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# Changes in cerebral functional organization during cognitive development

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It has been just under a decade since contemporary neuroimaging tools, such as functional magnetic resonance imaging, were first applied to developmental questions. These tools provide invaluable information on how brain anatomy, function and connectivity change during development. Studies using these methods with children and adolescents show that brain regions that support motor and sensory function mature earliest, whereas higher-order association areas, such as the prefrontal cortex, which integrate these functions, mature later.

## Addresses

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## Introduction

A fundamental goal of developmental cognitive neuroscience is to understand how age-related changes in the anatomy and physiology of the brain are linked to the maturation of cognitive abilities. It is well established that brain development and cognitive maturation occur concurrently during childhood and adolescence [1–3], but much less is known about the direct relationship between neural and cognitive development. Here, we review the available evidence linking patterns of change in neuroanatomy and neurophysiology to development in cognitive ability during childhood and adolescence.

This review is timely as neuroimaging tools, such as functional magnetic resonance imaging (fMRI), were first used to address developmental questions only a decade ago [4]. Measures of brain anatomy and connectivity, together with fMRI, are important tools in clarifying changes that occur in the brain during development. So, what has been learned about the biological substrates of cognitive development? What impact have studies had on our understanding of the biology of developmental

disabilities and effective interventions? Finally, which directions is the field of developmental cognitive neuroscience currently moving towards?

## Tracking developmental change Magnetic resonance imaging technologies measure brain development

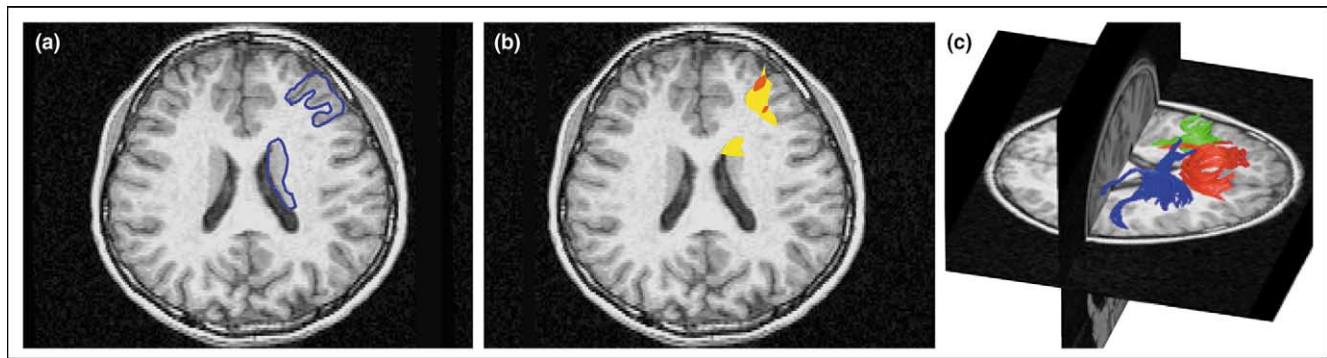
Magnetic resonance imaging (MRI) technologies have introduced a new set of tools for capturing features of brain development in living, developing humans. MRI is particularly well suited to the study of children, as it provides exquisitely accurate anatomical images without the use of ionizing radiation [5]. This method not only permits the scanning of children's brains, but also the repeated scanning of the same individual over time, thus providing precise measurements of neuroanatomical changes during learning and development. Durston *et al.* [6] provide an extensive review of MRI-based morphometry studies of development during the past decade.

MRI became especially important to cognitive and developmental scientists when its functional capabilities were discovered and developed. Whereas MRI is used to produce structural images of the brain useful for anatomical and morphometric studies, the functional component of fMRI allows an *in vivo* measure of brain activity. The functional methodology measures changes in blood oxygenation in the brain that are assumed to reflect changes in neural activity [7,8], and eliminates the need for exogenous contrast agents, including radioactive isotopes [9,10]. For an extensive review of developmental fMRI studies before 2002, see Thomas and Casey [11].

## Diffusion tensor imaging provides clues to neural connectivity

Diffusion tensor imaging (DTI) is a technique that provides data on brain connectivity and is sensitive to myelination and neuroanatomical changes in white matter microstructure *in vivo* [12]. This method is useful for examining the connectivity between structures and highlights the development of, and changes in, neurocircuitry beyond simple structural changes. DTI methodology moves us away from modular interpretations of findings in single brain regions, to interpretations that reflect brain connectivity and distributed neural networks. To date, only a handful of studies using this technique have examined the association between developmental changes and DTI-based measures of connectivity [13,14].

Figure 1



MRI methods are commonly used in the study of brain development and learning. **(a)** Structural MRI measures the size and shape of structures (i.e. caudate nucleus and inferior frontal gyrus shown in blue). **(b)** fMRI measures patterns of brain activity within those structures (yellow and red areas). **(c)** DTI measures the connectivity of fiber tracts (connectivity of fiber tracts shown in red, blue and green) between those structures. Adapted from [53].

MRI, fMRI and DTI are influential tools in the study of human developmental neuroscience, but it is important to note that these methodologies only provide an indirect measure of brain function (Figure 1). Although magnetic resonance methods measure changes in the volume of a structure or in the amount of its activity, they lack the resolution to definitively characterize the mechanism of such changes (e.g. dendritic arborization, cell death, synaptic pruning, myelination). Therefore, the interpretation of the imaging work reviewed in this article also builds on prior work from post mortem [15] nonhuman electrophysiological [7,16] and lesion studies [17], to build a fuller picture of the links between cognitive development and cortical structural and functional changes.

### What changes in the brain during development?

#### MRI-based anatomical studies show changes in gray and white matter

Several studies have used structural MRI to map the anatomical course of normal brain development [6]. Although total brain size is approximately 90% of its adult size by age six, the gray and white matter subcomponents of the brain continue to undergo dynamic changes throughout adolescence. Data from recent longitudinal MRI studies indicate that gray matter has an inverted U-shape pattern, with greater regional variation than white matter [18,19<sup>••</sup>,20,21<sup>•</sup>]. Further, these developmental changes in gray matter correlate with behavioral performance measures. Sowell *et al.* [3] showed an association between prefrontal lobe structural maturation and memory function [3]. In general, regions subserving primary functions, such as motor and sensory systems, mature earliest; higher-order association areas, which integrate these primary functions, mature later [19<sup>••</sup>,20]. For example, studies using MRI-based measures show that cortical gray matter loss occurs earliest in

the primary sensorimotor areas and latest in the dorso-lateral prefrontal and lateral temporal cortices [19<sup>••</sup>]. This is consistent with nonhuman and human primate post-mortem studies showing that the prefrontal cortex is one of the last brain regions to mature [15,22].

In contrast to gray matter decreases, white matter volume increases in a roughly linear pattern, increasing throughout development until approximately young adulthood [19<sup>••</sup>]. Thus, regressive (gray matter loss) and progressive (increased white matter) processes underlie brain development and presumably cognitive development.

#### fMRI studies reveal brain regions associated with cognitive control

What do changes in brain structure, such as prolonged development of the prefrontal cortex, mean in terms of brain function? The development of the prefrontal cortex is believed to play an important role in the maturation of higher cognitive abilities [23,24]. Tasks that recruit and rely on this region are therefore ideally suited for investigating the neurobiological changes that underlie cognitive maturation.

Mature cognition is characterized by the ability to filter and suppress irrelevant information, thoughts, and actions in favor of relevant ones (i.e. cognitive control) [23]. A child's capacity to filter information and suppress inappropriate actions develops during the first two decades of life. Susceptibility to interfering, and competing thoughts and actions diminishes with maturity [25–27]. Many paradigms used to study cognitive development require cognitive control tasks such as Flanker, Stroop and Go/NoGo tasks [28–30]. Collectively, these studies show that children recruit larger, more diffuse prefrontal regions when performing these cognitive control tasks than adults do. The pattern of activity within brain regions central to such task performance (that correlate with performance)

becomes more focal or fine-tuned with increased activity, whereas brain regions not correlated with such task performance decrease in activity with age, as indicated by cross-sectional [31\*\*] and longitudinal studies [32]. This pattern of activity, observed across a variety of paradigms, has been suggested to reflect development within, and refinement of, projections to and from these regions during maturation [24,26,29,31\*\*,33–37,38\*].

Developmental differences in patterns of brain activity during cognitive control tasks might reflect maturation, but might also reflect performance differences in task performance. As children almost always perform worse than adults on cognitive control tasks, it is difficult to specify whether such activation differences are age-related or simply reflect an overall difference in behavioral performance without equating performance between age groups or controlling for performance differences. To address this issue, investigators have adopted different approaches for teasing apart age- and performance-driven differences.

One such approach is to use performance matching to equate behavioral performance [28,31\*\*,33,35]. *Post hoc*, subjects are divided into subgroups based on behavioral performance and are either matched across groups or not matched [35]. Three patterns of activation emerge from performance-matching-based analyses: performance- and age-independent; performance-related; and age-related. These patterns help identify the basis of the observed activation and/or regional differences and how they relate, if at all, to the task demands. As such, this approach provides a good understanding of how maturation relates to increased cognitive abilities. For instance, in a study of cognitive control that showed performance-related neural recruitment [33], children were divided into ‘better’ and ‘worse’ performers. Children with effective cognitive control 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 less cognitive control (i.e. difficulty over-riding an action) did not recruit these posterior regions, suggesting that improved ability to withhold an inappropriate response may 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 appear to show age-related differences [39].

As not all tasks yield comparable performance across age groups, a second approach, involving the parametric manipulation of task difficulty, has been used to equate performance across groups [40,41]. In a parametric design, task difficulty is titrated according to increases in task demands (e.g. increased response competition, memory

load, or stimulus degradation), thus allowing comparisons between children and adults on trials equated for accuracy. Durston *et al.* [40] used a version of a Go/NoGo task that parametrically manipulated the number of Go trials (responses) preceding a NoGo trial (withhold response). Behaviorally, they showed that both children and adults had an increasing number of errors as a function of increasing number of responses preceding a NoGo trial. Children, however, had as many errors for NoGo trials following a single Go trial as adults had when a NoGo trial followed as many as five Go trials. Imaging data from these experiments show that adults displayed a monotonic increase in activity in association areas of the ventral prefrontal and posterior parietal cortices, as the number of Go trials preceding a NoGo trial increased; children, however, maximally activated these regions regardless of whether they had to withhold a response following one, three or five Go trials. These data suggest 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 regions. Immature cognition seems to correlate with an immature association cortex, specifically the circuitry related to prefrontal and posterior parietal regions.

Another pattern observed in developmental imaging studies of cognitive control is greater reliance upon subcortical versus cortical systems in children relative to adults [34,38\*,42]. In a study examining cognitive performance during an attention task that was superimposed on emotional information, Monk *et al.* [42] found greater amygdala activity in adolescents, but greater ventral prefrontal activity in adults when the task required them to ignore the emotional information. This finding is consistent with cognitive maturation being characterized by greater susceptibility to irrelevant information [23]. Further evidence of a bias in recruitment of subcortical over cortical regions in children is provided by reported inverse correlations between these brain areas in other developmental cognitive studies [38\*].

#### **DTI-based studies show changes in connectivity during cognitive development**

Few studies have linked brain connectivity measures with improvements in cognitive ability, although indirect measures of white matter suggest that regional development of prefrontal connectivity parallels cognitive development [43]. Recently, links between DTI-based measures of prefrontal connectivity and cognitive control have been shown in children. In one study, development of working memory capacity was positively correlated with prefrontal–parietal connectivity [13\*]. This result is consistent with imaging studies that show differential recruitment of these regions during cognitive control tasks in children when compared to adults. Using a

similar approach, Liston *et al.* [14] showed that connectivity in frontostriatal and posterior fiber tracts was associated with age, but only frontostriatal connectivity correlated with performance on a Go/NoGo task. In an fMRI study using the same Go/NoGo task, activity within these same frontostriatal regions was shown to be involved in cognitive maturation [40]. Similar combined DTI and fMRI analytical approaches have been used in adults [44\*].

These developmental studies show that general changes in brain connectivity (prefrontal and posterior fiber tracts) are correlated with age, but that connectivity within specific fiber tracts (e.g. prefrontal tracts) is related to individual variability in cognitive ability, regardless of age [14]. These findings underscore the importance of examining not only regional changes in activity, but also circuitry-related changes, when making claims about age- and performance-related associations regarding the neural substrates of cognitive development.

### Applications of imaging techniques to learning and intervention studies

MRI techniques are particularly well suited to tracking brain development and studying learning, as repeat scanning does not rely on ionizing radiation-based measures. Learning studies using these methods in adults show rapid training effects and changes in neural recruitment during the course of learning [45]. These studies show increasingly focal and enhanced activity in cognitive task-relevant regions, and decreased activity in task-irrelevant regions [46\*], not unlike the developmental changes seen in both cross-sectional [28,31\*\*,41] and longitudinal studies [32]. These findings highlight the importance of determining to what extent changes in the functional organization of the cortex observed with imaging methods are due to learning, development or both. Intervention and treatment studies have begun to take advantage of this approach, by examining how cognitive and pharmacological interventions influence neural recruitment in developmental disorders such as dyslexia [47\*,48] and attention deficit hyperactivity disorder [49,50].

### Conclusions and future directions

Overall, the structural and functional studies reviewed here suggest that brain regions subserving primary functions, such as motor and sensory systems mature before higher-order association areas that integrate those primary functions (e.g. prefrontal cortex). In structural imaging studies, this is evidenced by cortical gray matter loss occurring earliest in primary sensorimotor areas and latest in dorsolateral prefrontal and lateral temporal regions [19\*\*]. In functional imaging studies, development of brain function is evidenced by the fine-tuning of control structures, with a shift from diffuse to more focal recruitment of cortical regions specifically implicated in cognitive control [31\*\*,32].

Advances in neuroimaging technology have moved the field of human developmental neuroscience significantly forward [51,52]. The field as a whole has begun to move beyond simple claims of causality between coincidental changes in brain development and behavioral development. Simply assuming linear changes across systems during development is an easy trap in which to fall, but rarely are such claims empirically grounded. Such pitfalls can be avoided by the increasing use of converging methods (e.g. DTI, MRI, and fMRI) and by distinguishing between age- and performance-related changes in brain development observed with these methods. Training studies of typically developing children may provide the greatest insights into what truly changes in the brain during learning and development. Intervention-based imaging studies of children with developmental disabilities are examples of important work in this area.

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