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Clinical, Imaging, Lesion, and Genetic Approaches Toward a Model of Cognitive Control

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ABSTRACT: *The ability to suppress or override competing attentional and behavioral responses is a key component of cognitive processes. This ability continues to develop throughout childhood and appears to be disrupted in a number of childhood disorders (e.g., attention deficit/hyperactivity disorder and Tourette syndrome). At least two brain regions have been implicated repeatedly in these disorders—the frontal lobes and the basal ganglia. The common problem in cognitive control and overlap in implicated brain regions across disorders suggest a single underlying biological mechanism. At the same time, the distinct symptomatology observed across these disorders suggests multiple mechanisms are at play. This article presents converging evidence from clinical, neuroimaging, lesion, and genetic studies to provide a mechanistic model of cognitive control whereby the basal ganglia are involved in inhibition of competing actions and the frontal cortex is involved in representing the relevant thoughts and guiding the appropriate behaviors.*
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INTRODUCTION

A key component of cognitive processes is the ability to suppress or override competing attentional and behavioral responses (Allport, 1987; Cohen & Servan-Schreiber, 1992; Kahneman, Treisman, & Burkell, 1983). This process has been included in a number of theories of attention and memory (Baddeley, 1986;

Cohen & Servan-Schreiber 1992; Desimone & Duncan, 1995; Shallice, 1988) and referred to in a number of ways (e.g., ''central executive,'' ''attentional bias,'' ''cognitive control''). The terminology is suggestive of a mechanism that is required to direct or guide appropriate actions (Miller & Cohen, 2001). For example, Shallice (1988) proposed a ''supervisory attention system'' as a system for inhibiting or replacing routine, reflexive behaviors with more appropriate behaviors. Desimone and Duncan (1995) describe top-down biasing signals as important in attending to relevant information by virtue of mutual inhibition or suppression of irrelevant information. A common theme that has emerged from this work is that a primary function of cognitive control is to reduce conflict in processing of information (Allport, 1987; Cohen & Servan-Schreiber 1992; Kahneman et al., 1983). Thus, one critical component of cognitive control is the ability to suppress or override competing attentional and behavioral responses to resolve conflict. This aspect of cognitive control is the focus of the current article. We provide a background for the development, disruption, and neurobiological basis of cognitive control before presenting converging evidence from clinical, neuroimaging, lesion, and genetic studies for a mechanistic model of cognitive control.

Development of Cognitive Control

Clearly, the ability to suppress irrelevant information and actions becomes more efficient with age. A number of classic developmental studies have demonstrated that these cognitive processes develop throughout childhood and adolescence (Case, 1972; Flavell, Feach, & Chinsky, 1966; Keating & Bobbitt, 1978; Pascual-Leone, 1970). Several theorists have argued that the development of attention- and memory-related processes is due to increases in processing speed and efficiency and not due to an increase in mental capacity (Bjorkland, 1985, 1987; Case, 1985). According to this view, capacity limitations are constant across development. More recently, these resource theories have been extended to emphasize inhibitory processes in their account of cognitive development (Harnishfeger & Bjorkland, 1993) such that immature cognition is characterized by susceptibly to interference or conflict (Brainerd & Reyna, 1993; Dempster, 1993; Munakata, Morton, & Stedron, in press) in overriding an attentional or behavioral response (i.e., immature cognitive control).

The development in the ability to override inappropriate responses has a protracted course of development. A classic example of a paradigm used to examine this process in infants is the A not B task (Diamond, 1985; Piaget, 1937/1954). In older children, cognitive control is measured by negative priming or Strooplike tasks (Tipper, Bourque, Anderson, & Brehaut, 1989), card sorting tasks (Munakata & Yerys, 2001; Zelazo, Burack, Benedetto, & Frye, 1996), go/no go tasks (Casey, Trainor, Giedd, et al., 1997; Luria, 1961), incidental learning (Schiff & Knopf, 1985), and directed forgetting (Harnishfeger, 1991). In all cases, children have a more difficult time ignoring or inhibiting irrelevant salient information or prepotent responses in favor of the relevant items or responses. Performance on these Strooplike and go/no go tasks continues to develop over childhood and does not reach full maturity until roughly adolescence (Passler, Isaac, & Hynd, 1985). Similarly, attention tasks that include distracting peripheral information, as in the case of the flanker task (Eriksen & Eriksen, 1974), show comparable developmental changes (Enns & Akhtar, 1989; Enns, Brodeur, & Trick, 1998; Enns & Cameron, 1987; Ridderinkhof, van der Molen, & Band, 1997). These studies show a nice developmental trend in the ability to ignore irrelevant flankers over the ages of 4 to 12 years that appears to reach adult levels by 12 years as indexed by mean reaction times and accuracy rates. These age-related differences are not observed on these tasks in the absence of interfering information (Enns et al., 1998). In sum, the developmental literature provides sufficient data for charting the developmental course of cognitive control in terms of both overriding behavioral and attentional responses.

Disruption in Development of Cognitive Control

The importance of examining the development and neural basis of cognitive control is underscored by its disruption in a number of childhood disorders. Many disorders of childhood have as a core deficit a problem overriding or suppressing inappropriate thoughts and behaviors. Perhaps the most prevalent of these is that of Attention Deficit/Hyperactivity Disorder (ADHD). Children with ADHD have problems focusing attention and are often characterized as distractible and impulsive (Barkley, 1997; Casey, Castellanos, et al., 1997; Trommer, Hoeppner, & Zecker, 1991). There are many other examples of childhood disorders with a similar problem suppressing inappropriate behaviors, but the nature of the deficit appears more specific to a particular behavior. For example, children with Tourette syndrome have difficulty suppressing often quite complex movements in addition to vocalizations that are sometimes emotionally provocative in content (Leckman et al., 1987). Obsessive

Compulsive Disorder (OCD) in children and adults alike is characterized by an inability to stop intrusive thoughts and ritualistic behaviors that appear to be specific in content (Insel, 1988). Stereotypes and repeated self-injurious behaviors and ruminations also are examples of inhibitory problems observed in a wide range of children, including those with autism and mental retardation and affective disorders. Even in childhood-onset schizophrenia, the child appears unable to stop attending to irrelevant thoughts and information (Asarnow, Brown, & Strandburg, 1995). Clearly, the prevalence of this problem in the ability to regulate behavior in children with developmental disabilities highlights the need for a clearer understanding of these behaviors and their biological bases.

An important characteristic of these childhood disorders is that they all have been shown to involve the prefrontal cortex and basal ganglia. Abnormalities in these structures have been reported in ADHD (Castellanos et al., 1994; Castellanos et al., 1996; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989), Tourette syndrome (Peterson et al., 1998; Singer et al., 1993; Wolf et al., 1996), Obsessive-Compulsive Disorder (Baxter et al., 1988; Rosenberg et al., 1997; Swedo et al., 1989), and childhood onset schizophrenia (Fraizier et al., 1996). Abnormalities in size, asymmetry, and/or glucose metabolism and blood flow are typically reported. For example, MRI studies of ADHD have revealed abnormalities in the size and symmetry of the basal ganglia (Castellanos et al., 1994; Castellanos et al., 1996), and recent fMRI studies showed decreased activity in prefrontal cortex and basal ganglia regions (Bush et al., 1999; Vaidya et al., 1998). Abnormalities in the basal ganglia, specifically the caudate nucleus, in children with Tourette syndrome have been reported in positron emission tomography (PET) studies by Wolf and colleagues (1996) and by Peterson et al. (1998) in a more recent fMRI study. PET studies of Obsessive-Compulsive Disorder revealed hypermetabolic activity in these regions, particularly in the caudate nucleus, anterior cingulate cortex, and orbitofrontal cortex (Baxter et al., 1988; Swedo et al., 1989) and MRI-based decreases in volume of the striatum (Rosenberg et al., 1997). In addition, MRI-based decreases in size of the basal ganglia have been reported in patients with childhood-onset schizophrenia (Frazier et al., 1996), and adults with schizophrenia show hypofrontality when performing ''frontal lobe'' tasks such as the Wisconsin Card Sorting Task (Berman, Illowsky, & Weinberger, 1988). Thus, the basal ganglia and prefrontal cortex appear to be significantly involved in a range of disorders that have as a key symptom a problem over-riding inappropriate thoughts and behaviors (i.e., cognitive control).

Despite the distinctions between the major mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV; American Psychiatric Association, 1994), there has been increasing concern regarding the validity of the boundaries between discrete syndromes as well as the underlying dimensional nature of specific functional systems underlying these disorders (Frances, Pincus, Widiger, Davis, & First, 1990; Goldberg, 1996; Kendell, 1989). The presence of common disturbances in cognitive, emotional, and behavioral systems across discrete syndromes is therefore not surprising. One way to constrain a model of whether a single or multiple mechanism(s) underlies the observed behaviors is to turn to what is known about the neuroanatomy and neurophysiology of implicated brain regions (i.e., prefrontal cortex and basal ganglia). Identification of specific neuroanatomical or neurophysiologic function may ultimately provide valuable information for validating the core features of and distinctions between psychiatric disorders.

Neurocircuitry Involved in Cognitive Control

There are five different parallel circuits involving the frontal cortex and basal ganglia (Alexander, DeLong, & Strick, 1986) that include motor, oculomotor, prefrontal (dorsolateral and lateral orbital), and limbic circuits. These basal ganglia thalamocortical circuits involve the same general brain regions (basal ganglia, thalamus, and cortex), but differ in projection zones within each of these regions and in the set of behaviors they support. These behaviors range from skeletal and eye movements to cognitive and emotionally driven actions. These five circuits are assumed to facilitate cortically mediated behaviors by inhibiting conflicting behaviors. As such, the basal ganglia do not generate movements or behaviors, but rather the cerebral cortex (and cerebellum) generates these voluntary actions. The basal ganglia then act broadly to inhibit competing movements that would otherwise interfere with the desired action (Mink, 1996). This model is consistent with our hypothesis of the way in which prefrontal cortex and basal ganglia are involved in the inhibition of inappropriate thoughts and behaviors within the association and limbic circuits.

The projections within the basal ganglia are depicted in Figure 1. For the purposes of simplicity, the substantia nigra and subthalamic nuclei are included in the diagram although these regions are not always

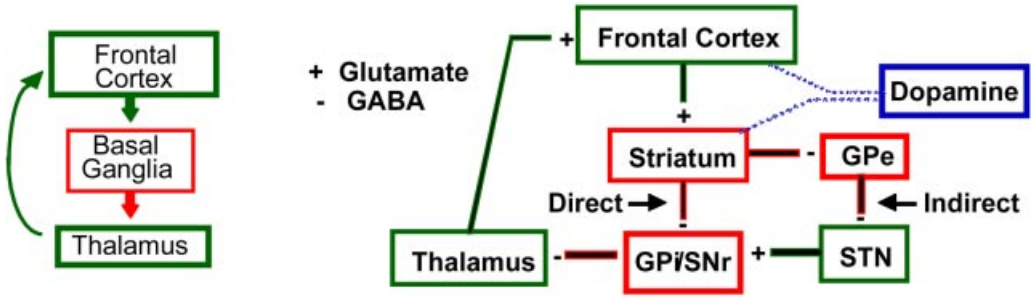

FIGURE 1 Basic circuitry of the basal ganglia thalamocortical circuit. On the left, the frontal cortex projects to the basal ganglia, then thalamus and the loop is closed with a projection back to the frontal cortex. On the right, this circuitry is better delineated. The frontal cortex projects to different areas of the striatum (i.e., putamen or caudate nuclei) and then projects to either the direct or the indirect pathway. The direct pathway involves an inhibitory projection to the internal capsule of the globus pallidus (GPi) and substantia nigra (SNr) resulting in the dampening of an inhibitory projection to the thalamus which results in disinhibition of the thalamus. The indirect pathway consists of an inhibitory projection to the external capsule of the globus pallidus (GPe) which dampens the inhibitory projection to the subthalamic nuclei (STN) resulting in excitation of the internal capsule of the globus pallidus and substantia nigra. This in turn leads to an inhibition of the thalamus.

defined as part of the basal ganglia. This cartoon shows how thalamocortical circuits are modulated by the basal ganglia via a direct (excitatory) and an indirect (inhibitory) pathway. The direct pathway presumably facilitates cortically mediated behavior. The indirect pathway is thought to inhibit cortically mediated behavior. The primary neurotransmitters of this circuitry are glutamate, which is excitatory (+), GABA, which is inhibitory (−), and dopamine, a critical neuromodulator of this system (Braver & Cohen, 2000; Cohen & Servan-Schreiber, 1992; Montague, Dayan, & Sejnowski, 1996; Schultz, 1997).

How does this circuitry relate to cognitive control or contribute to the symptoms and behaviors observed in the childhood disorders described previously? Assuming that the direct pathway is involved in facilitating cortically mediated behaviors, then its disruption may result in constantly interrupted behaviors such as those observed in ADHD or constantly interrupted thoughts such as those observed in schizophrenia. In contrast, if the indirect pathway is involved in inhibiting cortically mediated behavior, then its disruption may result in irrepressible repetitive behaviors and thoughts similar to those observed in OCD and Tourette syndrome or in ruminations of hopelessness in depression. Alternatively, neuromodulatory imbalances resulting in hypermetabolic activity in regions of the direct or indirect pathways could lead to problems in cognitive control. For example, overactivity of the direct pathway would lead to irrepressible repetitive behaviors as seen in Tourette syndrome whereas underactivity of this pathway would lead to constantly interrupted behaviors as seen in ADHD.

Thus, our model of cognitive control (Casey, 2000; Casey, Durston, & Fossella, 2001) suggests that the basal ganglia are involved in inhibition of competing inappropriate thoughts and behaviors (Mink, 1996) while the frontal cortex is involved in guiding these actions by supporting representations of relevant information from interference due to competing information (Cohen & Servan-Schreiber, 1992; Miller & Cohen, 2001). Information is maintained in an active state over time in prefrontal cortex by means of recurrent excitatory connectivity (Cohen & Servan-Schreiber, 1992). The frontal cortex, which consists primarily of excitatory projections (glutamate), is thus involved in maintenance of relevant information for action, and disruption of this brain region results in deficits in the ability to carry out the relevant actions. We hypothesize that the basal ganglia, which consist primarily of inhibitory projections (GABA), are involved in the inhibition of inappropriate competing behaviors, and disruption in the development of this brain region results in deficits in cognitive control.

Thus far, the evidence cited for the involvement of the prefrontal cortex and basal ganglia in cognitive control has been largely based on the clinical neuroimaging literature. However, there is an expansive neuroimaging literature based on studies of healthy adults implicating the frontal lobes in this ability (Cohen et al., 1994; D'Esposito et al., 1995; Duncan & Owen, 2000; Owen, 1997; Smith & Jonides, 1999), particularly when overriding or inhibiting interfering

information (D'Esposito, Postle, Jonides, & Smith, 1999). The basal ganglia (Mentzel et al., 1998; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000) and thalamus (Awh, Smith, & Jonides, 1996; Jonides et al., 1997) also are activated in such studies. More recently, computational models have been developed that specifically include aspects of prefrontal cortex, basal ganglia, and dopamine function (Braver & Cohen, 2000; Miller & Cohen, 2001; O' Frank, Loughry, & O'Reilly, 2001) to constrain theories of cognitive control. Munakata et al. (in press) and Morton and Munakata (2002) in this special issue describe a computational model of prefrontal function and development consistent with our view of the prefrontal cortex in cognitive control. The difference between this model and others is the emphasis on the basal ganglia in discussion of inhibitory mechanisms, as others (e.g., Diamond, 1990, 1998; Iversen & Mishkin, 1970) have emphasized the role of ventral and orbital prefrontal cortex in inhibitory function.

Role of Dopamine in Cognitive Control

The effects of dopamine have been examined in several computational models and are predicted to be essential for the protection of stable representations (Cohen & Servan Schreiber, 1992) as well as in the prediction of reward (Schultz, 1997). The influence of dopamine on cognitive control is further substantiated by psychiatric genetic studies of dopamine-related genes implicated in ADHD, OCD, and schizophrenia. In all cases, the dopamine receptor DRD4, DRD3, and DRD2 genes may differentially affect dopamine function in subcortical regions occupied by basal-ganglia thalamocortical loops. These circuits are thought to be critical for inhibition and attention (Casey, 2000; Casey, Castellanos, et al., 1997; Casey et al., 2001). Genetic variants in the Dopamine Transporter (DAT1) and catechol-O-methyltransferase (COMT)—genes known to contribute to the function of dopamine-producing neurons—may underlie performance in tasks involving cognitive control. Together, these data suggest that optimal levels of dopamine are needed to perform tasks requiring the maintenance of internal representations against interference.

The development of the dopamine system has particular implications for our model as well. In humans, the development of this system is coincident with the postnatal period of rapid synaptogenesis in dendritic spines followed by a slower plateau phase of growth until adolescence (Granger, Tekaia, Le Sourd, Rakic, & Bourgeois, 1995). Golgi staining studies of human cerebral cortex have shown the delayed development of dendritic architecture in the prefrontal cortex (Conel, 1939–1963). There are distinct anatomical domains of dopamine receptor gene expression. The DRD1 receptors are found most prominently in cortical regions while DRD2 receptors predominate in subcortical regions (Szele, Artymyshyn, Molinoff, & Chesselet, 1991) involving the basal ganglia. Thus, behavioral measures that depend more heavily on the activity of cortical networks may be more sensitive to genetic variation in the DRD1 receptors while tasks that show preferential activation of the basal ganglia may be more sensitive to variation in DRD2 gene function.

METHODS

There are at least five lines of converging evidence for our model of cognitive control. This work consists of a collection of clinical, magnetic resonance imaging (MRI)-based morphometry studies, functional MRI studies, and lesion studies. More recently, we have begun to examine the role of genetic variation in individual and development differences in cognitive control. Preliminary evidence from this method is presented as well.

Behavioral Studies

A theoretically driven approach to characterizing cognitive control is to probe inhibition of different types of information and/or at different stages of cognitive processing (stimulus selection, response selection, and response execution). Accordingly, we have developed a battery of tasks that require (a) inhibition of a stimulus set (e.g., distractors versus target), (b) inhibition of a behavioral set (e.g., remapping from one set of responses to a new set of responses), and (c) inhibition of a response altogether (e.g., go/no go task). These tasks (also known as stimulus selection, response selection, and response execution tasks, respectively) are described in detail elsewhere (see Casey, Castellanos et al., 1997; Casey, 2000; Casey, Durston & Fossella, 2001; Casey, Vauss & Swedo, 1994).

Data on these cognitive tasks have been collected on 108 healthy children (Casey et al., 2001) and plotted in Figures 2 and 3. Notice the improvement in performance up to 12 years consistent with the literature reviewed. In addition, 50 children with developmental disorders including children with Tourette Syndrome, ADHD (Casey, Castellanos et al., 1997), childhood-onset schizophrenia, and Sydenham's chorea (Casey, Vauss, Chused, & Swedo, 1994; Casey, Vauss, & Swedo, 1994; Swedo et al., 1993)

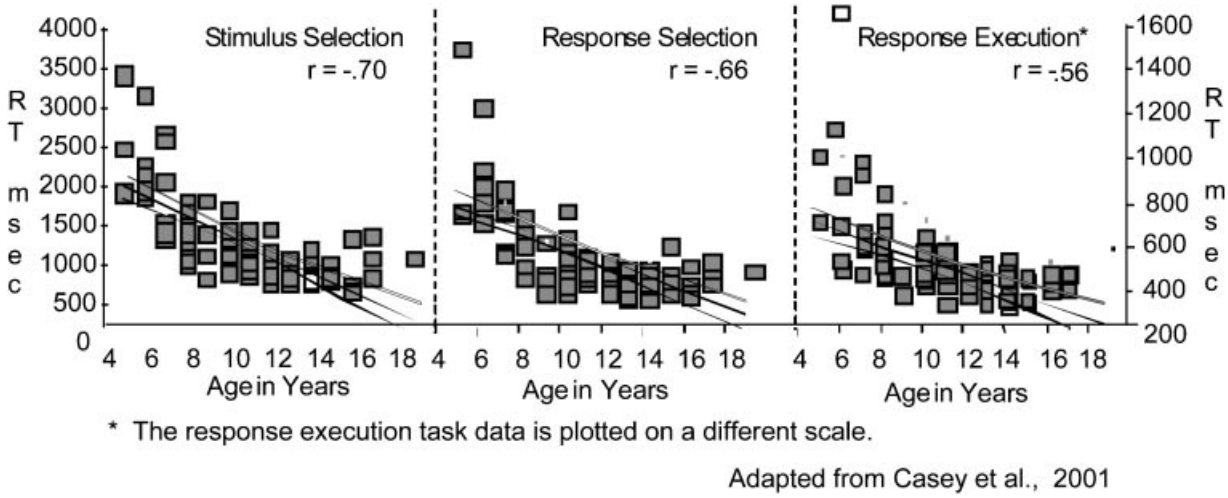

FIGURE 2 Mean reaction times on the stimulus-selection, response-selection, and response-execution tasks for healthy children between 4 and 18 years.

have been tested on this battery of tasks. Sydenham's chorea is an especially interesting disorder for testing our hypothesis of basal ganglia involvement in cognitive control because of the vulnerability of this region in the disorder. Sydenham's chorea is a known variant of rheumatic fever and follows streptococcal infection. Antibodies cross react with the host tissue. In cases of rheumatic fever, the heart is the primary focus of this reaction, but in Sydenham's chorea, portions of the basal ganglia also are involved. These children present with flailing movements of the limbs and with psychiatric symptomatology that often precedes the flailing movements. Approximately 75% of these children present with obsessive-compulsive symptomatology (Swedo et al., 1993), thus we have used this disorder as a medical model of obsessive-compulsive disorder as well as to test our hypothesis of the contribution of the basal ganglia in cognitive control. All of these disorders (Sydenham's chorea, ADHD, Tourette syndrome, and childhood-onset schizophrenia) were assumed to have a deficit in suppressing different types of information and behaviors given the distinct symptomatology across the disorders.

Figure 4 shows data from approximately 50 children with four different developmental disorders. To condense a number of studies into a single summary figure, the findings are reported as percent differences in reaction time (the left panel) and errors (right panel) from matched controls. The asterisks indicate a significant difference between the patient group and matched controls in the raw data rather

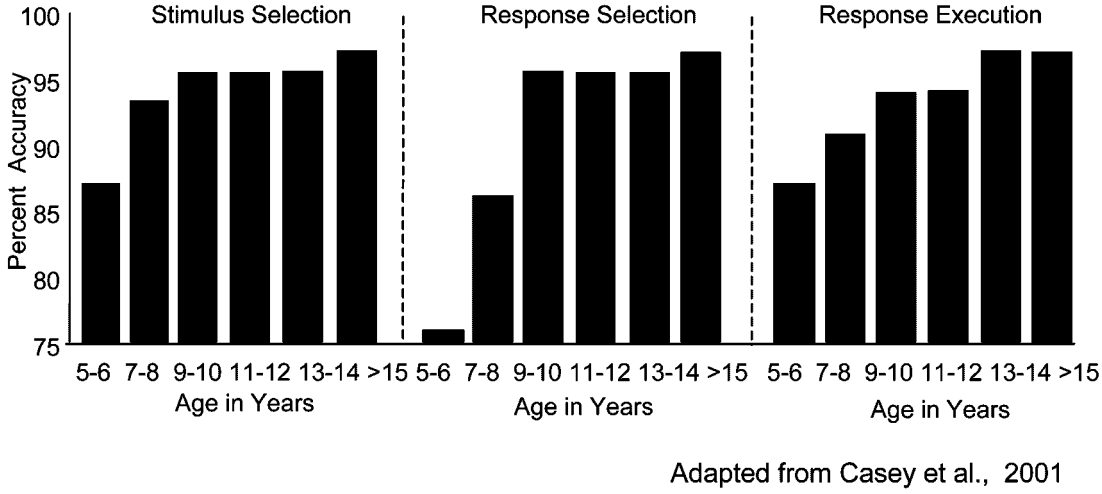

FIGURE 3 Mean accuracy rates on the stimulus-selection, response-selection, and response-execution tasks for children between 4 and 18 years.

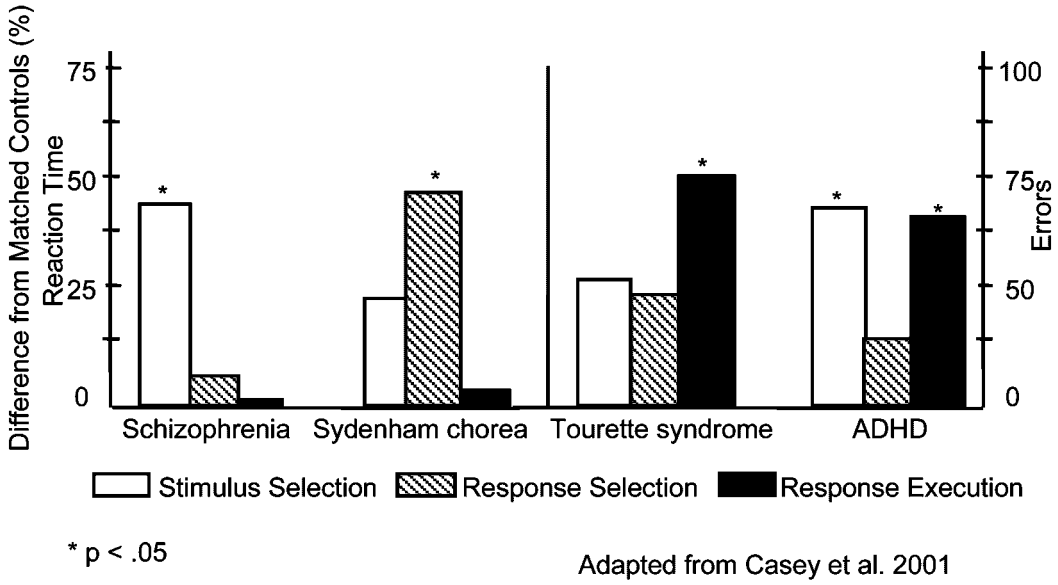

FIGURE 4 Percent difference in mean reaction times and error rates on the stimulus-selection, response-selection, and response-execution tasks for children with schizophrenia, Sydenham's chorea, Tourette syndrome, and ADHD relative to matched controls. Asterisks indicate significant differences between patients and controls in the raw data.

than the percent scores that are provided. First, data from 7 unmedicated adolescent schizophrenic patients, 11 to 16 years of age, showed deficits in performance of the stimulus selection task (mean reaction times of 1,048 vs. 697 ms, $p < .02$), but not the response selection or execution tasks relative to matched controls. Second, data from 10 unmedicated Sydenham's chorea patients, 7 to 15 years of age, showed deficits in performance on the response selection task (mean reaction times of 977 vs. 848 ms, $p < .05$), but not the stimulus selection or response execution tasks (Casey, Vauss & Swedo, 1994). Seven unmedicated children with Tourette syndrome, 7 to 13 years of age, showed deficits in performance on the response execution task ($p < .01$), but not the response selection or stimulus selection tasks. Finally, data from 26 unmedicated ADHD patients, 6 to 16 years of age, showed poorer performance in overall error rate on the stimulus selection ($p < .05$) and response execution tasks ($p < .01$), but not the response selection task relative to matched controls. In sum, the data show a four-way dissociation in the pattern of performance on these tasks: (a) The schizophrenic patients show deficits on the stimulus-selection task, (b) Sydenham's chorea patients show deficits on the response-selection task, (c) children with Tourette syndrome show deficits on the response-execution task, and (d) children with ADHD show deficits on both the stimulus-selection and response-execution tasks. The pattern of performance for the children with ADHD fits with the distractibility and impulsivity observed in this disorder.

These data fit with anatomical and clinical data implicating the involvement of different parallel basal ganglia thalamocortical circuits with distinct clinical disorders (Alexander, Crutcher, & DeLong, 1991). Thus, these three tasks may be used to assess the integrity of basal ganglia thalamocortical circuits, specifically the two association circuits (dorsolateral and lateral orbital) and the limbic circuit in different developmental populations.

MRI-Based Anatomical Studies

The previously reported behavioral findings suggest that our battery of cognitive tasks may map onto distinct frontostriatal circuits. In an effort to examine this relation more directly, anatomical correlates of cognitive control as measured by our three cognitive tasks were examined using MRI. The article by Kennedy, Makris, Herbert, Tsutomot & Caviness (in press) in the special issue on imaging in *Developmental Science* describes this methodology and its basis. Based on a sample of 25 children with ADHD and 25 age- and sex-matched controls, task performance correlated only with MRI-based anatomical measures observed to be abnormal in ADHD (Castellanos et al., 1996). Specifically, size and asymmetry of the right prefrontal cortex, caudate nuclei, and globus pallidum correlated with task performance,

but not other areas (e.g., putamen) (Casey, Castellanos, et al., 1997). For significant correlations, tests for parallelism in slopes between groups were performed. The groups differed in slope for the stimulus-selection and response-execution tasks, but not the response-selection task. The behavioral and anatomical measures typically correlated for the normal volunteers. In contrast, behavioral data from the children with ADHD typically did not correlate with anatomical measures or were in the opposite direction. These results imply that deficits in cognitive control observed in ADHD may be due to abnormalities of the basal ganglia and related frontostriatal circuitry. These correlational data indicate the ability of our cognitive tasks to assess the integrity of frontostriatal circuitry, but more importantly, support the hypo-thesis of the role of these regions in cognitive control.

Functional MRI Studies

Until recently, the use of functional neuroimaging techniques in developmental studies has been limited, primarily due to their reliance on harmful radiation and the vulnerability of developmental populations to such exposure. Within the past 10 years, a noninvasive neuroimaging technique, functional MRI (fMRI), has been developed to examine brain state changes based on changes in blood oxygenation. Perhaps one of the most important contributions of fMRI is its utility in studying human brain development in vivo. This methodology is central to work on the functional circuitry underlying cognitive control and described in the current issue of *Developmental Science* on imaging methods in developmental populations (see Casey, Davidson & Rosen in press).

We have recently completed a number of studies with healthy children (Casey et al., 1995; Casey, Trainor, Orendi, et al., 1997; Thomas et al., 1999). In one such study, prefrontal activity was examined during the performance of the previously described response execution task (i.e., go/no go task) that was modified for the scanner environment (Casey, Trainor, Orendi, et al., 1997). In this version of the task, participants were instructed to respond to any letter but X. Letters were presented at a rate of one every 1.5 s, and 75% of the trials were target trials to build up a compelling tendency to respond. We hypothesized that performance of the response-execution task would activate brain regions of the limbic basal ganglia thalamocortical circuit involved in avoiding or suppressing a response. This prediction was based on our previous behavioral findings summarized in Figure 4 together with evidence from other animal, clinical, and neuroimaging studies.

Based on the results from 18 participants between the ages of 7 and 24 years (9 adults and 9 children), we found that only activity in the orbitofrontal cortex and right anterior cingulate cortex correlated with behavioral performance ($p < .009$ and $p < .05$, respectively) (Figure 5). In addition, we observed significantly more errors and more overall prefrontal activity ($p < .001$) for children (490 mm^3) relative to adults (182 mm^3). This difference in overall prefrontal activity appeared to be specific to the dorsolateral prefrontal cortex, with children activating this region significantly more than adults ($p < .001$). The greater dorsal prefrontal activity may be due to differences in strategies between groups to perform the task. For example, the adults may have realized that simply remembering conditions specific to avoiding a response (i.e., to not respond to the X) was sufficient to complete the task. According to our working model of cognitive control, maintaining information about when to approach or avoid an event involves the limbic basal ganglia thalamocortical circuit, and thus medial orbitofrontal cortex would be the expected site of activity. Children, on the other hand, may have tried to remember when to approach and avoid a response as well as remember the entire stimulus target set (A–Z, excluding X). According to our model, maintenance of the stimulus set would involve the dorsolateral prefrontal circuit, and maintenance of when to avoid an event would involve the limbic circuit; thus, both dorsolateral and medial orbitofrontal activity would be expected. Alternatively, the activation of both orbital and dorsolateral regions in children may suggest an increased selectivity in representation of the prefrontal cortex with maturation. These interpretations are not mutually exclusive. Nonetheless, consistent with our hypothesis, activity of the limbic circuit (anterior cingulate and orbitofrontal cortex) was observed and directly related to our hypothesis of frontal lobe involvement in cognitive control.

Lesion Studies

How and when does disruption in the development of basal ganglia thalamocortical circuitry predispose a child to developmental disabilities? What are the effects of disruption in the development of this circuitry? For example, perinatal asphyxia during premature births is commonly associated with a hemorrhage in the region of the basal ganglia. The most metabolically active brain regions are most vulnerable to hemorrhage. In the preterm infant, this region is the germinal matrix, an area within the ventricular wall and adjacent brain regions such as the caudate nuclei

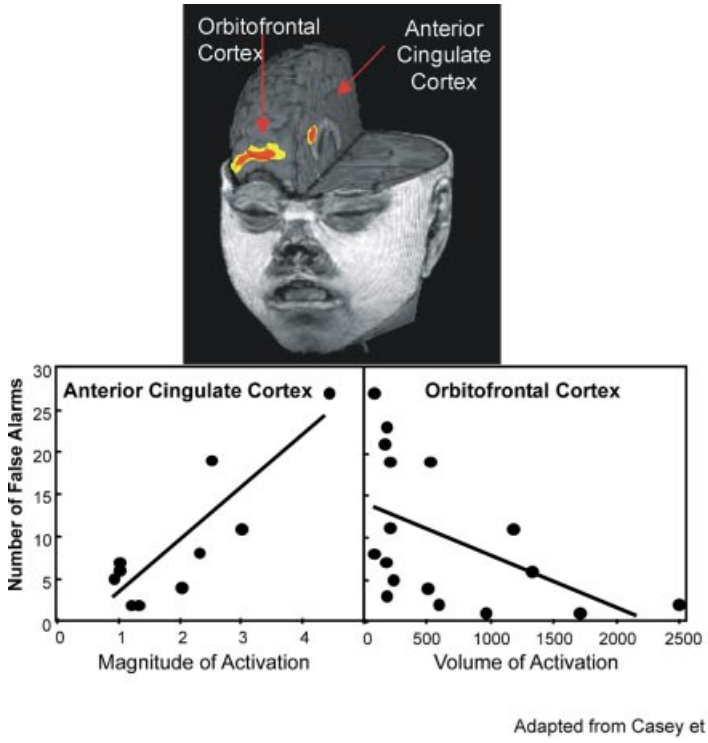

FIGURE 5 Correlations between number of false alarms on a go/no go task and fMRI-based brain activity in the anterior cingulate cortex and orbitofrontal cortex (adapted from Casey, Trainor, Orendi et al., 1997).

(i.e., basal ganglia). This population of premature children is an important one due to the continuing increase in their survival rate with advances in modern medical technology and because they are particularly susceptible to intracranial hemorrhage, especially in the region of the basal ganglia (Volpe, 1995).

We recently initiated a study to methodically investigate the long-term effects of mild to severe intraventricular hemorrhage (IVH) on cognitive and brain development. An article by Moses and Stiles (2002) in a special issue of *Developmental Science* addresses important issues for lesion studies of developing populations relative to adults. The objective of this study was to characterize the structural and functional effects of neonatal intraventricular hemorrhage in a systematic manner in comparison to unaffected, matched controls. The behavioral and imaging data follow from 17 of a cohort of 39 children between the ages of 6 and 9 years with histories of IVH of grade II or higher who have been tested on our three cognitive tasks. We compared their data to a subset of the previously reported data from our children with ADHD and their matched controls within the same age range. The average age for each group was 7.2 ($n = 17$), 7.8 ($n = 13$), and 7.4 ($n = 13$) years for the IVH, ADHD, and control groups, respectively. The results on the three cognitive tasks are summarized in Figure 6. The data are presented as percent differences in errors from the healthy control subjects. The patterns of errors made by the children with IVH are very similar

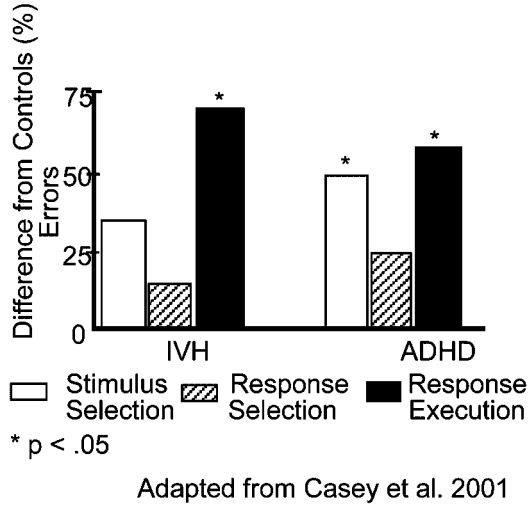

FIGURE 6 Percent difference in mean error rates on the stimulus-selection, response-selection, and response-execution tasks for children with IVH and ADHD relative to matched controls. Asterisks indicate significant differences between patients and controls.

to those observed for our sample of children with ADHD and even more similar to those reported previously for children with Tourette syndrome (refer to Figure 4). Specifically, the children with IVH performed worst on the stimulus-selection and response-execution tasks, but only performance on the response-execution task was significantly different from performance of healthy volunteers.

It is perhaps not surprising that our sample of children with IVH is similar to children with ADHD and tic disorders in their behavioral performance given the results of structured clinical interviews. Roughly 20% have a psychiatric diagnosis of ADHD (four times that of the general population), and there appears to be an increased risk for tic disorder and anxiety disorder. Males were more likely than females to have a disorder. These data are consistent with findings published by Whitaker et al. (1997) of children with neonatal insults. According to that study, 22% of children with neonatal insults had at least one psychiatric disorder, the most common being ADHD. An increased risk for tic disorders and anxiety disorders also was observed. No effort was made to acquire MRIs on the children in the Whitaker et al. study; rather, the study relied upon clinical classification of the insult from ultrasound data, which was nonetheless predictive of children at risk for behavioral problems.

We have quantified affected brain regions in 37 children with IVH using volumetric MRI-based measures of the basal ganglia (Giedd et al., 1996). The preliminary MRI data have revealed an overall 20% decrease in the size of the caudate nuclei in children with IVH of grade II or higher when compared to Matched Control 7 after controlling for total cranium volume, $F = 13.01$, $p < .01$. Figure 7 illustrates how the ventricles are clearly distended and the caudate nucleus (traced in white) is smaller in the case of the child with IVH of grades III and IV relative to an age-matched control. This pattern holds true for less severe grades of IVH, but for those cases, quantification is needed to see any significant decrease.

We have acquired functional brain imaging data on 17 of our 37 children with IVH during performance of the response-execution task (go/no go task). The mean error rate during performance of this task was 39% compared to 27% ($p < .05$) for our original sample of healthy children (Casey, Trainor & Orendi et al., 1997). In our previous study, we observed that activity in the orbitofrontal cortex negatively correlated with the number of false alarms ($r = -.41$, $p < .02$). The greater the volume of activity in mm^3 (i.e., number of significant voxels $\times$ voxel size) in the orbital frontal cortex, the fewer the number of false alarms. In our current study, error rate did not correlate with activity in the orbitofrontal gyrus ($r = -.28$) even though more than 70% of the subjects activated this region. Only 35% of our children with IVH had caudate activity. As expected, those children with the higher grades of IVH (II–IV) had little to no activity in this region. These data suggest that even though activity is reliably observed in orbitofrontal cortex, disruption at the level of the basal ganglia is sufficient to disrupt performance on inhibitory tasks. Therefore, these data further support our hypothesis of the role of the basal ganglia in cognitive control.

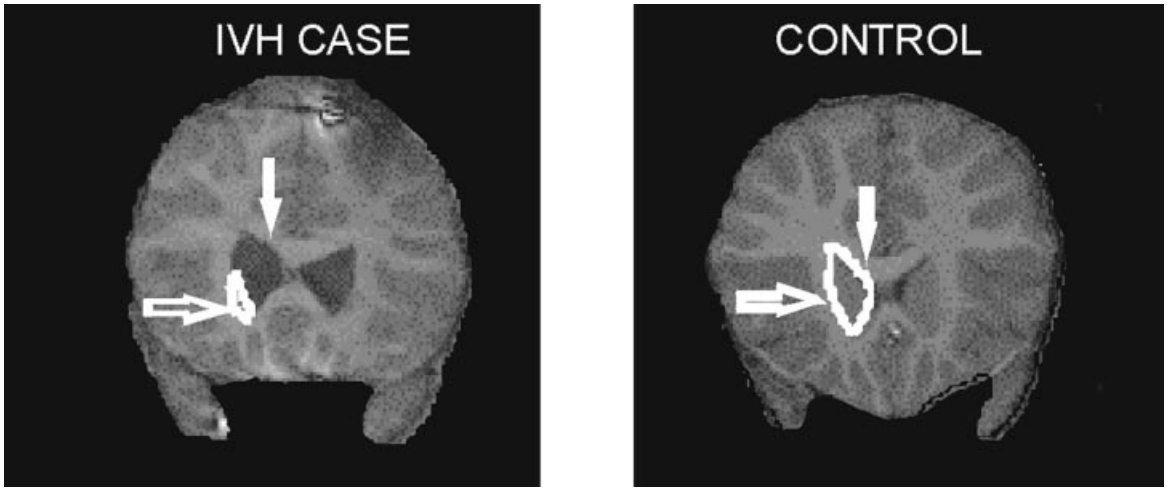

FIGURE 7 Representative MRI coronal slice from 2 preterm children, 1 with IVH of grade III and IV (left) and one without (right). The caudate nucleus is outlined in white for each subject. Note how the ventricles are distended at the expense of the caudate nucleus for the child with IVH.

Overall, the behavioral, clinical, and neuroimaging data from our children with IVH are consistent with our hypothesis of disruption in inhibitory control at the level of the basal ganglia. First, these children perform poorly on tasks that require them to suppress a compelling response (e.g., response-execution tasks). Second, these children are at greater risk of developing disorders with known inhibitory deficits (e.g., ADHD and tic disorders). Third, MRI-based morphometry measures show decreased volume of the basal ganglia, specifically the caudate nucleus, in children with IVH compared to age-matched controls. Fourth, fMRI results showed little to no activity in the caudate nucleus in children with IVH of grade II or higher, and while activity was reliably observed in prefrontal cortex (e.g., orbitofrontal cortex), it was not correlated with behavioral performance. In sum, disruption of the basal ganglia thalamocortical circuits at the level of the basal ganglia appears sufficient to disrupt cognitive control.

Genetic Studies

Optimal levels of dopamine are assumed to be needed to perform tasks requiring the maintenance of internal representations against interference. Variation in genes known to contribute to the function of dopaminergic signaling may underlie performance in tasks involving this ability. Accordingly, we have begun to examine the relation between variation in dopamine-related genes and measures of cognitive control.

For the purposes of this article, we selected four candidate genes. These genes were selected because they are involved in dopamine function, have been implicated in childhood disorders that involve disruption in cognitive control, and specific variants in these genes are fairly common in their occurrence in the general population. First, the dopamine D4 receptor gene (DRD4), located on chromosome 11p15, was selected since it has received the most attention in the literature because of its replicated association with ADHD (LaHoste et al., 1996; Smalley et al., 1998; Sunohara et al., 2000; Swanson et al., 2001; Swanson et al., 1998). The most well-studied DRD4 polymorphism is a 48 base-pair variable nucleotide tandem repeat (VNTR) in exon III affecting the size of the third intracellular loop of the receptor. This cytoplasmic loop is involved in G-protein coupling and mediation of postsynaptic dopaminergic signal transduction. In addition to the DRD4, the dopamine transporter gene (DAT1) located on chromosome 5p15.3 also was selected as a candidate. The most well-studied DAT polymorphism is a repeat in the 3′ untranslated region of the DAT gene (Mitchell et al., 2000) that may affect protein expression levels. The third candidate gene we selected was the catechol-O-methyltransferase (COMT) gene (22q11), which catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, adrenaline, and noradrenaline. This O-methylation leads to the degradation and clearance of these catecholamines. The most widely used polymorphism in COMT was identified by Lachman et al. (1996), who found a G-to-A change at codons 108 and 158 of the COMT gene, resulting in a valine-to-methionine substitution which accounts for a three- to fourfold difference in COMT activity in red blood cells and the liver. Recently, Weinberger and colleagues (Egan et al., 2001) found that the COMT genotype was related to performance on the Wisconsin Card Sorting Test and explained 4% of variance ($p = 0.001$) in frequency of perseverative errors. In addition, those with the Met108 alleles showed less prefrontal activity, as measured by fMRI, when performing normally on a working memory task. Interestingly, the Val108 allele was shown to be preferentially transmitted to ADHD probands and was associated with impulsive false-alarm errors on a continuous performance task (Eisenberg et al., 1999). The fourth candidate gene we selected was the SNAP-25 gene. This gene codes for a synaptic vesicle protein and was originally identified via a mutant strain of hyperactive mice. Further, Barr (2001) reported the increased transmission of the *Dde*-C allele to ADHD probands.

We have begun to examine the relation between this variation in dopaminergic genes and measures of cognitive control in terms of both overriding behavioral and attentional responses (e.g., go/no go and flanker tasks). Similarly, we have begun to relate these genetic measures with MRI-based measures of the basal ganglia. Our preliminary results are tantalizing, yet in no way are definitive given our small sample sizes.

The behavioral results are based on the performance of two tasks very similar to our stimulus-selection and response-execution tasks. They are the go/no go task described earlier and a flanker task (Casey et al., 2000; Eriksen & Eriksen, 1974). In the flanker task, subjects are presented with arrows that point to the left ($<$) or right ($>$) displayed in the center of a screen. Compatible and incompatible flankers are presented on either side of the target stimulus (e.g., $<<<$ or $>><>$). Subjects are instructed to press the left key if the center stimulus is pointing left ($<$) and the right key if the center stimulus is pointing right ($>$). Both the go/no go and flanker tasks used in this study consist of parametric

manipulations that have been developed to vary the salience of the interfering and irrelevant information (Casey et al., 2001; Casey et al., 2000; Durston et al., (in press)). The current versions of our tasks allow for comparisons of no go trials to one another that differ in the preceding context (one, three, or five preceding targets). In the flanker task, an incompatible trial is preceded by either one, three, or five compatible flanker trials. These task parameter manipulations result in longer reaction times and lower accuracy for the subject as a function of increasing number of preceding targets or compatible trials (Casey et al., 2001; Casey et al., 2000; Durston et al., (in press)), presumably because of the salience of the information or action to be inhibited.

We have examined performance on these tasks in 20 children (6 to 11 years) in relation to four candidate genes (DRD4, DAT1, COMT, and SNAP-25). The mean accuracy for each group (i.e., children with homozygous allele1/allele1, hetereozygous allele1/allele2, or homozygous allele2/allele2) is plotted for both the go/no go and flanker tasks for each genetic variant in Figure 8. In addition to relating these genetic variants to task performance, we also examined their frequency of occurrence in a small sample of 6 children with ADHD. Our results are as follows. First, in our sample, 40% of the ADHD subjects carry a DRD4 7-repeat allele. This bias over the population-wide frequency (0.12) is consistent with previous associations of the 7-repeat allele in ADHD. Second, in our sample, a bias in the frequency of the DAT1 9-repeat allele was observed among ADHD subjects (0.60), which exceeds the population-wide frequency (0.23). Neither of these genetic variants appeared specific to performance on the go/no go or flanker tasks; however, variation in the COMT and SNAP-25 genes did appear related. First, while the frequency of the Met108 allele in our sample was not different from the population-wide frequency, those subjects with the Met108 allele showed more accurate performance on the two cognitive control tasks relative to those subjects without the Met108 allele. This is consistent with evidence that the low activity (Met108) variant of this catabolic enzyme confers cognitive benefits. A similar phenomenon also was observed for a polymorphism in the SNAP-25 gene. This gene codes for a synaptic vesicle protein and was originally identified via a mutant strain of hyperactive mice. Barr and colleagues (2000) reported the increased transmission of the *Dde*-C allele to ADHD probands. Interestingly, as shown in Figure 8, subjects homozygous for this allele showed lower accuracy than those subjects that carry the alternate *Dde*-T allele.

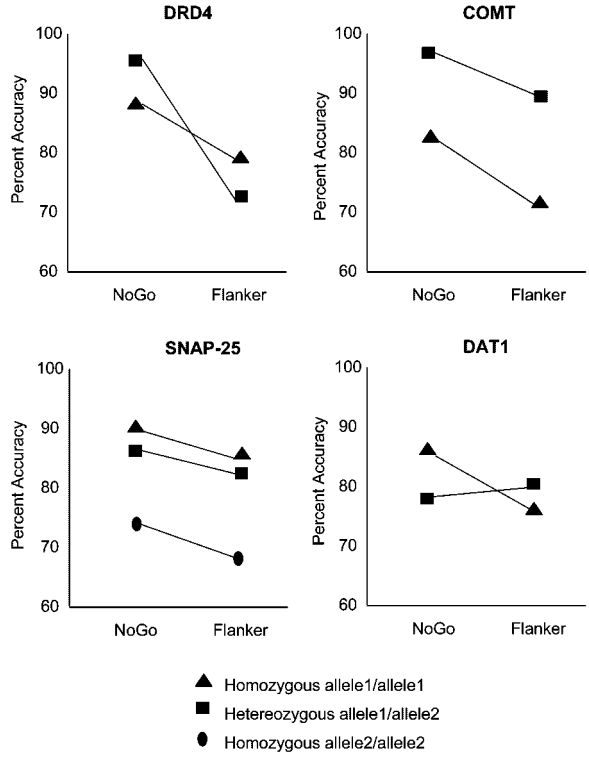

FIGURE 8 The mean accuracy for the go/no go and flanker tasks for each sample of children with either homozygous allele1/allele1, hetereozygous allele1/allele2, or homozygous allele2/allele2 in the dopamine-related genes of DRD4 (allele 1 = exon III 4-repeat, allele 2 = exon III 7-repeat) DAT1 (allele 1 = 10-repeat, allele 2 = 9-repeat), COMT (allele 1 = Val108, allele 2 = Met108), and SNAP-25 (allele 1 = DdeI "T," allele 2 = DdeI "C").

As described earlier, brain imaging studies reveal anatomical abnormalities in the right frontal lobe and caudate nucleus where dopamine receptors are highly expressed in ADHD (Castellanos et al., 1996). It is interesting to consider whether the genetic form of ADHD, and in particular, variation in catecholaminergic genes, is related to these morphometric findings. Such evidence would shed light on the specific effects of genes that are otherwise expressed widely throughout the brain. Anatomical studies in rodents, nonhuman primates, and humans have established that genes are major determinants of overall brain size (Cheverud et al., 1990; Finlay & Darlington, 1995). Most notably are studies on whole brain volume in monozygotic and dizygotic twin populations that show that individual variation in brain structure is highly heritable ($h^2 = 0.9$) (Bartley, Jones, & Weinberger, 1997). Thus, there is sufficient evidence to suggest that variation in catecholaminergic genes may underlie differences in brain structure. Accordingly, an ad hoc molecular genetic analysis was performed to

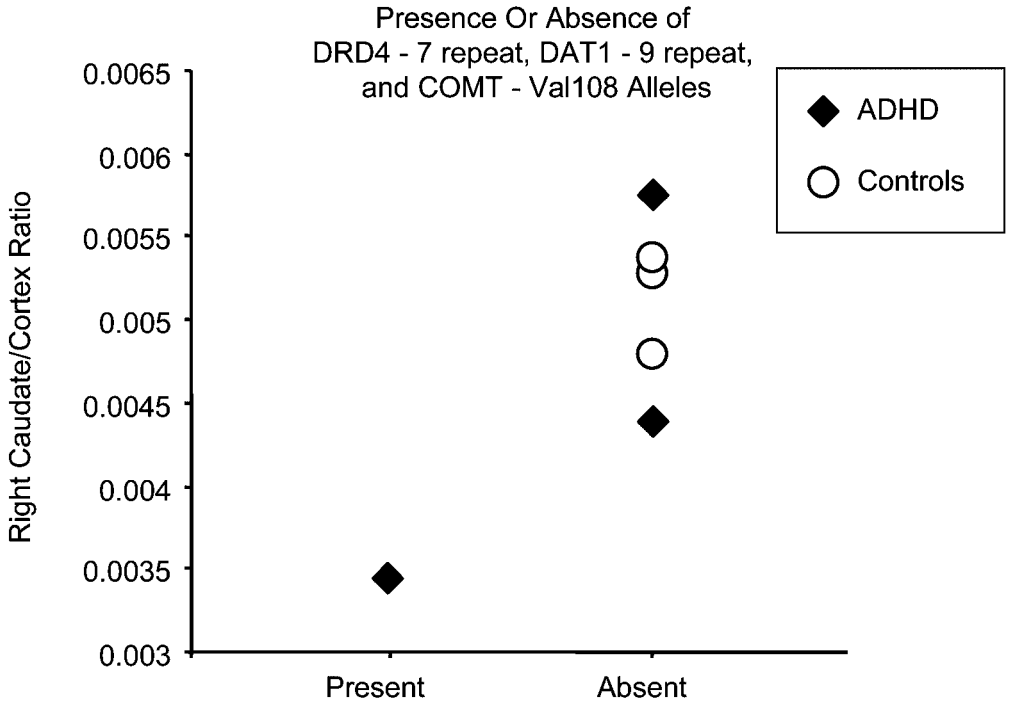

FIGURE 9 Ratio of caudate volume to cortex volume for a child with ADHD and variants in the DRD4, DAT1, and SNAP-25 genes relative to other ADHD and healthy age- and sex-matched children without these genetic variants.

evaluate the relationship between polymorphisms in catecholaminergic genes and basal ganglia volume. MRI-based morphometric data were collected on a small subset of children (mean age of 10 years), 3 with ADHD and 3 without. In this study, 1 subject showed a significantly smaller caudate volume (Figure 9). This subject carries the less common 9-repeat of the DAT1 allele, two copies of the high activity Val108 allele of the COMT gene, and the DRD4 7-repeat allele. All three of these alleles have been associated with ADHD.

In sum, due to the extremely small sample, we can make no definitive claims about genetic associations to these behavioral or imaging results. However, we can say that our data are fairly consistent with the candidate gene literature on ADHD and consistent with our notion that variants in dopamine-related genes may explain individual variability and pathology in overriding inappropriate behavioral and attentional responses.

CONCLUSIONS

This article presents a mechanistic model of cognitive control whereby the basal ganglia are involved in suppression of irrelevant actions while the frontal cortex is involved in representing and maintaining relevant information and conditions to which we respond or act. Developmentally, we propose that the ability to support information against information from competing sources increases with age, thereby facilitating cognitive control, and is the result of development within basal ganglia thalamocortical loops. Relevant projections from the prefrontal cortex to the basal ganglia are enhanced while irrelevant projections are eliminated, and these connections are reinforced with dopamine-related activity. This organization continues throughout childhood and adolescence as evidenced by the prolonged development of prefrontal regions in synapse elimination and myelination and by the maturation of the dopamine system.

More generally, we have taken the position that the basal ganglia thalamocortical circuits underlie cognitive control and that cognitive deficits observed across a range of developmental disorders reflect a disruption in the development of these circuits. Five lines of converging evidence for our model were presented including data from cognitive measures, MRI- based morphometry, functional MRI, lesion, and genetic studies. First, we reported that children with developmental disorders involving the basal ganglia and the prefrontal cortex perform poorly on tasks requiring

suppression of attention toward a salient stimulus or a competing response choice. Further, a dissociation in the pattern of performance on these tasks for each of four disorders was observed, implying the involvement of different basal ganglia thalamocortical circuits for each disorder. Second, MRI-based morphometry measures of the frontal cortex and basal ganglia correlated with performance on cognitive tasks, indirectly supporting our structure-function hypotheses. Third, a more direct line of evidence for the involvement of the prefrontal cortex in cognitive control was presented based on a functional MRI study. Fourth, behavioral, morphometry, and fMRI results from our children with neonatal basal ganglia insults showed deficits in cognitive control and a four- to fivefold increase in developmental disorders with cognitive control problems (ADHD and tic disorders). Finally, variants in dopamine-related genes were shown to be related to individual variation in cognitive control measures and the disruption of this ability in disorders such as ADHD.

NOTES

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