Studies of Brain and Cognitive Maturation Through Childhood and Adolescence: A Strategy for Testing Neurodevelopmental Hypotheses

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Abstract

Although neurodevelopmental models of schizophrenia are now widely accepted, there is minimal direct human evidence of dysmaturation in schizophrenia to support this theory. This is especially the case regarding maturational changes during late childhood and adolescence, which immediately precede the typical age of onset of the disorder. By integrating new noninvasive methods of functional magnetic resonance imaging with techniques of developmental cognitive neuroscience, it is now possible to begin systematic research programs to directly test hypotheses of neurodevelopmental abnormalities in schizophrenia. In this article, we describe strategies for characterizing developmental changes taking place during the critical period of adolescence that can elucidate dysmaturation processes in schizophrenia. We emphasize the need for studies characterizing normal development before examining at-risk or clinical populations, and the potential value of using neurobehavioral and neuroimaging approaches to directly characterize the dysmaturation associated with schizophrenia.

Keywords: spatial working memory, inhibition, eye movements, cerebellum, neuroimaging, prefrontal cortex.


Neurodevelopmental models of schizophrenia have gained considerable interest in recent years (Waddington et al. 1991; Hyde et al. 1992; Keshavan et al. 1994; Weinberger and Lipska 1995), and this has opened a new conceptual framework for thinking about the etiology of this debilitating disease. Onset of schizophrenia typically occurs during adolescence or young adulthood, which itself raises interest in the nature of brain maturational changes during adolescence that might be awry in individuals at risk for schizophrenia and thereby contribute to the etiology of the disorder.

Adolescence is an important period of development. Recent neurobiological and psychological research indicates that far greater brain and cognitive maturation occurs during this period than was traditionally believed. Although basic cognitive and brain functions are, for the most part, in place by school age, significant maturation continues throughout and after puberty. Concurrent with this brain maturation is the emergence of increasingly elaborate cognitive abilities. The prefrontal cortex, with the participation of other brain regions in widely distributed circuits, subserves many aspects of higher order cognitive function in which there is robust developmental change during adolescence. These functions include working memory, voluntary inhibition of context-inappropriate behavior, and developing preparatory sets for anticipated action (Goldman-Rakic 1990; Fuster 1997). All of these functions require that cognitive processes be held on line to allow for the appropriate binding of environmental cues and behavioral responses over time, so that behavior is properly timed and adaptive to specific environmental contexts. In schizophrenia, a wide range of behavioral and functional imaging studies document impairment in these higher order cognitive processes that undergo considerable maturational change during adolescence (Weinberger et al. 1986; Park and Holzman 1992; Merriam et al. 1999; Cohen et al. 1999). Evidence indicates that anomalies in the cytoarchitecture of prefrontal cortex, including a decrease in neuropil, occur in schizophrenia patients (Lewis 1997; Selemon and Goldman-Rakic 1999). The potential contribution of abnormal maturational processes during childhood and adolescence to the reduced synaptic connectivity seen in adult patients remains unclear.

Thus, cytoarchitectural, neuroimaging, and neurocognitive studies all converge in indicating abnormalities in the anatomy and function of prefrontal cortex in individ...
als with schizophrenia. Further, clinical neuropsychological studies of “first-episode” patients, evaluated shortly after illness onset, have reported robust disturbances of prefrontal cortical functions even at the point of illness onset (Hoff et al. 1992; Rubin et al. 1995; Merriam et al. 1999; Bilder et al. 2000; Riley et al. 2000). Available evidence in young and midlife adult schizophrenia patients does not suggest significant declines in cognitive function over time (Goldberg et al. 1993; Censits et al. 1997; Rund 1998). Thus, cognitive abnormalities in schizophrenia patients do not result primarily from treatment or course of illness effects; therefore, it appears that schizophrenia patients often fail to achieve an expected developmental level of these functions before illness onset. This notion is indirectly supported by studies showing that relatives of individuals with schizophrenia, who themselves do not manifest the illness, also have deficits in executive cognitive functions subserved primarily by prefrontal cortex (Franke et al. 1992; Park et al. 1995; Staal et al. 2000).

Although findings from studies of relatives have been somewhat inconsistent, observations of abnormalities of prefrontal functions in the unaffected family members of schizophrenia patients that have been reported suggest that brain dysmaturation in this disorder may be under genetic control and related to risk for the illness in a fundamental way. However, at present, we still lack the data needed to determine whether and how maturational disturbances might contribute to prefrontal and other cognitive abnormalities associated with schizophrenia.

The temporal contiguity of illness onset and the relatively late maturation of prefrontal cortical functions indicate that a failure to achieve adequate maturational changes in the intrinsic wiring or functional connectivity of prefrontal cortex could prove to be a major factor in the pathophysiology of schizophrenia. Such developmental failure could lead to inadequate inhibitory modulatory influence over mesial temporal cortex contributing to positive symptoms, and directly cause important neuropsychological deficits associated with the illness.

However, before we can test neurodevelopmental models of schizophrenia by establishing actual developmental and brain maturational disturbances in the illness, several preliminary steps need to be achieved. First, we need to learn much more about the normal maturation of cognition and functional brain systems during late childhood and adolescence. At present, little is known about normal cognitive and neurophysiologic dimensions of adolescent maturational processes. Developmental neurobiology and the study of cognitive development have concentrated on the stages of development from conception to the first years of life, leaving the investigation of late childhood and early adolescence a relatively understudied area of research. Much basic psychological research is needed to document the essential pattern of cognitive changes that occur during late childhood and early adolescence and the normal range of variability in these processes across individuals. This research is required to establish deviations from normal development in clinical populations of interest. Second, we need to better understand the brain substrates of cognitive development during adolescence. Neuroimaging research provides an important strategy for achieving this aim. Whereas positron emission tomography (PET) and single-photon emission computed tomography require radioactive tracers to examine functional changes in brain activity, functional magnetic resonance imaging (fMRI) is a noninvasive procedure that monitors regional brain function with high spatial resolution in a manner that can be used safely with pediatric populations. Studies of healthy children and adolescents with fMRI have just begun to appear in the literature. As findings are replicated and methods are validated in fMRI studies, we will be able to probe the maturation of brain functions in individuals at risk for schizophrenia, thereby identifying specific failures in normal maturational processes.

Although prefrontal deficits are prominent, impairments in other brain regions are suggested by the broader pattern of associated neuropsychological deficits (Saykin et al. 1991; Levy and Holzman 1997; Sweeney et al. 1998; Chen et al. 1999). Furthermore, human neuroimaging and monkey unit recording studies consistently indicate that higher order cognitive processes are subserved by widely distributed systems in the brain that not only include prefrontal regions but also striato-thalamo-cortical and cerebello-thalamo-cortical circuits (Strick 1985; Robbins 1990; Middleton and Strick 1998). Functional MRI studies provide the ability to visualize function in the whole brain to investigate localized abnormalities in different regions of interest, as well as impairments at the network level and impairments in functional connectivity.

We aim to briefly summarize what is known about brain maturation and cognitive development during late childhood and early adolescence and then describe our preliminary efforts to characterize normative changes in the maturation of brain function using neurophysiological and fMRI approaches during this period.

**Brain Maturation**

The degree of cortical folding (Armstrong et al. 1995), overall size, and regional functional specialization of the brain is, for the most part, in adult-like form by early childhood (Caviness et al. 1996). However, significant refinements of brain systems including pruning of synapses, elaboration of dendritic arborization (Changeux and Danchin 1976; Huttenlocher 1990), and increased myelination (Yakovlev and Lecours 1967; Jernigan et al. 1991; Pfefferbaum et al. 1994) continue...
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Cognitive Development

Developmental psychologists have primarily concentrated on understanding the cognitive milestones achieved in the first few years of life. Relatively little research has been dedicated to understanding the more subtle changes in cognition that occur after early childhood. However, available evidence does indicate that cognitive processes become significantly more sophisticated during adolescence.

Although basic cognitive processes, including working memory (Diamond and Goldman-Rakic 1989), are in place by childhood, the sophisticated use of these abilities increases throughout adolescence. This period is characterized by improvement in the capacity to manipulate one’s environment through abstract thought, planning, and cognitive flexibility that takes place concurrently with significant reorganization of neural connectivity in the neocortex. Performance on visual pattern spatial recognition and set-shifting tasks (Luciana and Nelson 1998), as well as performance on the Wisconsin Card Sorting Task (Chelune and Baer 1986; Levin et al. 1991), are adult-like by late childhood. However, complex planning skills show continued improvement past late childhood into adolescence on more complex problem-solving tasks such as the Tower of London and the Tower of Hanoi, as well as on verbal fluency and motor sequencing tasks (Levin et al. 1991; Welsh et al. 1991).

The maturation of higher order cognitive abilities is believed to result from improved processing and storing of information (Case 1992; Dempster 1993) afforded primarily by the automation of lower level cognitive processes and the ability to suppress or inhibit context-inappropriate responses (Bjorklund and Harnishfeger 1990; Case 1992; Ridderinkhof and van der Molen 1997; Wilson and Kipp 1998). Higher order cognitive processes are supported by the coordinated action of widespread neural networks that enable adaptive neocortical modulation of behavior, particularly the executive orchestration of activity in many brain regions by prefrontal cortex (Hudspeath and Pribram 1990; Stuss 1992; Diamond and Taylor 1996; Luciana and Nelson 1998). In this manner, cognitive maturation can be conceptualized as a feedback loop in which an increase of functional integration across widely distributed brain regions allows for quicker, more focused, and higher capacity cognitive processing, which in turn frees up local neuronal circuitry for more optimized performance of cognitive functions. This mature system provides a more dynamic and efficient processing stream that allows for the sophisticated online planning and flexibility needed for complex goal-directed behavior. The disruption in maturation of these elements could have significant consequences for higher order cognition.

There is much work that needs to be done to characterize the essential cognitive processes that benefit from...
brain maturation during the transition from puberty through adulthood. To characterize neurodevelopmental dysmaturation in psychiatric disorders, it is important to recognize the impaired cognitive elements and pinpoint the stage at which their disruption occurs. First, however, it is necessary to characterize healthy development during adolescence. Only after we have validated procedures and replicated findings with large samples of healthy individuals that document the patterns and their normal variability of development will we be prepared to begin hypothesis-driven clinical investigations to nail down the time course and essential components of developmental dysmaturation in schizophrenia.

**Probing Brain and Cognitive Maturation**

Given the need for normative cognitive and fMRI data regarding processes that mature during adolescence and are abnormal in schizophrenia, we began a set of studies using oculomotor tasks. Oculomotor tasks are especially well suited for investigating cognitive and brain maturation for several reasons. First, eye movement tasks can be used to test the integrity of basic sensorimotor function as well as multiple higher order executive processes including attention shifting, working memory, and voluntary response suppression. Second, specific cognitive processes can be isolated and tested with eye movement paradigms in a way that is rarely possible with standard neuropsychological tests. Third, single-cell recording studies of nonhuman primates and human lesion and neuroimaging studies have characterized the physiology, anatomy, and neurochemistry of the brain processes underlying the executive control of the oculomotor system, providing an especially strong base for designing and interpreting clinical and developmental studies (Leigh and Zee 1999). The same tasks used in lesion and neurophysiological studies of behaving nonhuman primates can be brought directly into the clinical laboratory. From these studies we know which brain regions are required for normal task performance and how they form a widely distributed circuitry (figure 1), including key brain areas known to be disrupted in schizophrenia including prefrontal, thalamic, striatal, and cerebellar regions. Fourth, eye movement tasks are particularly well suited for neuroimaging work in that they recruit robust increases in brain activity (O’Driscoll et al. 1995; Sweeney et al. 1996; Petit et al. 1997; Luna et al. 1998; Luna and Sweeney 1999; Luna et al. 2001). Finally, serious psychiatric and neurologic disorders are known to be associated with specific abnormalities in eye movement control (Kennard and Rose 1988; Park and Holzman 1992; Clementz et al. 1994; Sweeney et al. 1998; Levy et al. 1998; Leigh and Zee 1999).

The oculomotor system is a particularly appropriate target for developmental studies because children as well as adults can readily perform eye movement tasks. Additionally, cognitive studies using oculomotor tasks have revealed delayed maturation of executive processes in psychiatric disorders through adolescence (Rosenberg et al. 1997). Cross-sectional developmental studies have revealed improved performance throughout childhood in the speed of shifting attention and eye movements to visual targets, in the ability to suppress saccades to anticipated targets, in maintaining fixed gaze, and in accurately tracking moving targets (Miller 1969; Paus et al. 1990; Ross et al. 1993, 1994; Fischer et al. 1997; Katsanis et al. 1998; Munoz et al. 1998).

Different eye movement tasks can be used to probe different brain processes. Simple tasks such as the visually guided saccade task, which requires that subjects direct their gaze to suddenly appearing visual targets, and pursuit tasks in which subjects visually track a moving stimulus, can be used to study the integrity of basic sensorimotor and attention systems. Cognitive components can be added to simple eye movement tasks to probe higher order cognition and draw inferences about its underlying brain circuitry. The oculomotor delayed response task (also called a memory-guided saccade task)
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requires that subjects make an eye movement guided only by the memory of the spatial location of a stimulus. This task has been used to define the basic neuronal circuitry of spatial working memory in studies of nonhuman primates (Hikosaka and Wurtz 1983; Funahashi et al. 1989; Sawaguchi and Goldman-Rakic 1991). The antisaccade task requires that subjects suppress eye movements to visual targets that appear in the periphery, and instead look away from them. The antisaccade task is used to probe the capacity for voluntary response suppression. These eye movement tasks have been used in nonhuman primate single-cell and lesion studies as well as in human lesion and neuroimaging studies, providing a solid depiction of the brain circuitry subserving their performance (Funahashi et al. 1989; Pierrot-Deseilligny 1991; Darby et al. 1996; Everling et al. 1999).

We have used these eye movement tasks to assess working memory and voluntary response suppression to characterize the development of these higher order cognitive processes from 8 to 45 years of age, and have found significant improvements in these processes throughout adolescence (Luna et al. 2000, 2001). Although 8- to 10-year-old children demonstrate adult level performance in the velocity and accuracy of saccadic eye movements to visual targets, they do not perform as well as adults in the cognitive components of these tasks. The accuracy of eye movements made to remembered spatial locations during the memory-guided saccade task did not reach adult levels until mid-adolescence. Similarly, in the antisaccade task, not until mid-adolescence did subjects reach adult levels in the percentage of trials in which they could voluntarily suppress the reflexive tendency to look toward suddenly appearing targets (Luna et al. 2000). Improvement in the performance of the antisaccade task has also been found in large cohorts in other laboratories and appears to be a reliable measure of the development of the capacity for voluntary response suppression (Fischer et al. 1997; Munoz et al. 1998). These results indicate that there is significant cognitive development occurring throughout adolescence, and it can be evaluated using cognitively demanding eye movement tasks.

Given the multiple indications of frontal pathology in schizophrenia, it is not surprising that individuals with schizophrenia have a well-replicated diminished ability to perform antisaccade, memory-guided saccade, and pursuit tasks (Fukushima et al. 1990; Rosse et al. 1993; Clementz et al. 1994; Matsue et al. 1994; Crawford et al. 1995; Katsanis et al. 1997; Sweeney et al. 1998, 1999). Hence, investigations probing the oculomotor system are particularly well suited to study neurodevelopmental components of schizophrenia.

### Studying Development of Brain Function during Childhood and Adolescence

The study of development during adolescence has been composed, for the most part, of two major lines of research. One area has characterized changes that occur in brain structure through childhood and adolescence. This area has seen major recent advances in methodologies for characterizing region-specific changes in brain anatomy (Caviness et al. 1996; Kennedy et al. 1998), in approaches for measuring both the form and volume of brain structures (Rademacher et al. 1993; Gelenbe et al. 1996), and in the development of diffusion tensor imaging for evaluating white matter pathways (Pfefferbaum et al. 2000). The second area of study has focused on how cognitive capabilities improve with age. It is evident that cognitive development and brain maturation are inherently intertwined; however, until recently, we have not had the methods to systematically investigate how these two dimensions of developmental maturation fit together.

Functional brain imaging promises to provide the bridge between anatomic studies of brain maturation and neuropsychological studies of cognitive development that are needed to understand the dynamic relationship between brain and cognitive development. One approach with especially great promise is using fMRI to investigate how the functional organization of brain regions contributing to cognitive functions changes with development to support the emergence of adult cognition. Advances in this field will be extremely valuable for directly testing neurodevelopmental models of schizophrenia. As we delineate the brain circuitry underlying healthy cognitive development, we will be better able to identify specific abnormalities in functional brain circuitry and neurocognitive control that occur in individuals with schizophrenia and in those at familial risk for the illness during childhood and adolescence. As such, findings about brain function are linked to findings of anatomic abnormalities in brain maturation, we will be able to provide direct tests of neurodevelopmental models of schizophrenia.

Before the development of fMRI, brain function in children and adolescents was typically assessed with electroencephalography (EEG) and PET. Thatcher (Thatcher 1991) measured EEG coherence among neocortical regions and reported that the coherence of EEG activity increased throughout adolescence, especially between frontal and other cortical areas. Similar results were found using PET, with which Chugani et al. (1998) demonstrated that local cerebral resting metabolic rates...
decrease in frontal, parietal, and temporal regions throughout childhood and only reach adult levels in adolescence. Although the neurobiological substrate of this latter effect is not completely clear, the most likely cause is that synaptic pruning related to brain matura-
tion reduces net metabolic activity. However, there are limitations to these methods and findings. EEG studies lack sufficient spatial resolution to adequately localize developmental changes in specific brain regions. PET, because of the somewhat invasive nature of the procedure, has rarely been used to study healthy pediatric populations.

Functional MRI allows noninvasive imaging of brain function in vivo during cognitive activity. Because it is noninvasive, fMRI permits the characterization of changes in brain activity that occur during development in pediatric populations. The minimal risk from repeated exposure also permits longitudinal fMRI studies of developmental changes in brain-behavior systems. This is especially important because it provides a basis for actually following developmental trajectories in individual sub-
jects, rather than using only cross-sectional studies to investigate developmental trends. Because development often proceeds in bursts rather than in a smooth, gradual manner (Thatcher 1991), longitudinal studies provide a better way to characterize patterns of development. For these reasons, fMRI is likely to be a valuable tool for bridging cognitive and biological studies of brain development.

Functional MRI works on the principle that neuronal activation associated with cognitive activity results in increased metabolic demand and that metabolic demand, in turn, brings increased blood flow to the region. The increase in blood flow produces a change in the ratio of oxygenated to deoxygenated blood, which changes the magnetic properties of blood in a way that can be detected in MRI studies. Using sophisticated image reconstruction and analysis procedures, these changes in regional magnetic properties in the brain can be used to provide a detailed picture of brain regions involved in performing a particular cognitive act. The psychological tasks that sub-
jects perform in the MRI scanner need to be carefully selected to probe specific cognitive processes of interest. A diagram of the MRI environment is presented in figure 2.

Pediatric fMRI studies have been performed to guide excision of lesions (Stapleton et al. 1997), to localize language areas (Benson et al. 1996; Hertz-Pannier et al. 1997), to identify similarities between children and adults in the regions recruited for higher order cognition (Casey et al. 1995, 1997; Thomas et al. 1999; Luna et al. 2001), and to characterize functional impairments in attention deficit hyperactivity disorder (Vaidya et al. 1998; Rubia et al. 2000). Initial developmental neuroimaging studies sug-

![Figure 2. Diagram of functional magnetic resonance imaging environment](https://academic.oup.com/schizophreniabulletin/article-abstract/27/3/443/1835120)

**Figure 2.** Diagram of functional magnetic resonance imaging environment

Our own findings have revealed changes in the functional distribution of brain regions from childhood through adolescence during performance of a voluntary response suppression task (Casey et al. 1995). We conducted an fMRI study of 36 healthy subjects ranging in age from 8 to 30 years to study developmental changes in the brain substrate of antisaccade task performance. Blocks of antisaccade and prosaccade trials were presented. The stimuli used for the two eye movement tasks were similar except for the color of the fixation light. During antisaccade trials, the fixation light was red and subjects were instructed to look in the opposite direction of targets appearing in the periphery. During prosaccade trials, the fixation light was green and sub-
jects were instructed to look toward the peripheral targets. Activity during these two tasks was then contrasted to localize brain regions associated with voluntary response suppression, with the rationale that comparison with a visually guided saccade task would “subtract” activation effects associated with basic visual and sensorimotor processes. The difference in activation then would be attributable to the changes in regional neuronal activity related to the task demand for voluntary response suppression.

Results indicated that, across the age span, subjects recruited a widely distributed circuitry including frontal, supplementary, and parietal eye fields, dorsolat-
eral prefrontal cortex, thalamus, and striatum (figure 3). However, comparisons of children, adolescents, and adults revealed that only adults recruited some regions known to play a primary role in establishing the preparatory state needed to successfully perform anti-
saccades, including the superior colliculus (Everling et al. 1999), extensive regions of the frontal eye field (Everling and Munoz 2000), and regions in the lateral cerebellum that form a functional circuit with the pre-
frontal cortex (Kim et al. 1994). On the other hand, adolescents did demonstrate increased activation of dorsolateral prefrontal cortex and striatum relative to children, possibly reflecting their ability to more effectively recruit fronto-striatal circuitry to perform the antisaccade task.

These results provide evidence that brain function underlying response suppression as seen in the antisaccade task becomes more widely distributed throughout adolescence, likely providing the maturational refinements needed for efficient voluntary control of behavior on this task. We still need to characterize how synaptic pruning and myelination processes occurring during this age period are associated with this developmental change in functional organization. Further, from the perspective of the neurodevelopmental model of schizophrenia, whether there is a maturational failure in schizophrenia in the functional interconnectivity of brain regions subserving key cognitive functions such as the voluntary suppression of prepotent responses needs to be determined.

Conclusion

This is an exciting time for those interested in putting neurodevelopmental models of schizophrenia to direct test. Although a host of data points to developmental abnormalities in the perinatal period and early childhood in schizophrenia (Fish et al. 1992), developmental disturbances during late childhood and adolescence may be of equal, if not greater, importance (Marcus et al. 1993; Hans et al. 1999) given that the incidence rates for schizophrenia rise sharply at the age when these maturational events are being completed. Undoubtedly, there is a considerable likelihood that perinatal factors could influence brain maturation in adolescence, a possibility that certainly needs to be systematically examined.

Efforts to consider disturbances in late developmental processes as risk factors for schizophrenia have been hindered by two major factors: (1) a lack of a broad interest in this period by developmental psychologists and neurobiologists, which has led to a modest empirical framework for testing hypotheses about abnormal development associated with schizophrenia, and (2) a lack of validated methodologies for noninvasively assessing brain-behavior systems during this age period. The growing interest in adolescent development and the availability of MRI technologies for evaluating brain anatomy and function in new noninvasive ways now provide the basis for studying individuals at risk for schizophrenia during childhood and adolescence and determining what, if any, maturational abnormalities in brain and cognitive systems occur in these individuals.

The purpose of this article was to lay out a general strategy for testing models of "late" neurodevelopmental disturbances in schizophrenia. To pursue work in this area, one approach is to follow childhood onset cases (Gordon et al. 1994). Although this is an important approach, these cases can in some ways be atypical and rare, and the effects of illness and treatment on developmental parameters of interest are difficult to sort out. Even adolescent-onset cases can have especially poor...
courses of illness and treatment response (Pollack et al. 1968). An alternative approach is to study unaffected family members of patients or schizotypal individuals (Keshavan et al. 1991; Thaker et al. 1996) and to study developmental processes in these individuals. Although a difficult task in its own right, this approach provides one feasible way to directly test models of abnormal neurodevelopmental processes in schizophrenia.

There are multiple ways to conduct clinical in vivo studies to investigate dysmaturation in schizophrenia. MRI methods provide a useful approach for studying brain anatomy and function. To systematically study functional aspects of brain development that may be awry in schizophrenia, an approach with several steps is required. First, neurocognitive domains that are abnormal in individuals with schizophrenia need to be selected for developmental studies. Second, once a neurocognitive domain is identified, its developmental profile needs to be characterized in healthy individuals. This is essential so that hypotheses about dysmaturation can be tested by comparing development in healthy individuals with that of clinical groups or their unaffected family members. Third, when focusing on a clinical developmental hypothesis, clarifying the brain substrate of cognitive developmental abnormalities is a key issue. For this purpose, now that the utility of fMRI for studying pediatric populations is established, functional brain imaging is a natural approach for an integrative investigation of neurocognitive developmental disturbances associated with schizophrenia. This requires validating activation tasks assessing neuropsychological domains of interest in healthy pediatric populations to have a model of the brain circuitry involved and to test hypotheses about areas that may develop abnormally in schizophrenia.

One factor that is important to consider in selecting tasks and neurocognitive domains to study is the degree to which the neurophysiology of brain processes subserving cognitive functions of interest is understood. Using tasks such as cognitively demanding oculomotor paradigms, in which the brain substrates of cognition have been extensively investigated in behaving primates and are thereby understood in terms of biochemical processes and the time course of task-relevant neuronal activity, can facilitate a much more direct linkage of behavioral abnormalities to their brain substrate. Although establishing normal developmental trends in cognitive domains of interest and clarifying normal patterns of neurodevelopmental trajectories with fMRI are complex and consuming endeavors for conducting human in vivo studies of developmental dysmaturation in schizophrenia, achieving these aims will lay a firm foundation for testing neurodevelopmental models of schizophrenia. This work may not only be important for testing neurodevelopmental models of schizophrenia, but also may help facilitate identification of new approaches for early diagnosis, as well as identify individuals at risk and provide preventive interventions for them.

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