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DEVELOPMENTAL CHANGES IN COGNITIVE CONTROL THROUGH ADOLESCENCE

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I. Introduction

The main purpose of this review is a better understanding of the developmental transition in behavior from adolescence to adulthood. To distinguish our focus from earlier (infancy) and later (aging) phases of development, we will refer to processes of “maturation,” to emphasize the nature of this phase as a time when improvements are reaching a plateau and stable levels of adult behavior are achieved. During this phase of development many processes are changing that affect decision making including social, emotional, and cognitive aspects of behavior. In this review, I focus on the processes underlying the maturation of voluntary control of behavior (also referred to as cognitive control and executive function) because of its basic role in decision making.

Development refers to the mechanisms of change that ultimately lead to maturity in adulthood. Although much is known about the significant advances that occur in infancy and childhood, relatively less is known of the mechanisms that support the later parts of development in adolescence as mature-level behavior is approached. This chapter focuses on this particular phase of development as we transition from immature mechanism to mature adult-level behavior. Early development involves the *acquisition* of abilities that significantly change behavior, but as maturity is reached the changes are more subtle and involve the *sophistication* of abilities. This process begins in adolescence and can be conceptualized as occurring at the bend in the curve of development just before when the curve flattens representing adult stability (Figure 1). An important question during this phase of development is: what are the mechanisms that support this transition into mature levels of cognitive control of behavior? This is a phase of development when much of behavior appears adult-like, yet there is still pervasive evidence for limits in the efficacy of cognitive control. For example, adolescents are vulnerable to psychopathology, such as schizophrenia and mood disorders (Angold, Costello, & Worthman, 1998; Kessler *et al.*, 1994). In addition, sensation and novelty seeking peak in adolescence (Chambers, Taylor, & Petenza, 2003; Spear, 2000) and are associated with extreme sports, drug use, and unprotected sex. These behaviors appear to be characterized by poor judgment and decision making with limited appreciation for long-term consequences and are often impulsive in nature.

A significant landmark of this phase of development is the maturation to adult levels of the flexible and controlled manner of voluntarily guiding goal-directed behavior. In contrast to exogenously driven behavior (i.e., reflexive, automatic, and guided by outside stimuli) that is present early in development, endogenously driven behavior (i.e., voluntary, planned, and driven by internal goals) matures later. Central to endogenous behaviors are executive processes such as voluntary response inhibition and working memory that allow planned responses. When planning a response, alternatives often must be considered and goal inappropriate responses that may be more reflexive need to be suppressed. This process is

referred to as response inhibition and is central to cognitive control (Fuster, 1997). Working memory refers to the 'sketch pad' that allows us to retain relevant information on-line to make a planned goal-directed response and it is also central to cognitive control (Fuster, 1997). These processes, as described later in this chapter, are present in infancy but continue to improve throughout adolescence into adulthood and may underlie the emergence of adult-like behavior. We discuss what is known to be unique regarding the cognitive control of behavior during adolescence.

The emergence of cognitive control is driven by continuous interaction of environmental and biological factors. Biological mechanisms determine a timeline when environmental factors can have a lasting effect, and the environment establishes the course of biological mechanisms. For example, in the process of synaptic pruning (discussed later), the environment determines which synapses will be kept and which will not be needed but biological mechanisms determine the times in development when different parts of the brain will be most affected. In terms of cognitive control, brain development constrains the processes that can be performed at different ages. Characterizing the state of brain mechanisms during adolescence can help determine the nature of the cognitive tools that are available or not during this period. The interaction of brain and behavior thus becomes crucial in understanding maturation. These interactions have been studied with functional magnetic resonance imaging (fMRI); later we discuss what neuroimaging has revealed regarding onset of adult-like behavior in adolescence.

Adolescence commonly is considered to encompass 12–17 years of age, with the precise timing varying with gender and puberty (Spear, 2000). Puberty occurs when secretion of hormones in the pituitary gland stimulate ovarian development in females and spermatogenesis in males (Ojeda, Ma, & Rage, 1995). The timing is determined by age as well as metabolic and neuronal factors. Gonad hormone levels have direct effects on molecular mechanisms throughout the brain (McEwen, 2001) including influencing cortical development. Mood and social processes are affected by hormonal changes (Alsaker, 1996) which influence sex steroid receptors in the hippocampus and are associated with the regulation of the neuro-transmitter dopamine (DA) especially in the part of the midbrain, namely the nucleus accumbens (NAcc), known to be critical in reward processing (Chambers *et al.*, 2003). There is no clear association between puberty and cognitive processes. Some studies have found a link between spatial abilities and pubertal timing (Petersen, 1976; Waber, Mann, Merola, & Moylan, 1985), but others have not (Orr, Brack, & Ingersoll, 1988; Strauss & Kinsbourne, 1981). Puberty may influence the degree to which one can exert cognitive control in situations of high arousal but in itself may not be directly linked to the development of cognitive control. Still, it is a pivotal aspect of this stage of development that must not be over-looked.

In this chapter, I analyze available evidence regarding the behavioral and brain processes present during adolescence. I discuss immaturities in the brain and how these may limit voluntary control. I also discuss the evidence indicating continuing development of cognitive control through adolescence, assessing the nature of what is still immature during this period. A critical review of the results of neuroimaging studies provides a forum to integrate the mechanisms of how brain and behavior interact during this time. A developmental theory emphasizing the role of the integration of widely distributed circuitry underlying the transition from adolescence to adulthood is contrasted against the traditional view that cognitive development is primarily driven by the unique protracted maturation of prefrontal cortex. Finally, I delineate a theory of maturation that is specific to this time of development and can be used to make predictions of behavioral performance.

II. What is Maturing in the Brain during Adolescence?

Identifying the progression of structural brain maturation in adolescence can further understanding of the brain functional systems that are available to support complex behavior such as cognitive control. The gross morphology of the brain is apparent early in life. The delineation of cortical folding in the brain is in place by birth (Armstrong *et al.*, 1995). The brain rapidly changes from a smooth surface to a convoluted one postnatally with well-defined sulci and gyri that are organized in predetermined fashion and that have different functional roles and cytoarchitecture. This early gyrification indicates the potential early in life for brain structure to support distinct regional specialization. The gyrification index, the ratio of exposed versus entire cortical contour, reaches adult levels in the second decade of life (Armstrong *et al.*, 1995). The brain achieves 95% of adult levels of size and weight by 7–11 years of age and adult weight by adolescence (Caviness *et al.*, 1996; Giedd *et al.*, 1996). These later changes in brain morphology are believed to be the result of processes such as synaptic pruning and myelination (Huttenlocher, 1990; Yakovlev & Lecours, 1967). I discuss each in turn.

A. SYNAPTIC PRUNING: INCREASING REGIONAL PROCESSING EFFICIENCY

Humans are born with an over-abundance of neuronal synaptic connections. After the first two years of life, throughout infancy, and into adolescence, synaptic connections that are used remain and those that are not used are eliminated or *pruned* through activity-dependent stabilization (Rauschecker & Marler, 1987). This process is largely understood to be a mechanism of plasticity that allows the brain to mold to a best fit with the individual's environment. The loss of unused connections enhances the computational capacity and speed of information processing of regional circuitry.

The early morphological studies characterizing these changes indicated that different parts of the brain pruned on different schedules. The initial study measured synapses in primary visual cortex in the occipital lobe and compared this to the rate of elimination in the middle frontal gyrus, a critical prefrontal region implicated in executive reasoning (Huttenlocher, 1990). Visual cortex reached maturity by 7 years of age whereas middle frontal gyrus did not reach adult levels until 17 years of age. A later study found that auditory cortex matured by 12 years of age (Huttenlocher & Dabholkar, 1997). These results are frequently cited to indicate that unlike non-human primate cortex, which develops concurrently across the brain (Rakic *et al.*, 1986), the human brain develops in a hierarchical fashion with sensory areas developing before executive regions. These results have major implications for developmental theory by suggesting that the maturation of cognitive control is guided to a great degree by the late maturation of prefrontal cortex (Casey, Giedd, & Thomas, 2000; Diamond, 2002).

Although the morphological findings are not in dispute, they focused on small regions that do not represent the entire brain. Neuroimaging studies allow assessment of changes across the whole brain. Positron emission tomography (PET) measures brain metabolism, which reflects levels of brain activity. In the resting state, glucose metabolism is believed to reflect synaptic activity and age-related changes in resting state glucose metabolism are believed to indirectly reflect synaptic pruning. Specifically, PET results indicate that resting state glucose metabolism achieve mature levels in many brain regions (e.g., parietal and temporal regions), during adolescence, not simply in frontal regions (Chugani, 1998). In addition, MRI has been used to measure gray matter thickness, which is believed to be determined, in large part, by synaptic pruning. Reductions in gray matter have been found throughout the cortex in association areas, notably in frontal and temporal regions (Gogtay *et al.*, 2004; Toga, Thompson, & Sowell, 2006) as well as basal ganglia (Sowell *et al.*, 1999). Association areas are unique in connecting different regions and supporting complex integration of function. Association areas within each of the cortical lobes demonstrate continued thinning into adolescence with temporal language-related regions developing last (Gogtay *et al.*, 2004).

(Figure 2). These findings are important because they imply that the late maturation of cognitive control may not be guided by prefrontal specialization alone but by the ability to integrate information in association cortex throughout different regions of the brain.

B. MYELINATION: SPEEDED NEURONAL TRANSMISSION

Myelination is the process of insulating nerve tracts with glial cells. It significantly increases the speed of neuronal transmission (Drobyshevsky *et al.*, 2005). The increase in the speed of neuronal transmission allows for distant regions to integrate function, enhancing the efficiency of information processing and importantly supporting the integration of widely distributed circuitry needed for complex behavior (Goldman-Rakic *et al.*, 1993).

Myelination increases through adolescence (Wozniak & Lim, 2006). A classic histological study by Yakovlev and Lecours (1967) is widely cited to refer to the maturation of myelination throughout adolescence and, similarly to Huttenlocher and Dabholkar (1997), has been used as evidence for a posterior to anterior maturation of the brain. Motor and sensory areas were found to myelinate early in the first decade of life whereas associative areas in frontal, parietal, and temporal regions were found to continue to myelinate into the second decade of life. This finding has been used to indicate that frontal regions myelinate last. However, the findings indicate that frontal, parietal, and temporal areas all show similar protracted myelination. These results have been confirmed and expanded to provide evidence for protracted development of hippocampal structures as well (Benes, 1989). Similar to synaptic pruning, an implication of hierarchical maturation of the brain is that development is guided by the emergence of prefrontally guided executive function. However, evidence for protracted myelination throughout cortex supports the view that development may be guided by the establishment of mature connectivity that supports the integration of function of widely distributed circuitries throughout the brain known to support executive function (Goldman-Rakic, 1988). Given that the changes in white matter are a gradual enhancement of established connections, these results also support the notion that the nature of the protracted progressions through adolescence is a refinement of executive control processes that are in place early in development.

Although neuroimaging techniques do not provide the same high level of spatial resolution as morphological studies, they do allow the whole brain to be assessed *in vivo* providing information regarding changes throughout the extended circuitry. T1-weighted magnetic resonance images, which allow the measurement of white matter volume, indicate its continued growth into the second decade of life throughout the brain, especially frontotemporal regions that underlie language processes (Paus *et al.*, 1999; Pfefferbaum *et al.*, 1994). In addition, Diffusion Tensor Imaging (DTI) has been used as an indirect measure of developmental changes in myelination (Klingberg *et al.*, 1999; Mukherjee & McKinstry, 2006). DTI is a non-invasive magnetic resonance imaging method that measures the coherence of water diffusion in the brain parenchyma. Water diffuses in an anisotropic manner. That is, it does not have a preferred direction of movement. However, within the boundaries of white matter tracts, water diffuses in a predominantly preferred direction allowing the definition of white matter. Greater coherence of water diffusion reflects better integrity of white matter of which myelination has been found to be a major contributor (Moseley *et al.*, 1990; Song *et al.*, 2003).

Fractional anisotropy is often used as a measure of the index of directionally dependent diffusion reflecting white matter integrity. Fractional anisotropy values increase throughout childhood and adolescence, then stabilize in the second or third decade of life, paralleling known increases in myelination (Ben Bashat *et al.*, 2005; Li & Noseworthy, 2002). Studies have found age-related increases in fractional anisotropy across cortex in the major groups of tracts that provide functional integration supporting fine motor control, language processing, and executive control, such as the internal capsule (connects cortical and subcortical regions), corticospinal tract (connects cortex and spinal cord), arcuate fasciculus (connects temporal,

parietal, and frontal regions), and corpus callosum (connects left and right hemispheres) (Ashtari *et al.*, 2007; Schmithorst *et al.*, 2002). Fractional anisotropy values have been found to be correlated with cognitive performance. Across different cortical regions, values of fractional anisotropy are associated with diverse measures of cognitive performance, including working memory, reaction time, reading, and IQ. For example, increases in fractional anisotropy in fronto-parietal regions have been found to correlate with cognitive performance especially in visuo-spatial tasks (Liston *et al.*, 2006; Nagy, Westerberg, & Klingberg, 2004).

This pattern of enhanced connectivity across cortical regions is supported by findings from studies of electroencephalography (EEG), which measures the brain's electrical activity. The correlations of resting state brain electrical activity across different brain regions provides a measure of the number and strength of brain connections (Otnes & Enochson, 1972). EEG studies indicate enhanced connectivity with development across neocortical regions throughout adolescence, primarily between frontal and other cortical areas (Thatcher, Walker, & Giudice, 1987). These results underscore the importance of functional integration throughout the brain as a significant aspect of later stages of development as adulthood is reached.

Taken together, synaptic pruning and myelination indicate that adolescence is marked by refinements across the brain that support integration of information and thereby foster higher-order cognitive processes (Goldman-Rakic, 1988). Although the establishment of widely distributed processing is nearing adult levels in adolescence, continued increases in myelination through this period indicate persistent limitations in connectivity. The circuitry available in adolescence thus would allow for approximations to adult control of behavior but with remaining immaturities limiting both efficient higher computations afforded by synaptic pruning and the establishment of widely distributed circuitry. These enhancements in regional circuitry and connectivity support a more effective manner in which executive cortical systems can affect basic subcortical response systems that support mature executive control of behavior.

III. What Executive Processes Improve during Adolescence?

In parallel with maturation of brain mechanisms, *behavior* is becoming more controlled and voluntary during adolescence. Executive function is used to define the processes that allow for cognitive or voluntary control of behavior including response planning and preparation, response inhibition, and working memory that support cognitive flexibility, abstract thought, and rule-guided behavior. Executive function is apparent early in development but continues to improve through adolescence. Evidence for early executive function comes from 7- to 12-month-olds who are able to perform the A not B task, which requires the use of working memory and inhibitory control (Diamond & Goldman-Rakic, 1989). Continued improvements through childhood in executive function are reflected in performance on neuropsychological tests that measure processes associated with prefrontal cortex (Davies & Rose, 1999; Levin *et al.*, 1991). These results indicate that prefrontally supported executive functions are present early in development but have a protracted development through childhood as these processes become better defined. Importantly, it highlights that the phase of development from childhood through adolescence is characterized by refinement of existing processes and not the emergence of new ones.

Thus, understanding development has to go beyond the integration of prefrontal circuitry. To understand the more complex underpinning of the brain and development association it is imperative that we investigate the basic components of executive function. Voluntary planned behavior requires the ability to retain online the goal of the response (using working memory), to plan and prepare the response, and the ability to filter out task irrelevant responses (response inhibition). These processes take place in the context of an information processing stream in which stimuli and task demands are initially perceived then processed and then an appropriate

response is generated. In this section, I discuss what aspects of executive function improve during childhood and adolescence.

A. WHAT IMPROVES IN THE ABILITY TO VOLUNTARILY INHIBIT A RESPONSE?

As mentioned earlier, response inhibition, or the ability to suppress task-irrelevant responses for task-appropriate responses, is central to voluntary control of behavior (Davidson *et al.*, 2006; Fuster, 1989; Miller & Cohen, 2001). Most response inhibition tasks include competing responses including some that may be extremely prepotent, such as reflexive responses to external stimuli (e.g., antisaccade task, see further) or learned automatic responses (e.g., go-no-go task, see further), yet are task inappropriate. The ability to voluntarily inhibit responses provides flexibility to choose actions and for behavior to be guided by a task goal. Voluntary response inhibition is available early in infancy as demonstrated by studies using different paradigms wherein infants must suppress attention to a distractor stimulus to produce the most task appropriate response (Amso & Johnson, 2005; Bell & Fox, 1992; Diamond & Goldman-Rakic, 1989). Moreover, there is evidence that these early processes are supported by frontal systems (Bell & Fox, 1992). Studies of inhibitory performance through childhood indicate that what improves is the *rate* of correct inhibitory responses, not the ability to generate a correct inhibitory response (Bedard *et al.*, 2002; Luna *et al.*, 2004; Ridderinkhof, Band, & Logan, 1999; Van den Wildenberg & van der Molen, 2004; Williams *et al.*, 1999; Wise, Sutton, & Gibbons, 1975). These results suggest that the neural components that support the basic ability to inhibit a response as an isolated event are available early in development.

Studies have measured response inhibition by using tasks that require cessation of a reflexive response or suppression of interference from established responses that are incompatible with the goal of the task. Many such tasks have been used to measure developmental improvements in response inhibition. I expand on those that have been used most frequently, such as the go-no-go, flanker, stop signal, antisaccade, and Stroop tasks. In the go-no-go task subjects are presented with two types of stimuli, one that requires that participants press a response key, and one that requires that they refrain from responding. The “go” response is established by presenting a higher rate of response stimuli therefore requiring response inhibition for the infrequent “stop” stimuli. The typical flanker task presents a central arrowhead that is surrounded by arrowheads that are either in the same direction (compatible) or in the opposite direction (incompatible). Response inhibition is required to suppress distraction in incompatible trials which is reflected by a higher error rate and longer reaction times. In the stop-signal task, subjects are presented with a go signal which indicates that a response must be made (e.g., button press), however, some trials show a “stop” signal at different times after the “go” signal has been presented. This task requires inhibition of an already initiated response. Participants performing the antisaccade task are instructed to avoid looking at a visual stimulus that appears at an unpredictable location and time and instead look to an unpredictable location. Response inhibition is required to inhibit the reflexive response to look toward a light. Finally, the Stroop task is a prototypical neuropsychological task of response inhibition in which subjects must verbally say the color of the font of a color word that is sometimes in incompatible ink (e.g., “red” in green font). Participants must inhibit the tendency to say the word and instead say the font color. These tasks have been viewed as assessing different aspects of inhibitory control with the go-no-go, antisaccade, and stop signal task viewed as requiring active inhibition of motor commands and the Stroop and flanker tasks as tapping into focused attention (Kok, 1999).

On these tasks, younger children typically inhibit inappropriate responses on an above-chance number of trials. However the number of correct inhibitory responses throughout a task increases significantly with maturity. Therefore, one of the processes that improve throughout childhood and adolescence is the ability to inhibit *consistently* throughout a block of several

trials. The process that supports the *flexible and consistent use* of the ability to inhibit responses is what becomes better established in adulthood. Inhibitory control requires top-down modulation of response-related processes guided by a goal, while suppressing reactive responses. Immaturities in synaptic pruning and especially myelination could hamper the top-down modulation of behavior, that is, the ability for executive cortical regions to have an effect on subcortical sensory and motor regions by limitations in speed and efficiency in which information is processed. This is especially true of long connections and distributed circuitries that integrate function of frontal areas with parietal regions and subcortical regions that are known to underlie executive functions (Goldman-Rakic, 1988).

The trajectory of late development of inhibitory control is shown in our studies of 245 8- to 30-year-old healthy individuals who performed an antisaccade task (Luna *et al.*, 2004). In this task, participants were asked to refrain from looking at a visual cue that appeared in an unpredictable location in the periphery and instead to look in the opposite location. Even the youngest children were able to perform some correct antisaccades, indicating that the ability to inhibit a single response is available early in development. However, performance improved dramatically with age and reached adult levels of performance by 14–15 years of age (Figure 3). These results have been consistent across a range of studies (e.g., Fukushima, Hatta, & Fukushima, 2000; Klein & Foerster, 2001).

One aspect of behavior that may significantly contribute to consistent performance is the process of establishing a *response state*. In addition to the actual voluntary suppression of a reactive response, other sensory and cognitive demands must be orchestrated for inhibition to occur consistently. The attention literature has referred to this process as the establishment of a task-related state that allows for the executive organization and control of the processes guiding cognitive events (Logan & Gordon, 2001). The ability to retain a response state has been found to have a unique brain circuitry that is distinct from the circuitry supporting other aspects of cognitive processes (Dosenbach *et al.*, 2006). Because developmental improvements are evident in the number of correct inhibitory responses and not the ability to make a single inhibitory response, there may be developmental limitations in the ability to establish an inhibitory response state. Therefore the implications are that what characterizes development through adolescence is not the emergence of a new cognitive ability but the ability to efficiently use this tool in a flexible and consistent fashion by effectively establishing a response state. Furthermore, the implications would also suggest that the circuitry that supports response state, which is unique to this process (Dosenbach *et al.*, 2006), would also be immature. As discussed later, neuroimaging findings indicate that the circuitry supporting response state shows a protracted development through adolescence (Fair *et al.*, 2007).

B. WHAT IMPROVES IN THE ABILITY TO USE WORKING MEMORY?

To enact a voluntary response, there has to be a representation of the goal that is kept on-line. This process is referred to as working memory (Baddeley, 1986). Working memory, such as response inhibition, is central to executive function (Fuster, 1997; Miller & Cohen, 2001) and given its interaction with response inhibition is often considered to be part of the same process (Miller & Cohen, 2001). In other words, response inhibition and working memory may always operate in tandem. Yet studies have found evidence for independent developmental trajectories for working memory and response inhibition (Asato, Sweeney, & Luna, 2006; Luciana *et al.*, 2005; Miyake *et al.*, 2000).

Working memory, similar to inhibitory control, also shows a prolonged development through adolescence (Demetriou *et al.*, 2002; Luna *et al.*, 2004). Working memory tasks typically present a stimulus or instructions that have to be remembered over a delay period, which sometimes can have an interfering stimulus or manipulation requirement. For example, in the oculomotor-delayed response task, subjects must remember the location of a briefly presented

stimulus. After the to-be-remembered stimulus is presented there is a delay period during which the information (e.g., location, and sequence of letters) is maintained in working memory. In some working memory tasks, participants are asked to engage in a distraction during the delay period (e.g., counting numbers) which makes the task more difficult. After the delay period subjects have to make a response that is guided by the information that was kept on-line in working memory. The accuracy of that response with respect to the information initially presented is used to characterize the integrity of working memory. There is a consistent finding that although children can guide their behavior by instruction held in working memory, their responses are less accurate than those of adults. For example, children can identify the overall location of a previously presented cue (Luciana *et al.*, 2005; van Leijenhorst, Crone, & van der Molen, 2007) but are inferior to adults at the *precision* of this response (Luna *et al.*, 2004; Zald & Iacono, 1998). Measuring the precision of a working memory response allows detection of subtle differences in working memory performance that emerge in late childhood and adolescence. That is, processes that allow for the maintenance of general information regarding a working memory representation are available early in development. Later into adolescence general working memory processes are fine-tuned, which supports more detailed representations to be maintained on-line.

Typical tasks, such as those using verbal stimuli to probe working memory mechanisms, are not well-suited for characterizing of the level of fine tuning of working memory mechanism that occurs in adolescence. Language processes themselves continue to develop into adulthood, limiting the ability to assess age-related changes particular to working memory. Spatial working memory tasks, therefore, are better suited for developmental studies given that basic visual processes are available early in development and they allow for subtle changes in accuracy to be assessed. We have used the memory-guided saccade task, also known as the oculomotor-delayed response task, to characterize developmental improvements in working memory. Single-cell studies using this task have shown that the neural circuitry underlying working memory is recruited during this task, supporting its applicability to study the brain basis of working memory (Funahashi, Inoue, & Kubota, 1997; Hikosaka & Wurtz, 1983). Participants fixate a central target while a cue is briefly presented at an unpredictable location in the periphery and participants must remember the location during a delay period with no distraction or manipulation involved. The response to the memory-guided saccade task usually involves two or more saccadic eye movements. The first is a large saccade that approximates the target location and is driven both by processes supporting voluntary responses (directing the eyes to move with no visual guidance) and the working memory representation of the location of the previous target. Afterwards there are smaller corrective eye movements, which are more predominantly driven by the working memory representation and performance monitoring processes. We found that the accuracy of the initial saccade became adult-like by approximately 15 years of age (Figure 4). However, the last corrective saccade that provided precision continued to show improvements into the early twenties (Luna *et al.*, 2004).

These results suggest that although the ability to initiate a voluntary response guided by working memory reaches maturity in adolescence, corrective responses that afford precision continue to improve after adolescence. These results were present across different delay periods, suggesting that maintenance processes alone do not account for developmental differences but that also encoding may have developmental improvements. That is, the spatial resolution of the ability to encode a representation in working memory may be more refined in the adult system. Thus, although working memory is evident in infancy (Diamond & Goldman-Rakic, 1989), the ability to use working memory precisely and flexibly develops through adolescence. This is a recurring theme in cognitive maturation: Basic abilities are available early in life, while sophisticated use of cognitive abilities improves into adulthood. These results parallel those from response inhibition and from the timeline of brain maturation showing organization and specialization of central processes that are present early in life.

The protracted development of response inhibition and working memory underlie the late appearance into adolescence of adult-level performance in neuropsychological tasks (for reviews see: Diamond, 2002; Welsh, 2002). Neuropsychological tasks involve an array of processes including working memory and response inhibition that underlie planning and rule-guided behavior. The Wisconsin Card Sort, a widely used neuropsychological test, requires that participants match cards based on their own perception of the dimension at play (e.g., “red” figures) and are given feedback if they are correct. Then unexpectedly the dimension on which to match the cards changes (e.g., shape) and responses based on the old criterion are incorrect. Different performance components are scored to assess set shifting. Working memory is required to keep online the previous successful rule while inhibition is needed to suppress the tendency to perseverate responses that are no longer valid. In the Tower of London, participants need to arrange stimuli in as few steps as possible to match a presented arrangement. For example, subjects are presented with three columns on which 5 disks of distinct colors are arranged. Their task is to arrange the disks to match the presented arrangement. Working memory is needed to keep on-line the arrangement of cues as well as the possible steps to match the target arrangement. Response inhibition is needed to suppress responding to the apparently easiest yet task inappropriate steps. Stroop and Contingency Naming Tasks require keeping the task instruction in working memory while suppressing the more established response. Performance on the Wisconsin Card Sort can appear mature by childhood (Chelune & Baer, 1986; Somsen, 2007) however performance on the Tower of London task continues to improve into adolescence (Asato *et al.*, 2006). Our results indicate that underlying developmental improvements in the Tower of London task are improvements in inhibitory control and working memory. Therefore, underlying improvements in neuropsychological tasks are improvements in central cognitive abilities.

There are mechanisms separate from central working memory processes that also can limit performance, including processing interference and failure to use strategies. Owing to immaturities in inhibition, children experience greater interference from distractors than adults, undermining the ability to show mature working memory performance in tasks that present competing stimuli in the delay period (Bjorklund & Harnishfeger, 1990; Dempster, 1981). Similarly, strategies such as verbal rehearsal or making associations between to-be remembered items during working memory maintenance also can enhance performance by using systems in addition to working memory, such as long-term memory, to assist in task performance. Results show that in working memory tasks in which it is possible to use strategies, such as verbal rehearsal of the to-be-remembered stimuli, adults take advantage of this more so than adolescents (Cowan, Sauls, & Morey, 2006; van Leijenhorst *et al.*, 2007). These results highlight that developmental differences in working memory tasks may be related to strategy use rather than or in addition to age-related changes in working memory *per se*.

Taken together the literature indicates the presence of working memory abilities early in development that support executive function. What continues to improve into adolescence is the ability to perform complex tasks, be more precise, and control distraction, resulting in more efficient and adaptable working memory. Abstract thought and decision making benefit from an efficient and adaptable working memory system and immaturities in this system can therefore limit decision making.

C. WHAT DRIVES DEVELOPMENTAL INCREASES IN SPEED OF PROCESSING?

The speed with which stimuli and instructions are processed to produce a response indicates efficiency of information processing and is considered a mental capacity (Kail & Salthouse, 1994). Processing speed is believed to reflect the integrity of the brain processes underlying functional integration such as myelination and synaptic pruning (described earlier), which support improvements in cognitive processes such as response inhibition and working memory

(Kail, 1993; Luna *et al.*, 2004). Across reflexive and cognitive tasks, processing speed has been found to increase exponentially throughout childhood and adolescence (Hale, 1990; Kail, 1993). Developmental decreases in reaction time have been found using simple reaction time tasks where the speed to look at a visual target is assessed (Fischer, Biscaldi, & Gezeck, 1997; Fukushima *et al.*, 2000) as well as those that have cognitive demands such as inhibitory control (Luna *et al.*, 2004; Munoz *et al.*, 1998) (Figure 5). Developmental improvements in speed of processing have also been found in manual reaction time (Elliott, 1970) and visual matching tasks (Fry & Hale, 1996). Regardless of the actual latency to initiate responses, which are extended in tasks with cognitive demands, there is a similar developmental profile with maturity being reached in adolescence. The fact that improvements in reaction time to an automatic response are similar to those with a cognitive load suggests that the development of speed of processing is independent from cognitive processing and in fact may assist the development of executive processes.

IV. What have Developmental Neuroimaging Studies Revealed about Maturation of the Cognitive System?

The co-occurrence in adolescence of changes in brain processes such as synaptic pruning and myelination that support cognition and speed of processing as well as changes in cognition and behavior suggest an important link between brain and behavior through development. However, investigating the association between changes in brain structure and behavior does not provide information regarding the maturity of dynamic brain function. That is, although pruning and myelination throughout cortical and subcortical regions are still occurring through adolescence, we do not know how this affects the functioning brain systems and which aspects of the system are associated with behavioral improvements.

One way to investigate functional circuits during cognitive function across development is with neuroimaging methods. fMRI is a non-invasive technique that provides an indirect measure of neuronal activity by measuring regional changes in blood oxygen levels that result from increased metabolism in areas of neuronal activity. Since the late 1990s, fMRI has been used to study cognitive development and the results have had a great impact in how we understand the brain behavior relations during development.

A. WHAT CHANGES IN BRAIN FUNCTION ACCOUNT FOR DEVELOPMENTAL CHANGES IN INHIBITORY CONTROL?

Response inhibition is supported by a widely distributed circuitry of which prefrontal areas are undoubtedly central. Different regions of prefrontal cortex have been implicated in unique aspects of inhibitory control such as inferior frontal gyrus supporting interference resolution during response *execution* versus dorsolateral prefrontal cortex and anterior cingulate cortex supporting response *selection* (Nee, Wager, & Jonides, 2007). Prefrontal cortex is highly interconnected within itself and with other cortical and subcortical regions of the brain, permitting quick executive control by suppressing internal and external inputs and disrupting any ongoing behavior. Its contributions to inhibition are in the preparatory activity in anticipation of an inhibitory response (Nyffeler *et al.*, 2007) and in organizing the temporal processes of the task (Fuster, 1997).

The literature on the development of executive function has focused primarily on the contributions of age-related changes in regional processes of prefrontal cortex. However, given evidence that the beginning of complex executive behavior is present early in life and that age-related improvement in inhibition take the form of an increase in the rate of successful executive inhibitions, structural changes in prefrontal cortex alone cannot account for the bulk of developmental changes. Early in development prefrontal cortex has the capacity to perform

complex computations supporting executive function as evidenced by the ability to perform executive responses. Improvements through childhood in the ability to flexibly use executive function, which is supported by a widely distributed circuitry (Dosenbach *et al.*, 2006), suggest that a significant contributor to the development of executive function is the integration of brain function, which in turn is supported by continued myelination known to occur during this period. Continued myelination in turn enhances the ability of prefrontal cortex to effectively influence on the rest of the brain (Chugani, Phelps, & Mazzotta, 1987; Olesen *et al.*, 2003; Thatcher, 1991). Furthermore, other cortical association areas also undergo protracted refinements that may allow them to perform complex computations that can collaborate with prefrontal cortex in providing inhibitory control.

For example, inhibition of reflexive visually guided eye movements in the antisaccade task is supported by a circuitry including cortical and subcortical regions wherein preparatory activity is crucial to successful inhibitory control. In this task, participants are instructed to avoid looking at a peripheral visual target, which appears at an unpredictable time and location, and to look instead toward the mirror location. Single-cell studies in non-human primates have found that preparatory activity in eye movement regions predicts successful inhibitory responses (Everling & Munoz, 2000). During the preparation to make an inhibitory eye movement, activity in subcortical (superior colliculus) and cortical systems (frontal eye fields and intraparietal sulcus) that generate eye movements is dampened while activity in the regions supporting fixation (the suppression of eye movements) is increased. Dorsolateral prefrontal cortex and medial prefrontal cortex also show preparatory activity. Unlike superior colliculus, frontal eye field, and intraparietal sulcus, which also show activity during saccade response, prefrontal cortex is only recruited in the preparatory phase, indicating that it is involved in response planning only (Brown, Vilis, & Everling, 2007). The instruction to inhibit a response is processed in prefrontal cortex, which then influences oculomotor cortical and subcortical regions, with the goal being to influence the superior colliculus in a timely fashion to stop the reflexive saccadic response. These results indicate that inhibiting an impending saccade relies on the concerted activity of prefrontal, premotor, and subcortical regions. The ability to make correct antisaccades in childhood indicates that this circuitry is available during this period. However, as described previously, the *proportion* of correct inhibitory responses increases with age, indicating that this circuitry is engaged in a more reliable and more consistent fashion with age.

Most developmental fMRI studies of response inhibition focus exclusively on results in specific regions of prefrontal cortex as opposed to larger neural systems. Across studies there have been findings indicating that aspects of the inferior frontal gyrus (Brodmann's areas 45 and 46 or BA 45/46) and premotor regions (BA46) increase activation with age (Bunge *et al.*, 2002; Rubia *et al.*, 2000). These regions have been found across inhibitory tasks such as the go-no-go (Rubia *et al.*, 2006; Tamm, Menon, & Reiss, 2002), flankers (Bunge *et al.*, 2002), stop tasks (Rubia *et al.*, 2007), Stroop (Adelman *et al.*, 2002; Marsh *et al.*, 2006), and antisaccade tasks (Luna *et al.*, 2001), with equivalent performance or with behavior that changes with age. Most studies have interpreted this finding as reflecting the late structural changes in prefrontal cortex that may allow this region to better participate in inhibitory control and therefore show more activity. However these same studies as well as others also have found evidence for age-related *decreases* in other prefrontal regions including inferior and medial frontal gyri. A go-no-go study with 8- to 20-year-olds showed both increased activation in the medial frontal gyrus as well as *decreases* in the inferior frontal gyrus (Tamm *et al.*, 2002). Age-related increases in the participation of the medial frontal gyrus was interpreted as reflecting actual improvements in the brain for supporting inhibitory processes, whereas age-related decreases in inferior frontal gyrus participation were thought to reflect developmental differences in the effort required to exert inhibitory control. The interpretation of developmental increases and

decreases in brain function is an area of the literature that needs clarification and I discuss this in detail later.

Some of the developmental results can be interpreted in the context of the functions that certain prefrontal regions are known to support. For example, increased recruitment of inferior frontal gyrus, which often includes BA 45 (Broca's area) and premotor regions (BA 6), may indicate both increases in the capability of inhibiting a response as well as the use of strategies for enhancing a basic inhibitory function. The recruitment of BA 45, which is an area central to speech production, could represent a verbal strategy that is being implemented by adults but not by younger participants. Increases in activation in premotor regions, which as described previously are known to support preparatory activity in inhibitory control, may indicate enhanced ability to plan for stopping a response. Our work using the antisaccade task has indicated that the frontal eye fields (BA 6) show enhanced activity when adults perform better than younger participants (Luna *et al.*, 2001).

The ability to detect errors and monitor performance is crucial to inhibitory control and has been found to be supported by a well-delineated neural circuitry of which the anterior cingulate cortex is central (Braver *et al.*, 2001; Carter *et al.*, 1998). Initial studies found that the integration of the anterior cingulate cortex as well as prefrontal systems improves with development, perhaps enhancing the ability to influence overall performance influenced by error commission. Rubia *et al.* (2007) found that when equating performance across childhood to adulthood in an inhibitory task by adapting the task by skill level, adults still demonstrated increased recruitment of anterior cingulate and prefrontal cortex, suggesting a more mature anterior cingulate cortex structure that can participate in performance monitoring. The anterior cingulate cortex has connections with prefrontal cortex as well as striatal and brain stem regions (Devinsky, Morrell, & Vogt, 1995) making it particularly suitable to detect errors and influence behavior. An adult study examining the evolution of anterior cingulate cortex participation in error commission during the antisaccade task indicated different stages of error processing (Polli *et al.*, 2005). To make a correct inhibitory response it is necessary to suppress activity in "default-mode" regions, which supports the state of brain systems when they are not engaged in an active task, that persists during rest and undermines focused goal directed responses and recruit a rostral part of the anterior cingulate cortex (Simpson, *et al.*, 2001). After an error has been committed, regions that integrate the failure of the response to benefit future performance are recruited, including a dorsal aspect of the anterior cingulate cortex. Results indicate that inhibitory errors are characterized by failure to deactivate the rostral anterior cingulate cortex, which was evident immediately after an error and by the later recruitment of dorsal anterior cingulate cortex to influence performance. It is important to determine whether performance monitoring shows protracted development and hence accounts for developmental improvements in performance. Our own developmental fMRI study demonstrated increased activity in anterior cingulate during errors of inhibition that was specific to different stages of error processing. The ventral anterior cingulate cortex had equivalent activation in initial stages of error processing across age groups. However, during the second stage of error processing only adults recruited the dorsal anterior cingulate cortex reflecting immaturities even in adolescence (Velanova, Wheeler, & Luna, 2008) (Figure 6). These results imply that whereas the detection of errors may be available early in development, later stages that may influence subsequent behavior may have a protracted development.

When taking into consideration circuitries that include frontal regions, fMRI studies have found evidence indicating that age-related integration of fronto-striato-thalamic and fronto-cerebellar neural pathways support enhanced inhibitory control and correlate with better performance in a range of inhibitory tasks (Rubia *et al.*, 2006; Rubia *et al.*, 2007). Our own work provides evidence for a more circuit based maturation (Luna *et al.*, 2001). Using the antisaccade task we found that activity in dorsolateral prefrontal cortex showed increased activation from

childhood to adolescence whereas its participation decreased from adolescence to adulthood. Instead, adults recruited a much more distributed circuitry including premotor and parietal eye fields as well cerebellum (Figure 7). Age-related increases in the participation of parietal and cerebellar regions also have been found in other developmental studies of inhibition (Bunge *et al.*, 2002; Rubia *et al.*, 2006) as well as recruitment of frontostriatal and frontocerebellar pathways (Andersen *et al.*, 1990; Rubia *et al.*, 2007). These results indicate that developmental improvements are supported by the integration of a distributed brain system and not by the enhanced participation of prefrontal cortex alone.

As discussed previously, the ability to establish a response set may be a crucial element in maturation of inhibitory control and may have an independent developmental trajectory. A distinct circuitry including dorsal anterior cingulate cortex, medial prefrontal cortex, and bilateral anterior insula has been found to be recruited across different tasks (e.g., verb generation, matching, and motor timing) when maintaining a task-set compared to periods of rest (Dosenbach *et al.*, 2006). Our initial results reveal important developmental improvements in the ability to retain an inhibitory response state that are separate from those that support the ability to make a single correct inhibitory response. The circuitry supporting the ability to make a single correct response is present by childhood but shows decreased participation with age. The decreases in activity may reflect the reduced effort for older participants to perform a correct inhibitory response relative to younger children. Developmental changes in the ability to retain an inhibitory *state*, however, indicate *increases* in activity in prefrontal and posterior regions suggesting that the circuitry is more successfully recruited with age. These results support the proposal that inhibitory processes are available by childhood whereas the ability to flexibly and consistently execute control continues to improve through adolescence and may be primary in age related improvements in executive function.

B. WHAT CHANGES IN BRAIN FUNCTION ACCOUNT FOR DEVELOPMENTAL CHANGES IN WORKING MEMORY?

As is the case for response inhibition, there is a widely distributed circuitry known to underlie working memory in the adult, including premotor, parietal, temporal, and subcortical regions (Passingham & Sakai, 2004; Sweeney *et al.*, 1995). However, the focus of most research, including developmental fMRI studies, has largely been on the contributions of prefrontal systems. Prefrontal regions undoubtedly play a role in central aspects of working memory but many studies indicate that other regions, mainly in parietal areas, also play an important role. Prefrontal areas apparently support executive aspects of working memory such as the manipulation of information, whereas parietal regions appear to support the actual storage (ability to maintain information on line) of information in working memory (D'Esposito *et al.*, 1999; Postle *et al.*, 2006). Our studies on the mature system have also indicated that maintenance is supported by parietal regions (Geier, Garver, & Luna, 2007).

fMRI studies consistently indicate that prefrontal systems are engaged in working memory processes as early as 8 years of age but the magnitude of engagement varies with age. Studies that use the n-back task, where responses depend on keeping on-line the arrangement of previous cues, show equivalent prefrontal recruitment in children and adults (Nelson *et al.*, 2000; Thomas *et al.*, 1999). However, most studies that use working memory tasks that examine task manipulation and the accuracy of responses show age-related increases in the recruitment of prefrontal cortex (Ciesielski *et al.*, 2006). These increases have been found to be due to immaturities in the ability to manipulate information in working memory (Crone *et al.*, 2006; Olesen *et al.*, 2007), to generate an accurate response (Klingberg, Forssberg, & Westerberg, 2002; Scherf, Sweeney, & Luna, 2006), and to suppress distractors (Olesen *et al.*, 2007).

We performed the memory-guided task in children, adolescents, and adults in an fMRI study to investigate circuit-level changes with development (Scherf *et al.*, 2006). In the memory-guided saccade task subjects must remember the location of a peripheral target that is presented briefly in an unexpected location in the periphery. After a varying delay period (typically 1 to 10 sec), during which the location of the target is sustained in working memory, subjects must move their eyes in the absence of a visual target to the location they remembered the target to have been. The accuracy of the memory-guided eye movement is used to assess the fidelity of the working memory response. Dorsolateral prefrontal cortex was found to be recruited across age groups. However, similar to our results with response inhibition, the magnitude of right dorsolateral prefrontal cortex participation followed an inverted “U” shape, peaking in adolescence. These results may be due to the fact that children do not perform at adolescent or adult levels, which may be due to immaturities in executive processes supported by prefrontal systems. In contrast, adolescents perform similar to older participants and use prefrontal executive systems, but it may be more difficult for them to perform at adult levels, which results in increased recruitment of prefrontal cortex.

The implications for adolescent behavior are similar to those of inhibitory control: Although adolescents may demonstrate executive function that is similar to that of adults, their functional circuitry resembles that of adults performing a more difficult task. Additionally, as shown in Figure 8, activity across brain regions becomes more evenly distributed with age, suggesting that as we reach adulthood there is more distributed function across the brain which may decrease the need to recruit prefrontal systems. The hypothesis that integration across the brain is central to cognitive development (Edin *et al.*, 2007; Olesen *et al.*, 2003) is supported by DTI studies (described earlier) showing that age related improvements in working memory are related to increased functional connectivity within cortical regions and in corticostriatal pathways.

V. Limitations in Developmental Studies of Brain Function

A number of factors underlying differences across studies need to be taken into consideration when interpreting the results reported here. The most controversial in the literature has been the issue of how to interpret age-related differences in brain function when performance also differs by age. On the one hand, differences in performance could simply reflect that unique strategies are adopted and may not capture developmental change in the brain processes themselves. On the other hand, equating performance also limits what can be characterized to purely differences in effort. Higher cognitive loads or increased complexity of tasks require overall more “effort” in adults. Age-related changes in effort may be due to the use of unique strategies but may also reflect decreases in the recruitment of basic brain processes engaged in adulthood. Moreover, equating performance can misrepresent developmental differences such as in comparing children who are outliers in that they perform at adult levels with adults who are also outliers in performing at low levels. Finally, only considering tasks in which performance is similar across ages limits the ability to assess the mechanisms that underlie the inability of children and adolescents to perform at adult levels.

There is no clear solution to this problem except for integrating different interpretations in the results. When groups differ in performance, there is the possibility of defining what the circuitry looks like when it is immature. In this manner, the regions that fail to be recruited and the alternative circuitry that has been used can provide insight into the immaturities of specific brain systems. However, as stated earlier, the developmental differences may be due to the use of unique strategies that recruit specific brain systems and not to differences in the integrity of brain systems themselves. When learning is used as a model for development, age related differences in the use of strategies and their related brain circuitry is supported. Studies with adults in which simple learning tasks are used indicate that the circuitry that is initially recruited

when a task is novel is qualitatively different from the circuitry that is recruited once the behavior has been learned. This may reflect a shift in the strategies that are used and would not indicate immaturities in the ability to use the learned systems (Ungerleider, Doyon, & Karni, 2002).

When performance is equivalent, the developmental differences become somewhat obscured because now the task has become simpler and the differences can only be attributed to differences in the degree to which executive regions need to be recruited. A typical finding when performance is equated is that younger children rely more on executive regions needed to perform the task, which is similar to results in adults when cognitive load is increased. However, similar performance could also be achieved by the use of different strategies.

Even so, the question remains regarding why children do not use adult strategies. Strategy use may be the result of learned responses with similar demands and be independent from brain maturation. However, immaturities in brain regions and connectivity could also undermine the ability to recruit strategies that are supported by complex circuitry. Parametric studies where different levels of cognitive complexity can be assessed would assist in the ability to see if similar strategies can be used for easier tasks. Lack of age-related differences at simple versus complex levels of cognition would indicate that basic brain systems are available but need further specialization or that processes specific to cognitive complexity are not being accessed. Parametric manipulations also allow for identifying at what level of cognitive complexity there is a failure to instate the proper circuitry. Similarly, longitudinal designs could be used to assess the availability of different circuitries at the individual level, as well as changes in brain structure using DTI or measures of gray matter thinning. Another approach is to use tasks that have minimal opportunity for strategy formation. Oculomotor tasks that tap into cognitive systems are not as amenable to strategies given that the responses are quick and to unpredictable locations. The go-no-go task and stop tasks are similar in this respect as there is little preparation to stop an automatic response and verbal cues are not used. These tasks which appear simple compared to typical neuropsychological tasks that involve many cognitive processes, can inform us regarding the status of basic aspects of individual systems. There are processes that are common and therefore basic to executive function that these simpler tasks can help us model. For example, inhibitory control always requires top-down modulation from frontal executive systems to processes related to motor responses. Characterizing the status of inhibitory control using these tasks that focus on specific aspects of executive function can inform us regarding their availability at different stages of development. Evidence of limitations in performance or in the recruitment of brain systems supporting these “basic” systems would indicate that central processes are still immature undermining the ability to perform more complicated tasks.

There also are methodological issues that affect how we interpret developmental neuroimaging results. fMRI studies can be performed using a “blocked” design, where brain activity represents the collective activity of a block of similar trials, or an “event-related” design where brain activity is assessed at the single trial level. In block designs, periods (typically lasting 10–40 s) of experimental trials with cognitive demands (e.g., Stroop) are compared to periods of a baseline task with minimal cognitive demands (e.g., fixation). The brain regions that show significant increases in activity in the experimental versus baseline blocks are deemed to support processes underlying the cognitive demands of the experimental period. Because of the engagement of continuous performance of a specific behavior, the block design offers optimal signal to identify the brain regions participating in a task. In this design, however, error and correct trials are grouped and processes supporting the ability to retain a task state are also included therefore measuring more than the processes of interest. Event-related designs provide an alternative by allowing the characterization of brain function that underlies a single trial. This approach generates lower signal than the block design and necessitates more trials. The

benefit of event related designs is that it allows for only correct trials to be assessed therefore comparing similar performance since the same behavior is being generated. Additionally, if sufficient incorrect trials are performed, the brain circuitry underlying error commission also can be investigated. An ideal approach would be to use a mixed block event related fMRI design that permits the assessment of correct and incorrect trials as well as the block-level processes that can reflect the status of response state, which as indicated earlier, may be key in understanding the basis of developmental improvements in cognitive control.

Another factor that can affect the definition of changing circuitry is the level of analyses. The gross morphology of the brain is stable from childhood on, but the continued thinning of gray matter into adolescence could result in some age-related anatomical differences. Voxel-wise analyses, where comparisons are made on the 1–5 mm area that the data was acquired, could be affected by subtle anatomical differences. Fitting the variable anatomy of a group of subjects to a common brain atlas is crucial in ensuring that the same regions are being compared. However, the match may not always be to 1–5 mm resolution and the identical voxels may not always correspond across subjects. Region of interest (ROI) based analyses can overcome this limitation as a large region of voxels are selected to perform analyses (e.g., Brodmann's Area 6 in the precentral sulcus, which defines the Frontal Eye Field) and these can be more consistently matched across individuals and groups of individuals. How regions of interest are defined is also a contributing factor. Hypothesis-driven selection of regions is highly regarded in the field because it is theory driven and protects from spurious findings. However, mapping developmental changes in brain function is still at the early stage of discovery where exploratory analyses are essential. Limiting studies to only investigating the regions that have already been implicated in the literature, such as prefrontal cortex, assumes that this is where developmental change will occur and limits the ability to test other possibilities.

There are well-delineated approaches that can be used that allow exploratory analyses to avoid the pitfalls of fishing expeditions. One approach is to select regions of interest based on the circuitry generated from analyses of adults. The question then becomes the extent to which younger groups use the same regions, when they do, whether they are used in the same magnitude and manner. Inspection of the temporal development of the fMRI signal changes within a region becomes crucial. When groups differ in activation, many qualitatively different processes might be involved and each has distinct implications for development. The most common interpretation of age-related differences in activation is that both groups recruited a region but one group activated it to a larger magnitude. If the older group showed higher activity than the younger group, this would be interpreted as indicating that although children recruit this region for the task, region-wise immaturities do not allow the level of processing needed to support performance at adult levels. That is, that due to for example, immature myelination, this region is not being integrated into the circuitry to the required level. If the younger group demonstrates higher activity this would be interpreted as indicating that due to lack of specialization (diffuse to focal theory, Durston *et al.*, 2006), or larger exerted effort, the younger group had to drive the region to a higher degree. For example, lack of synaptic pruning may result in a larger extent of grey matter being recruited to activate the region. Alternatively, the task may be perceived as more difficult by younger subjects and may need a higher degree of involvement to be effective such as in executive regions of prefrontal cortex.

However, there are many other possibilities including that different groups are using the region in qualitatively different manners. For example, one group may actively engage the region while the other actively suppresses it, or one group simply does not engage that region at all. Both groups may recruit a similar region but may be using it to support different aspects of behavior such as response preparation or response execution, or for maintaining information on line. These results would indicate a more complex change in development where regions are online early but their role is still being defined.

Another approach that can be taken to examine developmental differences is to see how activity changes in comparison to adult activation. This can be of value in identifying which brain regions younger subjects are not accessing. However, this approach undermines the ability to characterize the alternate circuitry that may be being used by the younger group. That is, it is quite possible that younger subjects recruit completely different regions than the older group. For example, children may be recruiting regions in parietal cortex to compensate for immaturities in prefrontal systems but these would not be captured if older subjects did not also recruit this region. Identifying alternative circuitries would allow us to determine the circuitry that younger subjects are using to perform a task. Consequently, another approach defines regions based on a main effect of task across subject groups therefore identifying the regions that were relevant to the task at hand regardless of developmental differences. Compensatory regions only recruited by younger subjects or supplementary regions recruited by older subjects would also be evident. In this manner, the possibility that older subjects are using supplementary regions in posterior areas while showing reduced activity in prefrontal regions could suggest a mechanism by which the mature system can better distribute function. Another limitation present in many studies is the erroneous reporting of age differences in regions that were not recruited during the main task but that appear significant during age comparisons. Regions that are not statistically defined to participate in a task are part of background activity that contributes to artifact. These results should not be interpreted.

The task used for baseline comparison also is crucial. It is important that the baseline comparison task used in a study does not itself have developmental differences. Differences in the comparison task would undermine the ability to assess developmental changes in the experimental task. For example, a Stroop study found a set of regions that showed age-related differences in *deactivation* that were hard to interpret. As the authors acknowledged, this may have been due to developmental differences in how the baseline condition (congruent name and color) was processed (Marsh *et al.*, 2006). The baseline condition used in this task was to say the name of the color word that was printed in an ink color that corresponded to the letter (“red” in red ink). This baseline task was used to assess activity in the experimental task where participants had to say the name of the color word that was printed in a font color that did not correspond to the color word (“red” in green ink). There may have been differences in language processes in children that undermined the ability to assess the experimental condition.

Finally, the ages chosen to represent different developmental stages can influence outcomes. Some studies group children and adolescents into a homogenous group (Rubia *et al.*, 2000, 2006) limiting the ability to observe differences between childhood and adolescence and developmental differences in general. Given the variability in individual development, there are no steadfast ages that define a particular period. Adolescence defined through pubertal staging can vary tremendously starting as young as 10 and continuing to late teens. Several factors can help determine appropriate ages. Pubertal assessments can help *post hoc* to investigate possible stage related differences. Narrowing the age range can increase the probability of including participants within a stage (e.g., 13–17 years for adolescence as opposed to 10–19 years). Optimally, a task should be used for which behavioral performance has been established across different ages and this information can be used to guide the appropriate age ranges to test.

An alternative is to consider age as a continuous variable and analyze the data with regression-based approaches. This approach can be very useful in capturing linear trends. Although many developmental changes in behavior from childhood to adulthood are linear, studies have found that age-related changes in cognitive control and speed of processing are best represented by a log function or curvilinear approaches that can integrate the period of adolescence when adult plateau levels are reached (Kail, 2007; Luna *et al.*, 2004). However, the large samples required

for typical regression analyses can make this approach less feasible for imaging work, where relatively small samples are the norm.

VI. The Transition to Widely Distributed Circuitry

Adolescence differs qualitatively from childhood in that adolescents can appear to have mature cognitive control. Our developmental studies on both response inhibition and working memory show that adolescents typically behave at adult-like levels (Luna *et al.*, 2004; Scherf *et al.*, 2006). Adolescents recruit many of the same circuits that adults use, yet there are important differences that are telling of the adolescent period. Adolescents appear to use dorsolateral prefrontal cortex to a higher magnitude than adults while not recruiting the other regions to the same degree. In the response inhibition task, adolescents showed more activity in the dorsolateral prefrontal cortex than adults and less in frontal and parietal eye fields known to be involved in response preparation. In a working memory task, adolescents also recruited dorsolateral prefrontal cortex to a higher degree than adults but did not show the distribution of function and temporal involvement evident in the adult system. These results suggest that although the adolescent can demonstrate adult-level cognitive control, the circuitry being recruited to perform at this level may not be optimal for the flexible and consistent performance evident in adults. Limitations in the ability to have consistent performance may make adolescents vulnerable to making errors.

Prefrontal cortex is recruited early in development and undergoes refinement both in focalization of function—reflective of improved efficiency—and in increased participation, indicating optimal organization of function. In other words, by childhood prefrontal processing is available and developmental change thereafter consists of establishing reliable circuitry. Cognitive control is supported by a widely distributed circuitry that is highly functionally integrated (Goldman-Rakic, 1988). The strengthening of functional connectivity across cortex and subcortical regions with development supports access to this widely-distributed circuitry that supports cognitive control. Regional changes undoubtedly also contribute to developmental change. Decreases in gray matter in association areas through development (Gogtay *et al.*, 2004), reflective of regressive events including synaptic pruning, indicate that there are important changes occurring at the regional level. That is, that localized neuronal computations become more efficient which may support more rapid and complex computations underlying complex behavior such as cognitive control. The combination of both enhanced regional computational processing and long distance functional integration, supported by myelination, across the brain would support both the ability to enact a goal directed plan and to effectively implement it throughout the brain.

The substantial behavioral changes observed from childhood to adolescence (Luna *et al.*, 2004) are accompanied by consistent changes in prefrontal participation. Performance changes are significant yet subtle from adolescence to adulthood and prefrontal recruitment may actually decrease during this period. We propose that the years from childhood to adolescence represents a significant shift to prefrontally mediated behavior (Fassbender *et al.*, 2004; Fuster, 1997). However, from adolescence to adulthood there is a qualitatively different shift in which adults distribute function across cortex more evenly, which allows cognition to be more efficiently supported and relieves prefrontal cortex from being primary in determining executive function. This could imply that there is less reliance on executive processes or that executive processes are achieved by circuitry other than prefrontal systems. For example, there is evidence that parietal regions support the mnemonic aspects of working memory while prefrontal cortex is preferentially involved in the manipulation of information (Postle, Berger, & D'Esposito, 1999). The adult system may reflect a better distribution of function among regions that support executive function (e.g., parietal and prefrontal recruitment) while adolescents may depend primarily on prefrontal systems.

Taken together, developmental fMRI studies indicate that the pre-frontal cortex is involved in cognitive control early in childhood and that its relative participation becomes magnified and restricted with age. However, the ability to demonstrate flexible and reliable cognitive control characterizes the transition to adult-level performance, and this process necessitates a widely distributed circuitry (Goldman-Rakic, 1988). Most studies have focused primarily on the role of prefrontal cortex and have not considered the impact of a circuit-based mechanism. Evidence that functional integration across neocortex is present throughout adolescence (Chugani, 1998; Thatcher *et al.*, 1987) indicates that, in conjunction with developmental improvements in the intrinsic computational capacity of prefrontal cortex, there is increased integration of prefrontal cortex with other brain regions during adolescence. Several studies have indicated that additional areas become active in adulthood, including parietal, striatal, and cerebellar regions (Luna *et al.*, 2001; Tamm *et al.*, 2002), which through connections with prefrontal cortex, may establish an efficient circuitry supporting mature cognitive control.

Recent work delineating developmental changes in brain circuitries underlying cognitive control support the proposal that development is supported by the integration of widely distributed circuitries. Characterizing the association of the temporal evolution of signal changes across brain regions recruited for a cognitive task can inform us regarding the strength of the relationship between regions which is believed to reflect functional connectivity. Functional connectivity in fronto-parietal and fronto-striatal-thalamic pathways during performance of inhibitory and working memory tasks have been found to strengthen from adolescence to adulthood (Edin *et al.*, 2007; Stevens, Kiehl, Pearlson, & Calhoun, 2007).

Functional connectivity also can be assessed by cross correlating spontaneous neural activity during rest (not performing a cognitive task) using rs-fcMRI (resting state functional connectivity MRI). Resting state fMRI in contrast to fMRI can assess capability of basic connectivity of large brain circuits that can be used for cognitive processing. Fair *et al.* (2007) assessed the strength of connection of two circuitries known to support cognitive control. The frontoparietal network supports cognitive abilities such as inhibitory control and working memory (Dosenbach *et al.*, 2006). The cingulo-opercular network, which includes the anterior cingulate cortex, insula, anterior prefrontal cortex, and thalamus, underlies the ability to retain a response state. As described earlier, *response state* refers to the ability to orchestrate cognitive demands to apply cognitive abilities in a consistent and flexible manner. Results indicated that these circuitries continue to reorganize through adolescence by becoming distinct and segregated from one another and by integrating long distance connections. Specifically, regions in medial prefrontal cortex initially part of the frontoparietal network that supports cognitive abilities such as inhibition and working memory, become part of the cingulo-opercular network supporting response state. These results imply that the nature of development is the process of specializing and segregating circuitries that support task ability and response state. Therefore, both the ability to perform a response guided by cognitive control as well as the ability to retain a response state improves with development as the circuits that support these distinct processes become independent.

The mechanisms by which these circuits develop are not known. Synaptic pruning and myelination interacting with experience may support the development of these circuits. As synaptic pruning supports more efficient computations at the regional level, brain regions can more effectively coordinate activity with other regions. Myelination would support the ability for regions to interact in a timely fashion but spontaneous synchronous activity such as through Hebbian process independent of myelination may also underlie development (Fair *et al.*, 2007). Experience would provide the guidance for which regions become entrained to work in a collaborative fashion.

Immaturities in brain function across development especially in adolescence, when mature performance is available, reflect a system in transition that therefore may be particularly vulnerable to limitations in cognitive control and may contribute to the emergence of psychopathology and risk-taking behavior. We propose that similar to adults who are more prone to error when performing a difficult task, the adolescent may be overall more vulnerable to error due to the yet immature circuitry recruited. This implies that the nature of “maturation” as the transition from immature to adult-level cognitive control is a switch to a more organized and efficiently recruited distributed circuitry. This transition from adolescence to adult brain integration however may be a period of vulnerability to impaired development that could contribute to the emergence of psychopathology that occurs at this time. Characterizing a normative system allows the investigation of the abnormal development usually associated with failures of cognitive control, specifically, disorders such as ADHD, Tourette’s, and autism (Luna *et al.*, 2002; Luna & Sweeney, 1999). Major psychopathology is characterized by impaired executive function and its appearance in adolescence (Luna & Sweeney, 2001). Comparing a normative template of developmental changes in brain systems with groups of individuals with psychopathology could contribute to identifying the basis of impaired brain mechanisms. Additionally, characterizing periods of immaturities and the nature of the changes in brain systems in typical populations could potentially provide insight into risk-taking behavior, which is recognized as a failure in decision making that is supported by cognitive control and peaks in adolescence (Chambers *et al.*, 2003; Spear, 2000). Risk-taking behavior can lead to substance abuse which typically begins in adolescence (Call *et al.*, 2002; Resnick *et al.*, 1997). Understanding individual variability in the development of brain systems could inform us of individuals that may be vulnerable to substance abuse.

VII. How does Immaturity in Executive Processing Inform us about Real Life Decision Making?

Adolescence is the peak of sensation seeking and risk-taking behavior across species (Hodes & Shors, 2005; Stansfield & Kirstein, 2006). Sensation seeking is believed to be important for obtaining experience in independent decision making needed for survival as an adult. Risk-taking behavior occurs when sensation-seeking involves decision making that results in a risk to survival. Drug use, unprotected sex, and extreme sports are examples of risk-taking behavior. During adolescence, sensation seeking becomes increasingly appetizing as anxiety is not associated with risk-taking to the same degree as in adulthood (Hodes & Shors, 2005). The ability to control desired sensation seeking behavior for safe lower risk behaviors requires the ability to inhibit responses and to make goal directed plans in working memory. The decision making processes involved in risk-taking behavior are many, including motivation and reward processing in addition to inhibitory processing. The inhibitory processes involved in risk-taking behavior are also multi-dimensional involving an array of domains (visual, somatosensory, auditory) and cognitive processes (language, reasoning).

In order to understand the brain basis of such a complex process it is useful to begin by investigating basic aspects of this model. It would be of significance to understand the status of basic aspects that allow proper decision making. Probing the integrity of basic executive processes can provide insight into the capability of successful decision-making. If these are not yet at adult levels, then they already indicate a limitation in the general process of decision making. Investigating basic processes of cognition allows for direct comparisons to be made between brain and behavior. Risk-taking behavior *per se* is not a unitary concept that can be readily and directly examined. Breaking down its main components such as response inhibition and working memory allows us to begin to understand the brain behavior relationships that underlie adolescent behavior. Using tasks that tap into basic aspects of cognitive control allows us to directly examine the neural basis of individual components of complex decision making such as is involved in risk-taking behavior. The inferences that can be made are limited but

highly relevant. What can be said is that immaturities in the neural circuitry of basic executive function contribute to limitations in decision making.

Studies indicating immaturities in the ability to make simple inhibitory motor responses suggests that adolescents still have limitations in implementing basic cognitive control. Children however, also have limitations in inhibitory control but they do not demonstrate the degree of risk-taking behavior evident in adolescence. The added peak in sensation seeking in adolescence coupled with immature cognitive control however could add to processes that lead to risk taking behavior. Given additional variables that make decision making more difficult, an immature executive system becomes an important factor in risk-taking behavior. Therefore, although these basic studies can not explain or justify risk-taking behavior, they enlighten us regarding the limitations that are specific to the adolescent system. Importantly, it provides a model as to the neural basis of poor decision making. I propose that adolescents have the ability to make executive decisions. However they demonstrate limitations in the ability to effectively exert top-down modulation and possibly to establish a response state that can affect clear decision making. Additionally, immature reward processing can further influence cognitive control. Studies that provide a view of the integrity of brain functional systems of basic cognitive components can provide a template for understanding the limitations that are unique to adolescent decision making.

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Fig. 1.

Depiction of developmental change across the age span. Adolescence is highlighted as a unique stage past childhood when adult-level stability is coming on-line.

Fig. 2. View of cortical surface of the brain generated from longitudinal MRI scans. Darkening shade represents degree of gray matter thinning. We have added a box surrounding the brains that represent adolescence. (Figure transformed to black and white and reprinted with permission from Gogtay et al., 2004).

Fig. 3.

Solid circles depict the $M \pm 1$ standard error of the M (SEM) for the percent of trials with a response suppression failure in the antisaccade (AS) task. Thick lines depict the inverse curve fit on the response suppression failures by age in years. The arrow depicts the age at which change point analyses indicate adult level of performance was reached (with permission from Luna *et al.*, 2004).

Fig. 4. Mean ± 1 standard error of the accuracy to initiate a memory-guided saccade (solid circles) and the accuracy of the final gaze location (open circles) in the ODR task for each age group. Thick lines indicate the inverse curve fit for these data across the age range studied. Arrows depict the age at which change point analyses indicate adult levels of performance were reached (with permission from Luna *et al.*, 2004).

Fig. 5.

$M \pm 1$ standard error of the M (SEM) of the latency to initiate a saccade in each task for each age group. Solid circles depict the latency to initiate a saccade to a visual stimulus during the visually guided saccade (VGS) task. Open circles depict the latency to initiate an eye movement to the opposite location of a visual target in the antisaccade (AS) task. Solid triangles depict the latency to initiate an eye movement to a remembered location in the oculomotor-delayed response (ODR) task. Thick lines indicate the inverse curve fit on the M latency to initiate an eye movement response in millisecond by age in years. Arrows depict the ages at which change point analyses indicate adult levels of performance were reached (with permission from Luna *et al.*, 2004.)

Fig. 6.

From Velanova *et al.*, 2008. Activity in medFG/rACC and dACC across time for correct and error AS trials in each age group on the partially inflated medial cortical surface of the right hemisphere for correctly performed antisaccade trials.

Fig. 7.

From Luna *et al.*, 2001. Mean group activity during a block antisaccade task for children, adolescents, and adults overlaid on top of the structure of a representative subject.

Fig. 8.

From Scherf *et al.*, 2006. Imaging results from both magnitude and extent of activation analyses. (A) Axial brain slices depicting regions of significant brain activity in each age group. Children showed stronger activation bilaterally in the caudate nucleus, the thalamus, and anterior insula. Adolescents showed the strongest right DLPFC activation, and adults showed concentrated activation in left prefrontal and posterior parietal regions. (B) Pie charts depict the distribution of brain activation across all brain regions recruited. Children showed disproportionate amount of activity in basal ganglia and adolescents in right dorsolateral prefrontal cortex. In contrast, adults showed more equally distributed recruitment of regions.