. Cross-sectional studies of normative brain maturation during childhood and adolescence have shown somewhat similar patterns concluding that gray matter loss during this period reflects a sculpting process of the immature brain into the fully functioning mature one [10,13–16]. As such, the pattern of development observed is suggested to reflect the ongoing neuronal regressive events, such as pruning and the elimination of connections.

Developmental changes in subcortical regions occur over this period of development as well [10,13,15–19]. One of the more reliable patterns reported is in subcortical regions to which association cortex projects. For example, both cross-sectional [19] and longitudinal studies [6] show patterns of development in portions of the basal ganglia to which the prefrontal cortex directly projects. Again, this pattern could reflect the gradual elimination of connections, with strengthening of others.

What is the corresponding pattern of change in white matter volume over this period? In contrast to an inverted U-shaped pattern of development in gray matter with age, white matter volume increases in a roughly linear pattern, increasing throughout development until approximately young adulthood [6,13,14,17,20], as evidenced by increases in volume and density [17]. These changes presumably reflect ongoing myelination of axons by oligodendrocytes enhancing neuronal conduction and communication. Therefore, both regressive and progressive processes are occurring in parallel, which could enhance neural and cognitive processes. Connections are being fine-tuned with the elimination of an overabundance of synapses and strengthening of relevant connections with development and experience.

How do these structural changes relate to cognitive changes? Developmental changes in cortical development have been found to correlate with behavioral performance measures. Sowell and colleagues [4] showed an association between prefrontal lobe structural maturation and memory function using neuropsychological measures. Similar associations have been reported between MRI-based prefrontal volume and specific measures of cognitive control (i.e. the ability to override an inappropriate response in favor of another) in cross-sectional studies [21,22]. Together these studies suggest that, perhaps not surprisingly, functional changes in brain development are reflected in structural changes.

Development of human brain connectivity

The MRI-based morphometry studies reviewed suggest that cortical connections are being fine-tuned with the elimination of an overabundance of synapses and the strengthening of relevant connections with development and experience. Recent advances in MR technology, such as diffusion tensor imaging (DTI), provide a potential tool for examining the role of cortical connectivity in the development of cognitive and brain development in greater detail. This method (see Box 1) provides information on directionality and regularity of myelinated fiber tracts (e.g. [23]).

Until recently, few studies have linked brain connectivity measures with cognitive development, although indirect measures of white matter suggest regional development in prefrontal cortex and presumably in function [23]. Of these studies, one showed that development of working memory capacity was correlated positively with prefrontal–parietal connectivity [24], consistent with imaging studies showing differential recruitment of these regions in children relative to adults [39,42]. Using a similar approach, Liston and colleagues [25] showed that DTI-based connectivity in both frontostriatal and posterior fiber tracts correlated with age, but only frontostriatal connectivity correlated with efficient (fast and accurate) performance on a Go/No-go task. The prefrontal fiber tracts examined were defined by regions of interest identified in an fMRI study using the same task [42]. Similarly, combined DTI and fMRI analytical approaches have shown the importance of the maturation of prefrontal–parietal connectivity in the performance of a working memory task [26]. As such, DTI and fMRI-based measures with these regions correlated across age. In these studies, measures of brain connectivity were correlated with development, but specificity of the involvement of particular fiber tracts in cognitive performance was shown by dissociating the particular tract [25] or cognitive ability [24]. These dissociations are important when distinguishing between performance and age-related differences in imaging measures.

Functional organization of the developing human brain

What do the previously described changes in brain structure, such as prolonged development of the prefrontal volume and connectivity, mean in terms of function? The development of the prefrontal cortex is thought to play an important role in the maturation of higher cognitive abilities [27,28]. Mature cognition is characterized by the ability to filter and suppress irrelevant information and actions (sensorimotor processes), in favor of relevant ones (i.e. cognitive control) [27]. A child's capacity to filter information and suppress inappropriate actions in favor of appropriate ones continues to develop across the first two decades of life, with susceptibility to interference from competing sources lessening with maturity [29–32]. Many paradigms used to study cognitive development require cognitive control such as the Stroop and Go/No-go tasks [33–35]. Collectively, imaging studies using these tasks as probes show that children recruit distinct but often more prefrontal regions, both ventral and dorsal, when performing these tasks than do adults. Based on cross-sectional [36] and longitudinal studies [37], regions whose brain activity correlates with task performance (reaction time and/or accuracy) become more focal or fine-tuned, whereas regions not correlated with task performance decrease in activity with age (see Figure 1). It has been suggested that this pattern of activity, observed across a variety of paradigms, reflects development within, and refinement of, projections to and from these regions [28,30,34,36,38], consistent with the DTI findings presented previously.

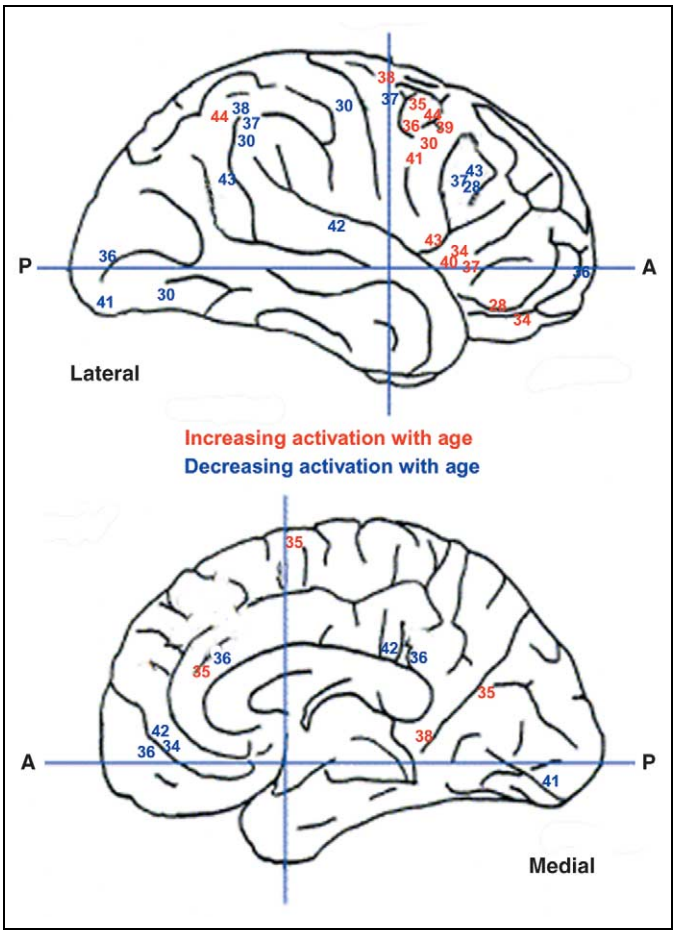

Figure 1. The development of human cortical function, as measured by contemporary imaging methods, reflects fine-tuning of a diffuse network of neuroanatomical regions [28,36,37]. Collectively, developmental neuroimaging studies of cognitive control processes suggest a general pattern of increased recruitment of slow maturing prefrontal cortex (references depicted here in red), especially dorsolateral prefrontal cortex [30,35,36,40,43] and ventral prefrontal cortex [28,34,37,39,42], and decreased recruitment of lower level sensory regions (references in blue), including extrastriate [36,40] and fusiform cortex [40] and also posterior parietal areas [30,37,38]. Importantly, specific activations vary with task demands, so working memory [43] and Stroop tasks [35] recruit different regions from response–inhibition tasks [28,34,37,39,41,42]. This pattern of activity, which has been observed across a variety of paradigms, suggests that higher cognitive abilities supported by association cortex become more focal or fine-tuned with development, whereas other regions not specifically correlated with that specific cognitive ability become attenuated. A = anterior; P = posterior.

Performance differences versus maturational differences

The region-specific differences in activation with age that have been reported could reflect maturation, but might also reflect simple performance differences. For this reason, the collection of behavioral responses is crucial across these studies. As children almost always perform worse than adults on higher cognitive tasks, without equating performance between age groups or controlling for performance differences it is difficult to specify whether the activation differences are age related or simply reflect an overall difference in performance. To address this issue, investigators have adopted different approaches for teasing apart age versus performance-driven differences. One key strategy is to use performance matching to equate behavioral performance [28,36,39,40]. Post hoc, subjects are divided into subgroups based on behavioral performance that is either matched across groups or not matched [40]. Three patterns of activation emerge from performance matching-based analyses: (i) performance/age-independent; (ii) performance-related; and (iii) age-related. These patterns help to identify the basis of the observed activation and/or regional differences and how they relate to the task demands.

As such, this approach provides a better understanding of how maturation relates to increased cognitive abilities. For instance, in a study of cognitive control that showed performance-related neural recruitment [39], children were divided into 'better and worse performers'. Children with effective response inhibition did not recruit the same prefrontal regions as those activated by adults, suggesting an age-related recruitment in this region. However, they did recruit a subset of the same posterior association areas (parietal regions) consistently activated in adults. Children with poor response inhibition did not recruit these posterior regions, suggesting that improved ability to withhold an inappropriate response might first require mature activation of posterior parietal regions that is task specific. Tasks of lesser cognitive demand (e.g. selective attention tasks without response competition) do not seem to show age-related differences [41].

As not all tasks yield comparable performance across age groups, a second approach that has been used to equate performance across groups is to manipulate task difficulty parametrically (e.g. [42,43]). In a parametric design, task difficulty is varied with increases in task demands (e.g. increased response competition, memory load or stimulus degradation), allowing comparisons between children and adults on trials equated for accuracy. Durston and colleagues [42] used a version of a Go/No-go task that parametrically manipulated the number of Go trials (responses) preceding a No-go trial (withhold response). Behaviorally, they showed that both children and adults had more errors as the number of responses preceding a No-go trial increased. Children, however, had as many errors for No-go trials following a single Go trial as adults had when a No-go trial followed as many as five Go trials. The imaging data from adults showed a monotonic increase in association areas of the ventral prefrontal and posterior parietal cortices as the number of Go trials preceding a No-go trial increased, but children activated these regions maximally regardless of whether they had to withhold a response after one, three or five Go trials (responses). These data are consistent with other reports showing [39] that immature cognition is characterized by an enhanced sensitivity to interference from competing sources (e.g. response competition) that coincides with immature association cortex, specifically in prefrontal and posterior parietal-related circuitry.

Cross-sectional studies versus longitudinal studies

Most of the developmental observations described above have relied on cross-sectional samples (e.g. [36]) or even comparisons across studies [1,44]. However, cross-sectional analyses might falsely suggest changes over time or fail to detect the specificity or magnitude of these changes, given the large individual variability in brain structure among individuals, especially during development [6,7,15].

In a recent study, Durston and colleagues [37] used fMRI to track cognitive and brain development from late

childhood into early adolescence during performance of a Go/No-go task. There was a developmental shift in patterns of cortical activation from diffuse to focal activity similar to those reported in large cross-sectional studies [36]. Regions uncorrelated with task performance were recruited less with age, whereas a region in the ventral prefrontal cortex that correlated with performance (speed and accuracy) in this study and prior studies [28,42,45,46] showed enhanced recruitment. This change in pattern of activity was associated with enhanced performance of the cognitive control task. Activation in earlier developing regions such as the primary motor cortex remained unchanged. A parallel cross-sectional analysis based on a second group of children, the same ages as the longitudinal group, showed less specific results, supporting the importance of longitudinal studies in evaluating cortical changes with age.

These studies, together with the longitudinal MRI-based morphometry studies [6], suggest differential developmental trajectories for sensorimotor relative to association areas such as the prefrontal cortex. Both the imaging-based neuroanatomical studies and the functional studies highlight the importance of examining changes in ability within individuals over time. As such, this work can begin to delineate processes specific to learning or development.

Cortical organization with learning

The importance of tracking cortical changes in individuals over time is perhaps most evident in the area of learning. Using repeated scanning of the same individuals, Karni and others (e.g. [47,48]) have shown rapid learning effects in primary motor cortex of adults during motor sequence learning that were apparent within a single imaging session, but that increased over weeks of training. This use of fMRI to trace learning-related changes in cortical areas is currently being used by others in adults (e.g. [49,50]). Across these studies, the pattern of results shows that activity in task-relevant regions becomes increasingly enhanced with training, whereas task-irrelevant regions become less activated over time [50]. This pattern of change during adult learning studies mimics the observed changes in cross-sectional [36] and longitudinal [37] developmental studies. The findings highlight the importance of examining and distinguishing between contributions from experience and learning compared to those associated more with maturational development, in driving the cortical patterns of activation observed.

Future directions

Future research will no doubt take advantage of the ability to image children multiple times with fMRI over the course of learning to delineate developmental and experience-based processes in cortical activity (see Box 3). For example, to determine whether the immature brain after extended practice engages in the same neural processes as the mature brain, we could compare brain activity in the mature system with brain activity in the immature system both before and after extended experience. Investigators are already beginning to take advantage of this approach in investigating the impact of behavioral and cognitive interventions on developmental disorders such as dyslexia [51,52] and attention deficit–hyperactivity disorder [53].

Box 3. Questions for future research

- Do the biological substrates of learning and development differ?
- On what timescale can we see neuroanatomical and physiological changes with learning and development?
- What neural changes coincide with enhanced learning during development that could hinder learning with maturity?
- How can we move beyond claims of causality between coincidental changes in brain and behavioral development with converging methods?
- Can typical human development provide important clues on the type and timing of interventions with atypical development?

Another future direction of developmental imaging studies will be in the combined use of complementary imaging methods. For example, a method not mentioned in this review, but one that has been used to address questions about cognitive and brain development, is electrophysiology. This technique records brain electrical activity that can be time-locked to presentation of a stimulus or to the production of a response (i.e. event-related potentials or ERPs). These electrophysiological measures have millisecond temporal resolution that can provide important information on the developmental changes in the temporal characteristics of neural and cognitive processes beyond that provided by fMRI [54]. Clearly, the combination of these two techniques, together with other methods such as DTI, will strongly enhance our ability to understand neural and cognitive development and constrain current developmental theories. Investigators have begun to move in that direction with parallel fMRI and DTI studies in adults and children [25,26].

Conclusions

Findings from both cross-sectional and longitudinal imaging studies of late childhood and adolescence show that brain regions associated with more basic functions such as motor and sensory processes mature first, followed by association areas involved in top-down control of thoughts and action. This pattern of development is paralleled by a shift from diffuse to more focal recruitment of cortical regions with learning and cognitive development. Fine-tuning of cortical systems occurs with protracted refinement of association cortex (e.g. prefrontal cortex) relative to sensorimotor cortex. These findings seem to parallel changes observed over shorter time periods in studies of adult learning. The reported shift in cortical architecture and function is presumably an experience-driven maturational process that reflects fine-tuning of neural systems with experience and development, but future work delineating how learning during development affects this pattern is needed. These imaging studies map onto findings from animal and human postmortem studies indicating that pruning and elimination of connections, in combination with strengthening of relevant ones, occur during this time period, and illustrate the subtle interplay between neuroanatomical and physiological changes in neural circuitry and cognitive maturation.

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