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PART

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Mechanisms

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CHAPTER
2

Development of Neural Networks Supporting Goal-Directed Behavior

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INTRODUCTION

One of the most salient facets of cognitive and socioemotional development is the emergence of goal-directed thought and behavior, a concept referred to as *cognitive control*, *executive function*, or *self-regulation* (Bunge & Wright, 2007; Luna, Padmanabhan, & O'Hearn, 2010; Somerville & Casey, 2010). We begin life with a broad focus of attention, registering incoming stimuli without attempting to filter them. Over childhood, we begin to selectively attend to, manipulate, and act on goal-relevant information; in so doing, we exhibit greater volitional control over our attention, memory, action, and emotions (Bunge & Crone, 2009; Munakata, Snyder, & Chatham, 2012).

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Implications of the healthy development of cognitive control are far-reaching. Self-control has been linked to health, wealth, and public safety on a population level (Moffitt et al., 2011). Moffitt and colleagues (2011) followed a cohort of 1,000 children from birth to age 32, and found that physical health, substance dependence, personal finances, and criminal offense in adulthood were predicted by a gradient of self-control in childhood, even after accounting for IQ and social class origins. Recent evidence has also linked failure of self-regulation to a host of neuropsychiatric problems—including attention deficit hyperactivity disorder, addiction, risk-taking behaviors, and conduct disorders—as well as suboptimal performance in school (Fjell et al., 2012). However, the mechanisms by which this important ability develops are not well understood.

COGNITIVE CONTROL IN THE DEVELOPING BRAIN

Crucial to understanding goal-directed behavior is an understanding of what it means to be *goal-directed*; it is deliberate, volitional, and governed by *top-down processing*. We have a limited capacity for processing information, and successful control depends on our ability to focus on relevant information and filter out irrelevant information. The prefrontal cortex (PFC) is integrally involved in top-down processing, as discussed in an influential theoretical review by Miller and Cohen (2001). Following on the theoretical work of Desimone and Duncan (1995), Miller and Cohen proposed that cognitive control rests on the active maintenance of patterns of PFC activity that represent goals, which signal "bias" to other brain structures and permit mappings between inputs, outputs, and internal states appropriate to achieve those goals.

Goal-directed behavior is subserved by widespread neural networks. Several frontal regions—including the anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), ventrolateral PFC (VLPFC), dorsolateral PFC (DLPFC), and frontal eye fields—and regions outside the PFC, including the posterior parietal cortex (PPC), striatum, thalamus, and cerebellum, are associated with inhibitory control and working memory (Hwang & Luna, 2013).

The protracted development of the PFC and parietal cortex into young adulthood (Gogtay et al., 2004) underscores the extended developmental trajectory of cognitive control from early childhood through adolescence. Until now, literature on the development of goal-directed behavior has focused on the PFC; we propose, along with others (Hwang & Luna, 2013), that changes in interactions between PFC and other cortical regions are at least as important as changes in the PFC itself.

The adult state is implicitly viewed as the ideal in developmental research (Poldrack, 2010). Developmental cognitive neuroscience (DCN) asks questions like: *Do we perform a particular task better as adults than as children because of increased efficiency of one or more cognitive processes? Or, do we perform the task better as adults because an additional, or different, cognitive process is involved?* (Bunge, 2008). For instance, many developmental theories have assumed that in the temporal dynamics of how goal representations are activated, children are like adults, only less skilled (Munakata et al., 2012). However, recent work suggests that children use a qualitatively different, *reactive* form of cognitive control, which is recruited on an as-needed basis (Andrews-Hanna et al., 2011; Chatham, Frank, & Munakata, 2009) and is supported by neural networks that are differentiable from those supporting the proactive control more likely to be observed in adults (Madsen et al., 2010).

Basic processes underlying cognitive control are evident early in development; gains in goal-directed thought appear to be linked to the reliable engagement of specific processes that fine-tune cognitive control (Hwang & Luna, 2013). Maturational changes in white and gray matter enhance the ability of the brain to integrate function between the PFC and other distributed cortical and subcortical regions, which is critical for processing complex information. Underlying these improvements in functional integration is the coupling of neural synchrony across neuronal assemblies. Prefrontally guided top-down connectivity continues to strengthen through early adulthood, supporting flexible executive control of behavior.

Executive functions develop most rapidly during preschool years and undergo another period of relative plasticity in the transition to adolescence (Zelazo & Carlson, 2012). Children become more flexible in attentional control during the preschool years, and at as young as 4 years of age can switch between two sets of rules in a card sorting task when instructed (Hanania & Smith, 2010). However, a hallmark of early executive function is externally driven behavior; without being told what rule to switch to, children tend to perseverate, demonstrating an immature capacity for generating goals *internally* (Kharitonova & Munakata, 2011; Munakata et al., 2012).

Bunge and Zelazo (2006) proposed that gains in flexible rule use reflect the growth of regions in lateral PFC. Specifically, the ability to represent hierarchical rule systems depends on the development of an increasingly complex hierarchical network of PFC regions. The order of acquisition of rule types—first one rule, then two rules, then two incompatible pairs of rules—corresponds to the order in which each of the implicated brain regions matures, with the orbitofrontal cortex (OFC) maturing earliest, and the dorsolateral (DLPFC) and rostrolateral PFC (RLPFC) maturing last. Bunge and Zelazo (2006) observed that 8-year-olds showed greater lateral PFC activation for bivalent than univalent rules, and that age differences in the pattern of PFC activation across rule conditions differs between 8- and 12-year-olds, 13- and 17-year-olds, and young adults. Other brain regions showed mature patterns of activation across age-groups, suggesting that age-related gains in rule use between 8 years of age and adulthood are associated with development of the lateral PFC.

Regions within the PFC also interact with multiple brain systems through complex networks, and development marks a period of mass neural network shifts. If we hope to understand why behavior becomes increasingly goal-directed over childhood and adolescence, it is imperative that we discover how the specific brain networks that regulate cognitive and emotional processes emerge over development (Fjell et al., 2012; Somerville & Casey, 2010; Stevens, 2009), and how they are shaped by genetic and environmental factors (Johansen-Berg, 2010). DCN calls for research on the underlying anatomy of pathways that support the development of cognitive control (Fjell et al., 2012). One likely suspect is myelination; reliable and timely transmission of signals is necessary to influence activity in a distal brain region, as is the case in PFC modulation of the parietal cortex and other regions. The child and adolescent brain undergoes substantial myelination and white matter growth (Fields, 2008; Giedd, 2008; Hua et al., 2009; Tamnes, Østby, Fjell, et al., 2010). Another likely suspect is the reorganization of local circuitry, achieved in part via cortical thinning (Gogtay & Thompson, 2010), enabling long-range fiber connections to play a greater role in altering local network dynamics.

DEVELOPMENTAL SHIFT FROM REACTIVE TO PROACTIVE CONTROL

Flexible rule-guided behavior develops gradually, and is essential for success in life (Munakata et al., 2012); it entails the ability to remember rules, switch between them as needed, and implement them in the face of competing information (Wendelken, Munakata, Baym, Souza, & Bunge, 2012). In a recent review, Munakata and colleagues outlined three key developmental transitions toward more flexible behavior (Munakata et al., 2012). First, children develop an increasing ability to overcome habits by engaging cognitive control in response to environmental signals. At first, infants rapidly detect regularities in their environments to bring order to what they see and hear (Romberg & Saffran, 2010), but show limitations in breaking out of habitual behaviors or responding flexibly to novel situations. Young children begin to show signs of overcoming this inflexibility (Hanania & Smith, 2010). Second, children shift from recruiting cognitive control reactively, as needed in the moment, to recruiting cognitive control proactively, in preparation for needing it. Goal representations also provide top-down support to speed responses and to support generalization to new situations. Finally, children become more self-directed. As their capacity for active maintenance increases across development—linked to maturation of lateral PFC regions (Bunge & Zelazo, 2006)—it increasingly becomes sufficient to support proactive control (Munakata et al., 2012).

Chatham and colleagues tested the temporal dynamics of cognitive control in 3.5- versus 8-year-old children on the AX-Continuous Performance Task using high-resolution pupillometry (Chatham et al., 2009). In this task, participants provide a target response to a frequent sequential pair of stimuli, and a nontarget response to all other pairs. The authors found that 8-year-old children resembled adults in their proactive use of cognitive control, whereas 3.5-year-olds exhibited a qualitatively different, reactive form of cognitive control, responding to events only as they unfold and retrieving information from memory as needed in the moment. These contrasting approaches were evident in distinct profiles of errors, reaction times, and pupillometric indices of mental effort. Three-year-olds exerted more effort—indexed by pupil diameter (Beatty & Lucero-Wagoner, 2000)—after the second stimulus in a pair was presented, an effect consistent with reactive engagement of cognitive control in that moment, whereas 8-year-olds exerted more effort after the first stimulus was presented, an effect consistent with proactive maintenance of this information until it is needed.

With regard to neural networks, proactive control is associated with sustained and/or anticipatory activation of lateral PFC, which reflects the active maintenance of task goals (Braver, 2012). This activity serves as a source of top-down bias that can facilitate processing of expected upcoming events that have a high cognitive demand (Miller & Cohen, 2001). By contrast, reactive control should be reflected in transient activation of lateral PFC, along with a wider network of additional brain regions (Bunge, 2004). In addition, the two control mechanisms should differ in terms of the involvement of the dopaminergic system (Braver, 2012; also Ezekiel, Bosma, & Morton, 2013), which changes through adolescence.

Building on Bunge and Zelazo's (2006) account of hierarchical rule representation, a recent study from our group probed the development of *arbitrary* rule representation (Wendelken et al., 2012). We collected task-related functional magnetic resonance imaging (fMRI) in children ages 8 to 13 years and young adults performing our so-called Nemo task, in which participants must switch flexibly from one task rule to another. One rule involves an arbitrary response mapping—"press the left button if the character is blue"—and the other a nonarbitrary response mapping—"press the left button if the character is facing left." The task involves three distinct manipulations: (1) rule type: a manipulation of rule representation, comparing arbitrary with nonarbitrary stimulus-response mappings, (2) switching: whether the rule switches or repeats, and (3) incongruency: whether a stimulus would elicit the same response or a different response depending on whether participants are required to make a judgment based on the color or the orientation of the stimulus.

Children performed fairly well overall on the Nemo task, although they were less accurate than adults and exhibited slower responses (Wendelken et al., 2012). Two key questions were addressed: *First, are overlapping or distinct networks taxed by these manipulations? Second, are there differences between children and adults in the networks engaged for these various aspects of rule use?* Several regions—left DLPFC, left posterior parietal cortex (PPC), and presupplementary motor area (pre-SMA)—were recruited by both the rule representation and the rule-switching manipulations, across age-groups. This is consistent with theoretical frameworks that emphasize the role of task-relevant activation in supporting a variety of executive functions, including shifting, inhibition, updating, and monitoring (Ezekiel et al., 2013; Miller & Cohen, 2001). However, evidence from functional selectivity and temporal dynamics also suggested that adults engage in more *proactive* control processing while children engage in more *reactive* control processing.

Figure 2.1 shows a hypothesized progression of an arbitrary rule trial in the Nemo task, accompanied by brain regions associated with proactive versus reactive control (Figure 2.1), and by brain regions differentially engaged by adults and children (Figure 2.2). Importantly, we found a difference in the networks engaged by better and worse performers that applied not only to *developmental differences*, but also *individual differences*. Top performers recruited the left frontoparietal network, especially the ventrolateral PFC (VLPFC; Bunge, 2004), posited to be associated with proactive control, while worse performers recruited the right cingulo-operculum network, posited to be associated with reactive control (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Madsen et al., 2010).

The time course of activation in left DLPFC also suggested that the children were more reactive, updating task rules more slowly than adults. In children, but not in adults, activation at the beginning of each trial reflected the previous trial's rule, rather than the current rule. This finding is consistent with developmental transitions observed in the temporal dynamics of cognitive control (Andrews-Hanna et al., 2011; Chatham et al., 2009; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010).

Employing a hybrid block/event-related fMRI Stroop design in conjunction with self-report measures, Andrews-Hanna and colleagues investigated the shift to proactive control in a cohort of individuals

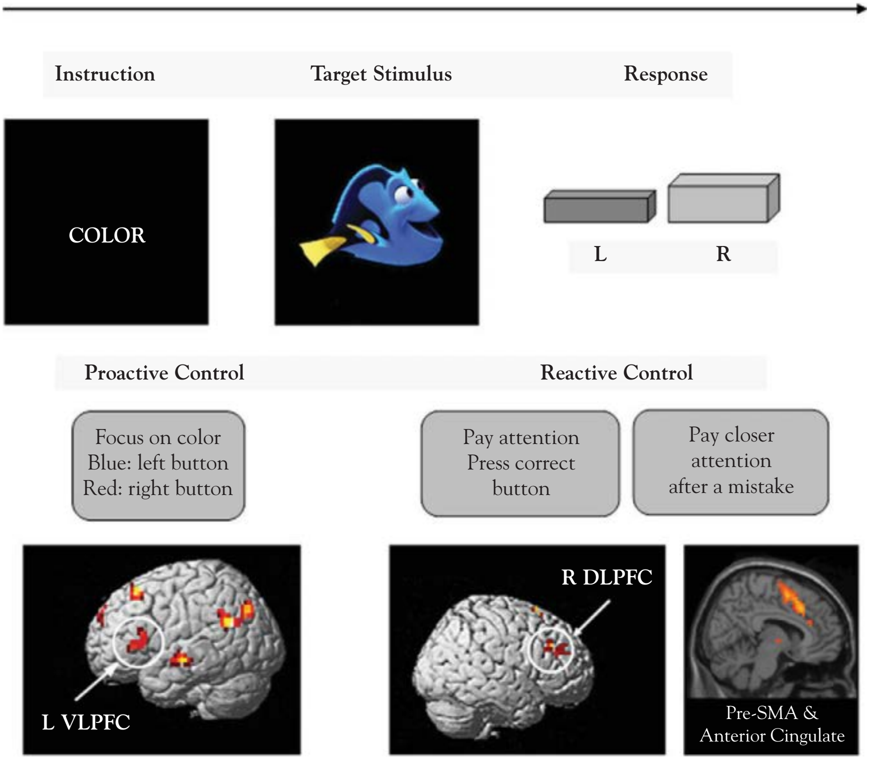

Figure 2.1 Hypothesized progression of a single trial.

From the cognitive control task: the “Nemo” task. Participants view the task instruction, followed by an image of a fish from *Finding Nemo* (protected by copyright), and respond by pressing one of two buttons. Best-performing participants engaged a brain network previously associated with rule representation, whereas worst-performing participants engaged a network associated with performance monitoring and conflict detection. We hypothesize that the best performers engaged in proactive control, retrieving and holding in mind the currently relevant rule prior to the onset of the target stimulus, whereas the worst performers engaged in reactive control, exhibiting heightened monitoring at the time that a response is required.

aged 14 to 25 years (Andrews-Hanna et al., 2011). They found that adolescents underactivated a set of brain regions implicated in proactive top-down control, especially left posterior DLPFC (Bunge & Crone, 2009; Gogtay et al., 2004; Paus, 2005). Furthermore, adolescents who exhibited greater activation of the inferior frontal junction (IFJ; which includes posterior DLPFC) exhibited better self-report composite measures of impulse control, foresight, and resistance to peer pressure, and tended toward more successful Stroop task performance.

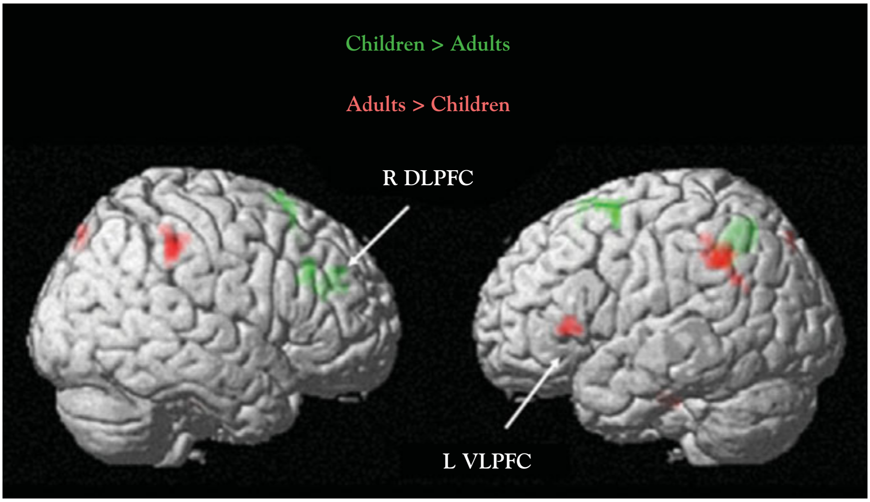

Figure 2.2 Age-related differences in PFC activation.

The left arrow points to areas where activation was greater in children than adults; the right arrow points to areas that were more activated in adults than children. From the cognitive control task: the Nemo task.

Although no differences in activation were observed between adults and adolescents for the ACC, heterogeneous patterns of ACC/pre-SMA activation within the adolescent group suggest a compensatory reactive response.

In contrast, adults exhibited the opposite relationship with Stroop performance, such that adults who activated IFJ to a lesser degree trended toward more successful Stroop behavior (Andrews-Hanna et al., 2011). The relationship between prefrontal activity and age was curvilinear, peaking approximately at age 21 years and decreasing thereafter.

Taken all together, these results suggest that children are more likely than adults to maintain prior rule information when it is no longer relevant, and to retrieve current rule information reactively rather than maintaining it proactively (Munakata et al., 2012). Results in adolescents suggest that maturation of cognitive control may be partly mediated by earlier development of neural systems supporting reactive control and delayed development of systems supporting proactive control (Andrews-Hanna et al., 2011). Future work is needed to determine whether the developmental progression from reactive to proactive control is governed by qualitatively distinct mechanisms or by a continuous developmental shift (Chatham et al., 2009).

STRUCTURAL DEVELOPMENT

Recent findings from developmental neuroimaging studies suggest that the enhancement of cognitive processes during development results from a fine-tuning of the structural and functional organization of brain. But the mechanisms by which this takes place are not yet understood. Looking at regional topological properties and interregional connectivity, Khundrakpam and colleagues found a "time window of plasticity" during late childhood, which they suggested may accommodate the changes that come with pubertal development (Khundrakpam et al., 2012). Importantly, they report early maturation of primary sensorimotor regions and protracted development of higher-order association and paralimbic regions, which have been linked to cognitive control (Hwang & Luna, 2013). However, studies that have compared structural and functional MRI measures of brain development have not provided evidence for a simple relationship between them (Lu et al., 2009).

Developmental Changes in Cortical Thickness

Cortical thickness is the distance from the gray matter/white matter boundary to the outer surface of the brain (i.e., the pial surface), which likely reflects the number of cells within cortical columns (Fjell et al., 2012). Thanks to the development of powerful analytic tools for measuring longitudinal changes in brain structure, we now have detailed information about within-person changes in cortical thickness over development (Gogtay & Thompson, 2010; Tamnes, Østby, Fjell et al., 2010). These data reveal piecemeal cortical thinning over childhood and adolescence, with association cortices—including but not limited to PFC—maturing later than primary sensory cortices. Within PFC, medial and ventral regions undergo thinning most quickly, such that DLPFC matures later than other prefrontal subregions. In another analysis, Fjell et al. (2012) found that developmental gains in cognitive control, as measured by a flanker task in a cohort of 725 individuals ages 4 to 21, were associated with changes in surface area in the anterior cingulate (ACC), an area that has been previously linked to impulse, attention, and executive problems across a range of neurodevelopmental disorders.

Specifically, surface area of the right caudal ACC accounted for a significant proportion of the variance in cognitive performance.

Cortical thinning is likely to reflect multiple changes at the cellular level, including decreased gray matter as a result of synaptic pruning and increased white matter as a result of myelination and/or increased axon diameter (Giedd, 2008; Tamnes, Østby, Fjell et al., 2010). Indeed, recent structural MRI analyses by Gogtay and Thompson (2010) and Hua et al. (2009) suggest that there is white matter growth underlying areas of thinning gray matter. Longitudinal studies of individuals ages 3 to 30 years have demonstrated general patterns of peaks of gray matter in childhood followed by declines in adolescence, increases in long-range structural and functional connectivity, and a shift of activation from limbic and subcortical regions to the frontal lobe in cognitive tasks (Giedd, 2008; also Finn et al., 2010). Histological studies have shown that sensory areas may develop first, followed by a longer trajectory in frontal executive regions linked to the late development of executive function (Casey, Tottenham, Liston, & Durston, 2005).

The functional significance of these changes in cortical thickness is not yet clear. While it is possible to find evidence for positive and/or negative relationships between cortical thickness and cognitive performance, recent work from our lab suggests a positive relationship between performance on a complex reasoning task and thinning in the inferior parietal lobule (IPL) across children and adolescents (Wendelken, O'Hare, Whitaker, Ferrer, & Bunge, 2011). Karama and colleagues previously found a positive relationship between cognitive ability and thinning across most multimodal association areas (Karama et al., 2009). These brain-behavior relationships can also be influenced by age, gender, and their interaction (Christakou et al., 2009), although such differences are not always linked to differences in cognitive performance (Lenroot & Giedd, 2010).

Developmental Changes in White Matter Pathways

The development of goal-directed behavior partly reflects the maturation of white matter pathways; for instance, white matter maturation has been shown to explain additional variance in cognitive control beyond cortical thinning (Fjell et al., 2012). Importantly, tracts that provide connections between frontal and other cortical and subcortical regions demonstrate the most protracted developmental trajectory, occurring in parallel with changes in gray matter (Hwang & Luna, 2013). The large number of reciprocal connections between PFC and other cortical regions position it nicely to coordinate, influence, and integrate information needed for executive control. As these connections develop to enhance neuronal transmission, the ability to form functional networks to support complex function improves, consistent with gains in executive control.

The advent of diffusion tensor imaging (DTI) has made it possible to measure within-individual changes in white matter tracts over development, and their relationship to changes in cognition. DTI provides an indirect measure of white matter tracts in vivo in the human brain (Fields, 2008). A diffusion-weighted MRI scan is sensitive to the movement of protons in the brain, particularly those within water molecules. Water molecules in white matter diffuse preferentially along axon bundles because the myelin sheath surrounding the axons impedes their diffusion across a tract. Water molecules that have high directionality are said to exhibit anisotropic diffusion. Two DTI measures are reported below: *fractional anisotropy* (FA), a widely used measure of white matter coherence, and *perpendicular diffusivity*, thought to be sensitive to levels of myelination.

Although white matter maturation takes place throughout the brain, it is possible to link cognitive performance to the strength of specific tracts (Johansen-Berg, 2010; Madsen et al., 2010; Niogi, Mukherjee, Ghajar, & McCandliss, 2010; Olson et al., 2009; Uddin, Supekar, Ryali, & Menon, 2011). Johansen-Berg (2010) found that, *independent of age*, white matter anatomy was linked with cognitive skills in healthy adults.

As shown in Figure 2.3, McCandliss and colleagues provided evidence of a triple dissociation in the brain-behavior relationships of three white matter tracts (Niogi et al., 2010). They examined performance across three dissociable functional components of attention—alerting, orienting, and conflict processing—identified by the Attention Network Task (ANT). The ANT is a simple computerized task that measures the speed and accuracy with which a participant can press one of two buttons to indicate whether the central arrow in a row of visually presented

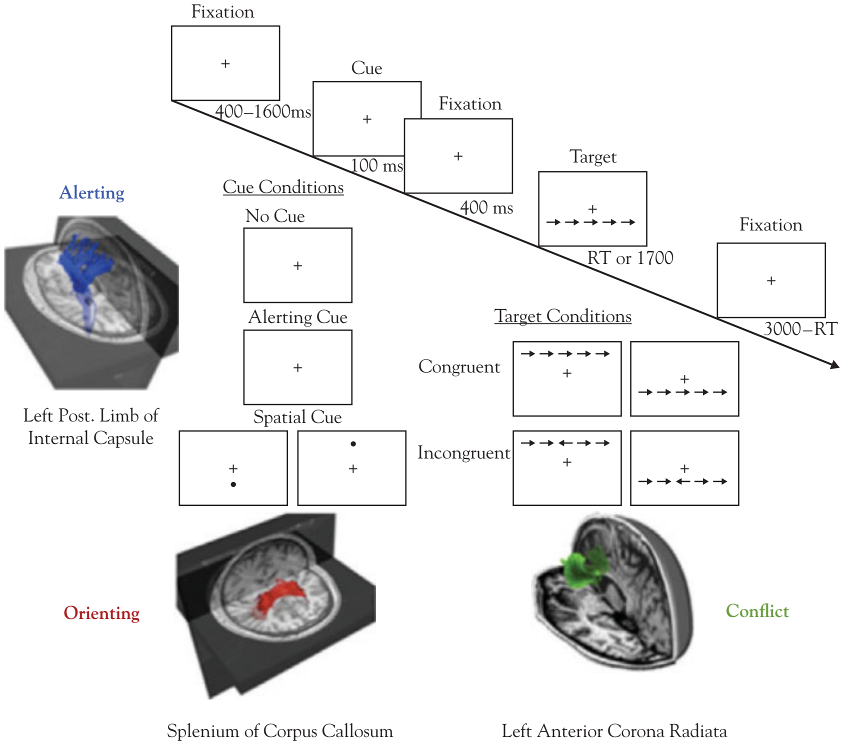

Figure 2.3 A triple dissociation is shown in the interindividual relationships between white matter integrity of three tracts and cognitive performance on the three components of the Attention Network Task (ANT): alerting, orienting, and executive function (specifically, conflict resolution).

Figure modified with permission and originally published in Niogi, S., Mukherjee, P., Ghajar, J., & McCandliss, B. D. (2010). Individual differences in distinct components of attention are linked to anatomical variations in distinct white matter tracts. Frontiers in Neuroanatomy, 4*(2). doi:10.3389/neuro.05.002.2010*

arrows points left or right. This task has three critical manipulations that tax different aspects of attention. To measure the alerting response, researchers measure how much better participants perform when the stimulus array is preceded by a visual warning cue versus when it is not. To measure the orienting response, they measure how much better they respond when the visual cue indicates where on the screen the stimulus array will appear versus when it is not spatially predictive. Finally, to measure executive/conflict processing, researchers measure how much better the participant performs when the arrows in the stimulus array all point in the same direction versus when the flanking stimuli point in the opposite direction from the central, target arrow.

Interindividual performance on each functionally distinct component was differentially correlated with coherence in a distinct set of white matter tract regions. Correlations were found between alerting and the left anterior limb of the internal capsule, orienting and the splenium of the corpus callosum, and conflict and the left anterior corona radiata. Analyses revealed a triple dissociation providing evidence of three anatomically and functionally separable networks.

It stands to reason, then, that the development of these and other white matter tracts may be partly accountable for the development of cognitive skills such as goal-directed behavior. Whole-brain analyses in individuals aged 9 to 23 years revealed that success on a delay discounting task—that is, less impulsive performance—was associated with increased FA in tracts in and across the bilateral frontal and temporal lobes (Olson et al., 2009). In a stop-signal task, faster response inhibition was associated with higher FA in the right inferior frontal gyrus (IFG) and right presupplementary motor area (pre-SMA) in typically developing children (Madsen et al., 2010). Furthermore, individuals with high verbal abilities may show accelerated white matter development compared to the steadier and prolonged development observed in their average-ability counterparts (Tamnes, Østby, Walhovd, et al., 2010).

Lebel and colleagues recently reported the results of longitudinal studies of white matter maturation that demonstrate clear age-related microstructural changes throughout the brain in individuals aged 5 years through adulthood (Lebel et al., 2012; Lebel & Beaulieu, 2011). The corpus callosum and fornix mature in early childhood, reaching peak FA by young adulthood. In contrast, they found that major tracts that connect PFC with posterior regions and have been hypothesized to support cognitive control, namely the cingulum, uncinate fasciculus, and superior longitudinal fasciculus, develop slowly. Because these changes in FA were driven by perpendicular diffusivity, results suggest that they result from changes of myelination and/or axonal density (Lebel et al., 2012). The researchers also found volume increases in several association tracts postadolescence (Lebel & Beaulieu, 2011). Corroborating evidence for the prolonged maturation of association tracts comes from an earlier cross-sectional study (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Other findings provide converging anatomical data suggesting that developmental gains in goal-directed behavior in adolescence may be associated with structural changes enhancing long-distance connections, coupled with synaptic pruning in the cortex (Giorgio et al., 2010).

DEVELOPMENTAL CHANGES IN FUNCTIONAL NETWORKS

While techniques like DTI help us to characterize the development of white matter tracts, research on patterns of correlated brain activation provide a complementary picture of developing cortical networks. Functional connectivity analyses identify regions with strongly correlated patterns of functional MRI activation over time, either during performance of a cognitive task or at rest. Brain regions that are not directly connected to one another via white matter tracts may nonetheless act in concert as part of a distributed network. Conversely, two brain regions that are anatomically connected may not yet be fully integrated into a shared network (Barnes et al., 2012; Biswal et al., 2010; Supekar et al., 2010). Therefore, a promising approach is to integrate these complementary measures of brain connectivity (Rykhlevskaia, Gratton, & Fabiani, 2008) to address inquiries regarding how and why changes in the “wiring” of neural networks promote the development of cognitive control (Stevens, 2009).

Developmental Shift From Local to Long-Range Functional Connectivity

Imaging the brain during rest (i.e., in the absence of task demands) reveals low-frequency fluctuations in the fMRI signal that are temporally correlated across regions presumed to be functionally related. Reproducibility across resting-state fMRI datasets suggests that the human *functional connectome* has a common architecture, yet each individual’s connectome is unique; age and gender are notable as significant determinants (Biswal et al., 2010). Over the past few years, there have been a number of studies characterizing changes in network connectivity in typically and atypically developing populations (Fan et al., 2011; Gao et al., 2009; Supekar et al., 2010; Thomason et al., 2008; for review, see Stevens, 2009).

These developmental changes in resting-state functional connectivity are sufficiently robust that multivariate pattern analysis can be used to predict an individual's age with a fairly high degree of accuracy (Dosenbach et al., 2010). Wang and colleagues (2012) found that these age-related changes in interregional functional connectivity exhibited spatially and temporally specific patterns over the lifespan (Wang, Su, Shen, & Hu, 2012). Functional connectivity decreased linearly in the sensorimotor system, increased linearly in the emotion system, and followed a quadratic trajectory—with increases through childhood and early adulthood, followed by decreases later in life—in systems associated with higher-order cognition, from childhood through old age.

In a recent functional connectivity MRI study, Barnes and colleagues (2012) demonstrated that cortical parcellation of the left lateral parietal cortex—part of a left lateral frontoparietal network correlated with proactive control (Wendelken et al., 2012)—in school-aged children resembled that of adults. However, age-related differences were found in its functional connectivity with other brain regions, suggesting that structure and function in this region mature along different developmental trajectories, with functional connectivity following a prolonged trajectory (Barnes et al., 2012). In contrast, Supekar and colleagues (2010) found that functional connectivity in children can reach adult-like levels despite immature structural connectivity. They proposed that the prolonged maturation of the posterior cingulate cortex (PCC)-medial PFC structural connectivity may be linked with development of the self-related and social-cognitive functions that emerge during adolescence (Supekar et al., 2010).

The maturation of executive function is dually supported by *functional specialization*—regional neural support of specific processes—and *functional integration*—large-scale neural network support (Hwang & Luna, 2013). One of the central developmental findings in recent functional connectivity work is the progression from short-range connections within cortical areas to longer-range cortico-cortico connections (Fair et al., 2009; Jolles, van Buchem, Crone, & Rombouts, 2011; Stevens, Pearlson, & Calhoun, 2009). As children mature, short-range functional connections become weaker, and long-range connections strengthen (Church et al., 2009). At first, the distributed network is composed of many weak connections, but as children move into adolescence and adulthood, functional connections tend to become stronger but sparser, reflecting the increasing specificity of emerging functional networks (Fair et al., 2009; Supekar et al., 2010). Jolles and colleagues investigated whole-brain functional connectivity in middle-aged children and young adults (Jolles et al., 2011). Interestingly, they found that while children and adults displayed similar patterns of functionally connected regions, the size (number of voxels) and strength (correlation value) of connectivity differed between brain regions into young adulthood. Regions associated with higher cognitive and emotional functions became more tightly coupled with age, while connectivity between regions linked to basic visual and sensorimotor functions showed the opposite effect (Jolles et al., 2011).

A study by Barber and colleagues (2013) showed developmental differences between late childhood and adulthood in the "default mode" network, comparing task-positive and task-negative regions, that is, the regions that are engaged and disengaged during task performance relative to when the participant is asked to rest, respectively (Barber, Caffo, Pekar, & Mostofsky, 2013). They found that task-positive regions showed greatest age-related discrepancy in the left DLPFC, a region strongly implicated in cognitive control. In contrast, task-negative regions, posited to play a role in social cognition and self-referential thought, showed greatest age-related differences in medial PFC and right parahippocampal gyrus. Connections between the task-positive and task-negative regions also displayed developmental differences. Importantly, there was a significant relationship between anticorrelations—that is, the extent of inverse correlation between activations in task-positive versus task-negative regions—in a swath of task-negative regions (right anterior insula, right IFG, right PCC, and bilateral parietal cortex), exhibited in adults, and successful inhibitory control performance on Go/No-Go tasks. This result suggests that the development of certain anticorrelations into adulthood supports mature inhibitory control (Barber et al., 2013).

Functional Connectivity in the Development of Cognitive Control

A lateral frontoparietal neural network underlies goal-directed behavior across diverse contexts (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Wendelken et al., 2012). Cole et al. (2012) have pointed to global connectivity—that is, the mechanisms by which regions in the frontoparietal network might coordinate other cortical networks—as the driving force of cognitive control. They found that a lateral PFC region's activity exhibited global connectivity and predicted performance in a high-demand working memory task. Furthermore, individual differences in lateral PFC global connectivity were related to individual differences in fluid intelligence (Cole et al., 2012).

Work from our lab has shown age-related changes in the temporal dynamics of DLPFC activation, such that children appeared to update rules more slowly than adults, engaging in reactive rather than proactive control (Wendelken et al., 2012; described earlier). Ezekiel and colleagues (2013) recently investigated a similar possibility, consistent with our finding of an age-related shift from the cingulo-operculum to the frontoparietal network (see Figure 2.1): Age is associated with changes in the functional integration of lateral PFC with a larger cognitive control network (Ezekiel et al., 2013). They tested middle-school-aged children and adults on a card sort/switch cognitive control task. Results demonstrated that adults engaged regions within a "cognitive control" network, including bilateral DLPFC, right IFG, ACC/medial PFC, inferior parietal cortex, and the ventral tegmental area (VTA). Children showed engagement of a different network; regions included anterior frontal gyri, bilateral rostrolateral PFC, right anterior insula, and left posterior temporal cortex. These findings are consistent with observations that children and adults may both have relatively efficient systems for cognitive processing, but that they solve problems in different ways (Fair et al., 2009).

Signals for updating representations in lateral PFC—a crucial aspect of a switch task like this one and our Nemo task (Wendelken et al., 2012)—originate in dopamine neurons in ventral tegmental area (VTA), which Ezekiel et al. (2013) found to be more strongly connected to lateral PFC in adults than children. They hypothesized that functional connectivity between lateral PFC and VTA is associated with the speed with which rule representations may be updated in lateral PFC (Ezekiel et al., 2013). Taken together, it is suggested that complex cognitive operations may be emergent products of rapid bidirectional interactions between functionally specialized brain regions; and shift or improve concurrently with various aspects of neural development.

Broadly, the differences between children and adults in patterns of functional connectivity are consistent with the trajectories of gray and white matter development. At the same time that local functional connections within the cortex are weakening, cortical gray matter is thinning—and, as long-range white matter tracts are getting stronger, so, too, is long-range functional connectivity. Supekar et al. (2010) found that some, but not all, changes in functional connectivity had obvious anatomical correlates. Thus, these structural and functional measures provide valuable and complementary views of brain development.

DEVELOPMENTAL COGNITIVE NEUROSCIENCE AND THE STUDY OF COGNITIVE CONTROL

As discussed earlier, developmental cognitive neuroscience (DCN) has begun to uncover the neural mechanisms governing the development of goal-directed behavior. First, fMRI has revealed that patterns of activation observed in the performance of cognitive control tasks in children versus adults are consistent with those observed in reactive versus proactive control. Second, structural MRI has shown that cortical thinning in association cortices is correlated with gains in behavioral performance. Third, DTI and functional connectivity analyses have shown that projections between the PFC and other cortical regions shift from local to long-range with development. Taken together, DCN has enabled us to show that gains in cognitive control observed with age are subserved by a confluence of factors in the developing brain.

The field of cognitive neuroscience, which straddles the gap between the mind and brain, is the right level at which to begin to understand how cognitive developmental trajectories are influenced by such important factors as genetic variants, hormonal changes during puberty, schooling, and socioeconomic and cultural contexts. Indeed, behavioral findings have often been considered controversial until accompanied by discovery of an underlying biological mechanism (Diamond & Amso, 2008). Neuroimaging has allowed, for instance, the delineation of how task-related and resting-state brain networks develop through strengthening and weakening of functional connections (e.g., Fair et al., 2009).

In both the temporal and spatial domains, the scale at which we examine brain development is at once an important strength and an important limitation of DCN. In the spatial domain, the fact that we can take neural measurements *across the entire brain* means that we can identify brain *networks:* sets of tightly coupled brain regions that underlie specific cognitive processes. Until recently, the bulk of DCN research has focused on specific brain regions of *a priori* interest—for example, studies focusing on maturational changes in the PFC that underlie improvements in cognitive control. Current DCN research is focusing more and more on analyses of neural networks. In the temporal domain, the fact that we can measure brain structure and function in vivo at multiple times in the life of an individual child means that we can examine true developmental change, rather than merely extrapolating from comparisons between samples of children from different age-groups. The possibility for longitudinal brain research is a clear advantage of noninvasive imaging techniques that has yet to be used to its full potential. We briefly discuss next promising future directions for DCN in the study of the development of goal-directed behavior.

Early Brain Development

Although most of the behavioral literature on cognitive development has focused on the period of rapid changes observed during early childhood, most of the DCN studies to date have, for practical reasons, focused on older children and adolescents (Poldrack, 2010). In recent years, researchers have refined pediatric imaging protocols that make it possible to obtain high-quality structural and functional MRI data from infants (Dehaene-Lambertz et al., 2010; Fan et al., 2011; Gao et al.,

2009) and young children (Cantlon, Pinel, Dehaene, & Pelphrey, 2011; Nordahl et al., 2008). This advance makes it possible to measure the functional organization of the newborn brain, and to examine the neural changes that support the emergence of new cognitive abilities over early childhood.

DCN has revealed that even at 2 weeks of age, infants exhibit spontaneous resting-state activity in some of the same regions as adults (Gao et al., 2009). At 1 month, infants already display modular functional connectivity (Fan et al., 2011), and by 2 years of age, children have the beginnings of adult-like connectivity and modular organization (Fan et al., 2011; Gao et al., 2009). Friedman, Miyake, Robinson, and Hewitt (2011) showed, in a longitudinal study of 950 twins, that self-restraint in toddlers predicted individual differences in three executive functions—inhibition, updating, and shifting—in late adolescence (Friedman, Miyake, Robinson, & Hewitt, 2011). Self-restraint was measured by showing the children an attractive toy and instructing them not to touch it for 30 seconds; capacity for self-restraint was measured by how long the toddler waits before touching the toy. The twin models indicated relative contributions of genetics and environmental factors to gains in these components of executive function; results suggested a biological relationship between individual differences in self-restraint and executive functions that begins in infancy and persists through adolescence.

Genetic, Hormonal, and Environmental Influences on Brain Development

An important next step in DCN is the elucidation of genetic, hormonal, and environmental factors that interact to influence brain and cognitive development. There has been research on gene x environment influences on behavior during development (Wiebe et al., 2009). Until recently, this work has left the brain out of the equation, but DCN is beginning to examine genetic and/or environmental influences on brain structure and function (Casey, Soliman, Bath, & Glatt, 2010; Chiang et al., 2009; Hackman & Farah, 2009; Lenroot et al., 2009; Thomason et al., 2010), and is also beginning to look at the influence of changing pubertal hormone levels (Blakemore, Burnett, & Dahl, 2010).

Links between cognitive control and dopamine suggest that the neurodevelopment of cognitive control should interact with age-related variability in the dopaminergic system (Braver, 2012; Ezekiel et al., 2013). Indeed, gene x environment effects—including variation in a polymorphism related to D2 dopamine receptor transmission—have been shown to differentially impact slow-developing functions such as self-regulation depending on the developmental period (Wiebe et al., 2009). Another study showed that typical white matter development was related to a common genetic variant in the dopamine signaling pathway, COMT, that influences dopamine levels in PFC (Thomason et al., 2010). Using a visual working memory task, Dumontheil et al. (2011) reported age × genotype interactions in the effects of the COMT genotype observed in the intraparietal sulcus (IPS), with greater gray matter volumes bilaterally and greater right IPS activation in the Val/Val group compared with the Met carriers. Genetic maps have also revealed the complex heritability of white matter integrity, cortical thickness, and even IQ (Chiang et al., 2009; Lenroot et al., 2009). Chiang and colleagues (2009) found that white matter integrity was highly heritable in a number of regions, including bilateral frontal, bilateral parietal, and left occipital lobes, and that common genetic factors mediated the correlation between IQ and white matter integrity. Lenroot et al. (2009) investigated gender differences in brain volume, and found, among other things, that males and females exhibited dissociable patterns of activation on cognitive tasks, without differences in performance.

Longitudinal Research

To examine—and interrelate—developmental trajectories for cognition, brain structure, and brain function, it is necessary to acquire data at multiple time-points per individual. Longitudinal research can provide important insights regarding typical and atypical cognitive development (Reichenberg et al., 2010). Although there are few published longitudinal MRI studies of children (Giedd et al., 2009; Gogtay & Thompson, 2010), and even fewer that include functional as well as structural measures (Fan et al., 2011; Shaw et al., 2009), a number of research groups are conducting this important work now.

Durston and colleagues conducted the first combined cross-sectional and longitudinal fMRI study on the development of cognitive control (Durston et al., 2006). They directly compared between-group measurements of brain activation with within-person changes in brain function during performance of a Go/No-Go task. These two analyses yielded somewhat different results in the lateral PFC, with only longitudinal findings showing attenuated activation in DLPFC areas and increased activation in focal VLPFC areas. These data underscored the need for further longitudinal brain imaging studies.

The past few years have seen several promising results from longitudinal behavioral and brain imaging research involving children and adolescents. Childhood self-control has been found to predict physical health, substance dependence, personal finances, and criminal behavior in adulthood (Moffitt et al., 2011), and early childhood self-restraint to predict executive functions in late adolescence (Friedman et al., 2011). Within-person tracking of brain structure and function shows peaks and dips in gray matter volume and white matter integrity over development (Giedd, 2008; Giorgio et al., 2010; Lebel & Beaulieu, 2011; Lebel et al., 2012), and a shift in neural networks engaged during performance of cognitive tasks (Finn et al., 2010). Finally, Moriguchi and Hiraki (2011) demonstrated how PFC engagement interacted with performance on cognitive shifting tasks in children studied at age 3 and again at 4 years of age. They found that better-performing children at age 3 showed significant activation of right inferior PFC, and that better-performing children at age 4 showed this activation bilaterally. These intriguing results underscore the importance and future potential of the longitudinal method to address the link between cognitive and neural development (Moriguchi & Hiraki, 2011).

CONSIDERATIONS AND FUTURE DIRECTIONS IN DEVELOPMENTAL COGNITIVE NEUROSCIENCE

As neuroimaging methods have grown more sophisticated, so, too, has DCN. Many new investigators have joined the field, including individuals with strong statistical and computational backgrounds. Researchers have developed procedures that facilitate pediatric fMRI data acquisition and analysis (Fonov et al., 2011; Ghosh et al., 2010), and have addressed many of the basic questions and concerns surrounding pediatric MRI methodology (Church, Petersen, & Schlaggar, 2010; Luna, Velanova, & Geier; 2010). Many have also moved on to tackle greater challenges, such as the acquisition of longitudinal MRI data (Fan et al., 2011; Lebel et al., 2012; Moffitt et al., 2011; Moriguchi & Hiraki, 2011; Shaw et al., 2009) and the integration of multiple measures in the study of brain development (Fjell et al., 2012; Paus, 2010; Thomason et al., 2010).

We have learned a lot over the past few years about the typical developmental trajectory of cortical thickness and white matter tracts. However, we still know little about how these changes relate to developmental changes or individual differences in brain function or behavior, and imaging the developing brain continues to pose unique challenges. With regard to functional connectivity MRI, Power and colleagues recently revealed that subjects' head motion in the scanner causes systematic but spurious correlations between brain regions (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Specifically, they found that subject motion produces substantial changes in time-course data; many long-distance correlations may appear less robust than they are and short-distance correlations may appear more robust than they are. This is especially pertinent for DCN, not only because functional network analyses are integral to the study of cognitive development, but also because motion artifacts are more pronounced in children than adults. The authors also noted explicitly that connections between lateral PFC and the anterior cingulate—which carry import for successful goal-directed behavior, as described in this chapter—may appear distorted from subject motion (Power et al., 2012).

This confound is important to consider, both because motion artifacts are more pronounced in children than adults, and because long-distance connections are thought to mature more slowly than short-distance ones. It is precisely the slow development of long-distance connections that has been linked to delayed maturation of the ability of one region to influence neural activity in distal regions. Thus, DCN research focused on functional brain networks must address this potential confound.

It is also important to note that most of the structural data purporting to characterize typical brain development are based on a fairly homogeneous sample of children, despite efforts to diversify the samples. It is necessary to cast a wider net to determine how well such findings generalize to children across a wide range of intellectual abilities, and from a variety of socioeconomic and cultural backgrounds.

There is still much to be discovered regarding the interplay of external and internal factors on cognitive and brain development, and an endeavor of this level of complexity necessitates a multidisciplinary approach with large research teams, large sample sizes, and data collection at multiple time points per individual. At the same time, it will be important in the coming years for DCN to strike the right balance between data-driven research—so-called discovery science (Biswal et al., 2010)—and hypothesis-driven research grounded in theories of cognitive development.

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