CHAPTER

39

Disorders of Cognitive Control

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OUTLINE

39.1 INTRODUCTION

A core feature of several neurodevelopmental disorders is the difficulty in overriding or suppressing inappropriate thoughts and behaviors in favor of appropriate ones. This ability is referred to as cognitive control. Examples of disorders of cognitive control include attention deficit hyperactivity disorder (ADHD), which is characterized by both distractibility and impulsivity; Tourette syndrome, which is characterized by difficulty suppressing repetitive movements and vocalizations that may be complex, emotionally provocative, and exacerbated by stressful situations; obsessive–compulsive disorder (OCD), which is characterized by intrusive thoughts and ritualistic behaviors; and schizophrenia, which involves disorganized thoughts, delusions, or hallucinations and difficulty suppressing them. Cognitive control problems are found in a range of disabilities with limited ability to regulate attention, thought, behavior, or emotions. The number of disorders with cognitive control problems underscores the need for a clearer understanding of the development and neurobiological bases of cognitive control.

Most theoretical and neuroanatomical accounts of cognitive control have focused on the role of the prefrontal cortex in this ability. This focus is based largely on the protracted development of the prefrontal cortex that coincides with cognitive maturity and the neuropsychological literature showing that frontal lobe damage impairs the ability to regulate behavior and suppress inappropriate thoughts or actions (e.g., Phineas Gage, as cited in Harlow, 1869). Although the approach has been important in describing problems in cognitive control, it has not captured the biological basis of how behavior is regulated or how it breaks down in disorders of cognitive control.

This chapter integrates findings on the neurobiological basis of disorders of cognitive control, highlighting the role of cortical and subcortical brain regions in signaling and implementing control. At first glance, the involvement of a number of the same brain regions across many disorders would seem too disparate to be informative. However, considering these findings in the context of cognitive control theory and development paints a clearer picture of each region's contribution to the regulation of behavior and potential disruption in different developmental disorders.

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39.2 DEVELOPMENT OF COGNITIVE CONTROL

A key feature of cognitive development is a steady increase in the ability to suppress irrelevant information and inappropriate actions in favor of appropriate ones. This ability becomes more efficient throughout childhood and adolescence. Failure to develop this ability results in cognition that is susceptible to interference from competing external or internal information without resolution.

A classic example of the child's developing ability to resolve behavioral conflict is demonstrated by the Piagetian A-not-B task. In this task, the child reaches for a hidden toy in one location (a covered well) and is then required to find the hidden toy in a new location. The infant continues to reach in the old well even though the toy is hidden in full view of the infant and even though the child may look in the correct new direction. This failure has been interpreted as reflecting inhibitory inefficiency rather than a lack of object permanence, as originally proposed by Piaget (Diamond, 1988). As such, obtaining the goal of reaching and finding the toy in the original location biases motor systems in that direction that compete with the new goal and the means to reach in the new opposing direction. Development of the prefrontal cortex has been implicated in the development of this goal-directed behavior.

The development of the ability to override inappropriate actions in favor of appropriate ones has a protracted course of development. In older children, this ability is measured by developmentally appropriate versions of adult neuropsychological tasks including go/no-go, working memory, and attention-switching tasks. In all cases, children have a more difficult time ignoring or suppressing irrelevant salient information or responses in favor of the relevant ones than adults. Performance on these tasks shows a developmental trend over the ages of 4–12 years, approximating adult levels by 12–13 years of age, as indexed by mean reaction times and accuracy rates (Enns and Cameron, 1987).

The age-related differences in performance of cognitive tasks are not observed on tasks in the absence of competing information. For example, tasks that measure the ability to detect and predict statistical regularities in the environment are mastered by infancy (Saffran et al., 1996). This ability is indicated by anticipatory saccades in the direction of the expected stimulus or by a longer duration of looking in the direction of an expected stimulus, when it is not presented (violation in expectation). Learning about one's environment is essential for adaptive functioning, as well as for the development of neural specialization and regulatory ability during toddler, childhood, and adolescent years. Knowing when or what or in which context to expect an event is critical for planning and maintaining appropriate actions in different contexts over time. Adjusting behavior when these expectations are violated is an essential element of cognitive control and an aspect of cognition that shows more protracted development (Mayr et al., 2005).

If this ability develops differently, or along a different trajectory, it may contribute to difficulties in the maturation of self-control abilities (or the concomitant neural systems in which these abilities are instantiated). Thus, with development, these cognitive systems become more differentiated as they are modulated both by experience and by the top-down cortical projections from the prefrontal cortex that help the organism alter behavior when these predictions are violated (Casey, 2005; Casey et al., 2006).

39.3 BRAIN DEVELOPMENT AND COGNITIVE CONTROL

A significant amount of brain development occurs *in utero*, but changes continue postnatally. These postnatal changes coincide with changes in cognitive control. This period is characterized by rapid synapse formation that begins well before birth in nonhuman primates (Rakic, 1974) and results in overproduction of synapses relative to its adult state. This process of synaptogenesis appears to occur concurrently across diverse regions of the nonhuman primate cerebral cortex (Rakic et al., 1986). In both human and nonhuman primate studies, the early synaptic density peaks are followed by a plateau phase that decreases during childhood and into adulthood. The plateau and pruning phases of some cortical regions (e.g., prefrontal cortex) in primates are relatively protracted in comparison to others (e.g., sensorimotor and subcortical regions; Bourgeois et al., 1994; Huttenlocher and Dabholkar, 1997). Positron emission tomography (PET) studies of glucose metabolism suggest that maturation of local metabolic rates parallel the time course of overproduction and subsequent pruning of synapses (Chugani et al., 1987). These studies imply different time courses in regional brain development.

Magnetic resonance imaging (MRI) technologies have introduced a new set of tools for capturing features of brain development in living, developing humans. MRI is particularly well suited to the study of children, as it provides exquisitely accurate anatomical images without the use of ionizing radiation. However, these methods lack the resolution to definitively characterize the mechanism of change with development (e.g., dendritic arborization, synaptic pruning, and myelination). The most informative studies to date are those based on volumetric measures and large sample sizes (Giedd et al., 1999a; Sowell et al., 2003). These studies have yielded three consistent findings. First, total cerebral

volume shows little significant change after 6 years of age. Second, there is a significant decrease in cortical gray matter by approximately 12 years of age in prefrontal and association cortices that is preceded by earlier maturing cortical development in sensorimotor regions. Finally, there is an increase in cerebral white matter throughout childhood and young adulthood, especially in prefrontal white matter tracts (Klingberg et al., 1999).

The protracted development of prefrontal and association cortices, along with white matter fiber tract development in this circuitry, contributes to children's developing capacity for cognitive control, as shown by diffusion tensor imaging (DTI). DTI is a measure sensitive to myelination and neuroanatomical changes in white matter microstructure (Liston et al., 2006). Further, variability in the myelination and regularity of prefrontal white matter fibers contribute to individual differences in cognitive control and have been linked to disorders of cognitive control such as ADHD (Casey et al., 2007a).

To investigate neural circuits underlying disruption of cognitive control in developmental disorders more directly, an *in vivo* assessment of the physiological time-course of behavior is needed. Functional magnetic resonance imaging (fMRI) provides this ability (Logothetis et al., 2001). These studies show that children recruit distinct but often larger, more diffuse brain regions when performing cognitive control tasks than do adults. The pattern of activity within brain regions central to cognitive control performance, such as prefrontal cortex, becomes more focal or fine-tuned, based on cross-sectional (Brown et al., 2005) and longitudinal studies (Durston et al., 2004). This pattern of activity is suggestive of development within, and refinement of, projections to and from the prefrontal cortex with maturation. Recent developmental functional connectivity data (Kelly et al., 2009) are consistent with this observation of diffuse correlations among frontal brain regions in children, whereas adults exhibit more focal connections with distal regions.

39.4 DOPAMINE AND COGNITIVE CONTROL

Structural and functional changes in the brain with development occur together with changes in neurotransmitter systems. For example, significant changes are observed in the dopamine system that innervates prefrontal circuitry. The development of the dopaminergic system parallels the development of performance on cognitive control tasks; postnatal innervation of dopaminergic neurons to cortical and subcortical targets peaks at times coincident with the development of cognitive control. Such age-dependent effects of dopamine have been best studied in humans using delayed response tasks and Piaget's A not B task in typically developing and phenylketonuria (PKU)-affected children (reviewed in Diamond, 1998). The genetic mutation that causes PKU results in decreased levels of tyrosine, a precursor of dopamine, in the central nervous system. In behavioral tasks such as the A not B task, typically developing children show sharp improvements in the first year of life and gradual improvements in age-appropriate versions of the task until age 10; however, in PKU children, the sharp increase in performance is not observed, and only mild improvements occur. In typically developing children, this task is highly dependent on prefrontal cortex activation, a brain area that shows extremely high dopamine turnover, and is thus impaired in PKU children.

In nonhuman primates, the A not B task also shows a sharp increase in performance during the first 6 months of life. Behavioral performance is paralleled by an observed postnatal increase in dopamine levels and in dopamine receptor gene expression (Goldman-Rakic and Brown, 1982; Lidow et al., 1991). An examination of the laminar distribution patterns of tyrosine hydroxylase (TH)-positive processes in prefrontal regions has revealed that a gradual maturation of axons and varicosities occurs up until 2–3 years of age in the monkey (Rosenberg and Lewis, 1995), which is roughly 10–12 years in the human.

In rats with a pharmacologically induced form of PKU, performance is also altered in delayed alternation tasks (Diamond et al., 1994). Neuroanatomical studies in rats have shown that dopaminergic cells in the ventral tegmental area (VTA) and substantia nigra (SN) are fully differentiated and have axons projecting into the prefrontal cortex by embryonic day 16. Only after birth, however, does a dramatic increase in arborization and innervation into deeper cortical layers occur. This postnatal innervation is also paralleled by an increase in dopamine receptor gene expression and in dopamine levels coincident with a postnatal period of rapid synaptogenesis in dendritic spines followed by a slower plateau phase of growth until adolescence (Granger et al., 1995).

Several dopamine-related hypotheses have emerged in an attempt to explain developmental disorders of cognitive control such as ADHD (Swanson et al., 2007) and schizophrenia (Snyder, 1976) based on pharmacological treatments for these disorders. Computational models of dopamine based on animal and human imaging studies suggest that dopamine controls the flow of information from other areas of the brain to the prefrontal cortex in gating and maintaining information (Braver and Cohen, 2000). Both gating and maintenance are important in overriding or suppressing inappropriate thoughts and behaviors in favor of appropriate ones (i.e., cognitive control). Thus, dysfunction in this system can result in dysregulated attention, behavior, and thoughts.

39.5 BRAIN CIRCUITRY IMPLICATED IN COGNITIVE CONTROL

Most functional and developmental studies have focused on the role of the prefrontal cortex in cognitive control. However, both cortical and deep subcortical structures have been implicated in disorders of cognitive control. Considering these findings in the context of development and cognitive control theory may paint a clearer picture of each region's contribution in regulating behavior and its disruption in developmental disorders.

39.5.1 Disorders of Cognitive Control

As depicted in Figure 39.1, clinical neuroimaging studies have identified several brain regions that appear to be altered in childhood disorders of cognitive control. These regions include the prefrontal cortex, anterior cingulate cortex, posterior parietal cortex, basal ganglia, and cerebellum. Abnormalities in these structures have been reported in ADHD (Bush et al., 1999; Castellanos et al., 1996; Durston et al., 2003; Tamm et al., 2006), Tourette syndrome (Leckman et al., 2010), OCD (Baxter et al., 1988; Fitzgerald et al., 2005; Swedo et al., 1992), and childhood-onset and adult schizophrenia (Carter et al., 2001; Frazier et al., 1996).

Abnormalities in size, asymmetry, function, or glucose metabolism are typically reported. For example, MRI volumetric studies of ADHD have revealed abnormalities in the size of the prefrontal cortex, basal ganglia, and cerebellum, showing decreased volumes in each. Decreased activity in these regions as well as in the anterior cingulate and parietal cortices during performance of cognitive control tasks has been reported (Bush et al., 1999; Tamm et al., 2006). Activity in these regions, and cognitive control, is largely normalized with stimulant medications (Epstein et al., 2007; Vaidya et al., 1998), presumably due to increases in the availability of dopamine (Volkow et al., 2001).

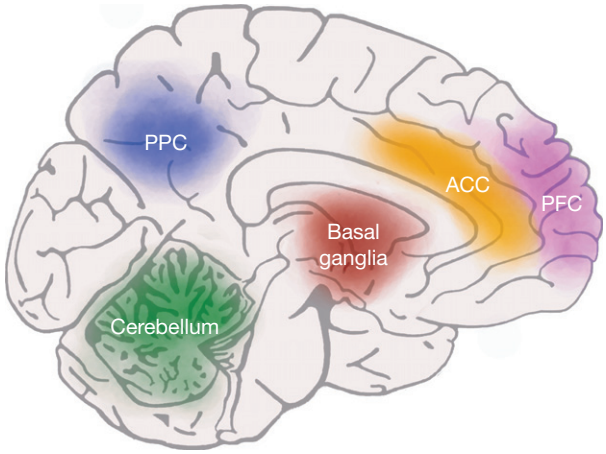

FIGURE 39.1 Brain regions implicated in disorders of cognitive control.

PET studies of OCD have 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). Both pharmacological and behavioral treatments have been shown to normalize these patterns of activity. Abnormalities in the basal ganglia, specifically the striatum, in children with Tourette syndrome have been reported in fMRI studies during provocation of symptoms (Peterson et al., 1998). Structural imaging studies have shown cortical thinning in the frontal and parietal cortices in individuals with Tourette syndrome relative to typically developing children (Sowell et al., 2008).

Individuals with schizophrenia show suboptimal levels of activity in prefrontal and parietal regions when performing cognitive control tasks such as the Wisconsin Card Sorting Task or the n-back working memory tasks (Barch and Csernansky, 2007; Berman et al., 1988). MRI-based decreases in volume of the basal ganglia and cerebellum have been reported in this disorder too, especially in those individuals with childhood onset (Frazier et al., 1996; Giedd et al., 1999b). Therefore, a number of cortical and subcortical regions appear to be significantly involved in a range of disorders that have as a key symptom a problem overriding inappropriate actions (i.e., cognitive control).

The presence of common disturbances in cognitive and neural systems across discrete syndromes may be surprising at first. However, 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 et al., 1990). Specific disorders may be associated with differential salience, valence, or combinations of the core underlying functional systems. The identification of core processes involved in a disorder can move a field from a disparate set of data-driven findings to a more theoretically coherent collection of findings. Theoretical understanding and identification of specific neurophysiologic function may provide valuable information for validating the core features of and distinctions between psychiatric disorders.

39.5.2 Theoretical Framework: Signaling and Implementation of Control

Cognitive control processes such as the ability to suppress or override competing attentional and behavioral responses have been included in a number of cognitive theories (Cohen and Servan-Schreiber, 1992; Desimone and Duncan, 1995; Shallice, 1988). 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. Finally, Miller and Cohen (2001) proposed a model of cognitive control based largely on their respective nonhuman primate and computational modeling studies of prefrontal function. According to this theory, the function of the prefrontal cortex in cognitive control is active maintenance of patterns of activity that represent goals and the means to achieve them. The prefrontal cortex biases relevant sensory and motor systems for goal-directed behavior, through the buildup and integration of rules learned throughout development (Bunge and Zelazo, 2006). Functional imaging studies of cognitive control have focused largely on this form of top-down cortical control in trying to understand the breakdown in regulating actions and biasing of attention in favor of relevant information.

The focus on prefrontal brain regions is based on the neuropsychological literature showing that frontal lobe damage impairs the ability to regulate behavior. Although this approach has been important in describing problems in cognitive control, it has not captured the biological basis of how this ability breaks down in such a broad range of clinical disorders. Figure 39.2 illustrates a theoretical framework that includes the popular construct of top-down implementation of control by the prefrontal cortex. In addition, it provides mechanisms by which control is called. Specifically, different brain regions can signal the prefrontal cortex for control. Each of the regions identified is part of unique circuitry that project both to and from the prefrontal cortex, thus providing a means for signaling prefrontal regions to help impose top-down control of behavior by biasing signals relevant to goal-related behavior.

Immaturity, developmental delay, or dysfunction within these circuits can lead to cognitive control problems. Ineffective signaling of control systems by any one of these regions could lead to poor regulation of attention or behavior, though with subtle differences, depending on the system impacted. Likewise, intact signaling of prefrontal systems in the presence of inefficient top-down control could result in poor regulation of attention or behavior, though presumably in a more general way. This theoretical framework of cognitive control moves findings of a variety of disparate brain regions' involvement in several disorders toward a cohesive understanding of where cognitive control can break down in these disorders.

The conditions in which these regions may signal the prefrontal cortex are summarized below in terms of frontocortical and frontosubcortical circuitry. Each circuit is generally described. Examples are provided for how each circuit might break down and lead to what appears to be an implementation of control problem, but which could simply be a signaling problem. For example, prefrontal dysfunction could result in a failure of top-down biasing of attention or behavior. Dysfunction in corticocortical signaling from posterior parietal cortex or from anterior cingulate cortex could result in a failure to resolve perceptual conflict among competing inputs or response conflict among competing outputs, respectively. Dysfunction in corticosubcortical signaling from the cerebellum or from the basal ganglia could result in a failure to detect and alter responses to violations in predicted timing or frequency of events, respectively. Finally, a detailed description of one of the frontosubcortical circuits is provided as an example of how a signaling or implementation problem could occur at one of many different locations within a given circuit. This

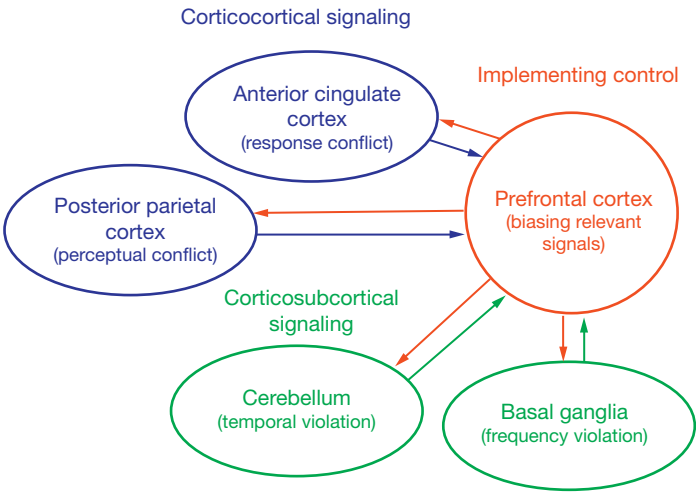

FIGURE 39.2 Locations within prefrontal circuitry where control might break down in disorders of cognitive control. Each region is part of unique circuits that project both to and from the prefrontal cortex, thus providing a means for signaling prefrontal regions to help impose top-down control of behavior and a location where control could break down.

example emphasizes the importance of circuit development and function rather than a homunculus approach of emphasizing a single brain region such as the frontal lobes to explain disorders of cognitive control.

39.5.2.1 Frontal Cortical Control Circuitry

There is an expansive literature implicating the prefrontal cortex in cognitive control from imaging studies (Cohen et al., 1994; D'Espostio et al., 1995; Duncan and Owen, 2000; Smith and Jonides, 1999) to studies of patients with frontal lobe lesions (e.g., Milner et al., 1985; Stuss et al., 1982) to electrophysiological and lesion studies in animals (Fuster, 1980; Mishkin and Pribram, 1955) to computational models (Braver and Cohen, 2000). Each of these approaches consistently supports the involvement of the prefrontal cortex in implementation of cognitive control.

Anterior cingulate and posterior parietal cortices have been shown to be involved in aspects of cognitive control too, especially in overcoming prepotent response tendencies and switching attentional sets (Barber and Carter, 2005; Liston et al., 2006). Activity in both regions has been shown to predict increased prefrontal activity and subsequently enhance behavioral performance in switching behavioral and attentional sets (Hedden and Gabrieli, 2010; Liston et al., 2006). These results are consistent with a network of cortical structures that regulate prefrontal activity by signaling the need for greater control (Birrell and Brown, 2000; Blais and Bunge, 2010; Dias et al., 1996a; Fox et al., 2003; McAlonan and Brown, 2003; O'Reilly et al., 2002).

Each of these brain regions has functionally been dissociated. There is a growing consensus that the prefrontal cortex acts to support task-relevant representations of stimulus information and stimulus–response mappings, thus favoring them in competitions with task-inappropriate representations in posterior cortex (Desimone and Duncan, 1995; Miller and Cohen, 2001). The posterior parietal cortex has been implicated in the generation of motor plans via transformations of sensory inputs from multiple modalities (Andersen and Buneo, 2002) in the service of perceptual decision-making (Gold and Shadlen, 2001; Platt and Glimcher, 1999). As such, this region helps to detect and resolve perceptual conflict. The anterior cingulate cortex, in contrast, has been shown to be involved in the response to conflict detection and its resolution (Botvinick et al., 2001; Posner and Petersen, 1990). One influential theory, known as the conflict-monitoring hypothesis, provides a plausible account of how anterior cingulate and dorsolateral prefrontal cortices act in concert to detect conflict and implement control to resolve it. Accordingly, the anterior cingulate cortex monitors conflicts in information processing and recruits lateral portions of the prefrontal cortex to resolve competition as needed (Botvinick et al., 2001).

While the prefrontal cortex, anterior cingulate, and posterior parietal cortex respond to manipulations of conflict, the role of the anterior cingulate is limited to conflict at the level of the response and not at the level of the stimulus representation (Bhanji et al., 2010; Milham and Banich, 2005). Just as the anterior cingulate is anatomically well situated to detect conflicts at the level of a motor response and signal these to the lateral prefrontal cortex (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993), several studies suggest that the posterior parietal cortex is anatomically well suited to detect stimulus conflict and signal this to the prefrontal cortex. The primate posterior parietal cortex receives ample, direct input from the extrastriate visual cortex and sends direct projections to the lateral prefrontal cortex (Wise et al., 1997). Previous studies have emphasized a role for the posterior parietal cortex in detecting unexpected or behaviorally relevant stimuli and facilitating goal-directed attention to task-relevant aspects of a visual stimulus (Corbetta and Shulman, 2002; Corbetta et al., 2000). Together, these findings suggest one mechanism by which these processes may be mediated: detection of conflicts in information processing at the level of the stimulus representation may signal to the prefrontal cortex the need for enhanced top-down control (Casey et al., 2000; Desimone and Duncan, 1995; Dias et al., 1996b; O'Reilly et al., 2002).

These findings are consistent with the anterior cingulate and parietal cortex being involved in signaling the prefrontal cortex in the presence of competing inputs and outputs (perceptual or response conflict) as depicted in Figure 39.2. The ability to detect conflict is necessary for triggering cognitive control to bias the relevant input or output being promoted to resolve the conflict (Miller and Cohen, 2001). If conflict is not detected, then the control system is not signaled and competition between inputs or outputs may not be resolved in the goal-oriented direction (e.g., the schizophrenic child attends to intrusive thoughts over appropriate ones).

39.5.2.2 Frontal Subcortical Control Circuitry

Subcortical regions implicated in disorders of cognitive control include the basal ganglia and cerebellum. The basal ganglia and cerebellum have been implicated in learning about the frequency and the timing of events (i.e., learning what to expect and when). These regions make up frontostriatal and frontocerebellar loops that have similar features. For example, both the cerebellum and the basal ganglia project to the prefrontal cortex via the thalamus. The primary neurotransmitter in both the basal ganglia and the cerebellum is GABA, an inhibitory neurotransmitter. Glutamate is found in the prefrontal cortex and thalamus, which is an excitatory neurotransmitter and dopamine is a critical neuromodulator of both circuits (Braver and Barch, 2002; Cohen et al., 1992;

Montague et al., 1996; Schultz et al., 1997) that is expressed preferentially in portions of the prefrontal cortex, basal ganglia, and dentate nucleus of the cerebellum, all regions implicated in disorders of cognitive control.

These circuits have been shown to support both motor and cognitive behavior with cognitive-related actions being driven by projections from the prefrontal cortex and modulated by input from the dentate nucleus of the cerebellum and from the dorsal and ventral striatum of the basal ganglia (caudate and nucleus accumbens). This circuitry is perhaps most well described within the basal ganglia thalamocortical circuitry for which at least five circuits have been identified (Alexander et al., 1986). The basal ganglia thalamocortical circuits include a motor, oculomotor, prefrontal (dorsolateral and lateral orbital), and limbic circuit. These circuits involve the same projection regions (basal ganglia, thalamus, and cortex), but differ in the exact projection zone within each region and in the set of thoughts and actions they support.

The general organization of these circuits involves prefrontal projections to different portions of the striatum (i.e., putamen or caudate nuclei), which then project to either a direct or an indirect pathway (see Figure 39.3). 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 (i.e., disinhibition). The indirect pathway consists of an inhibitory GABA projection to the external capsule of the globus pallidus (GPe) that 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 inhibition of the thalamus. The direct pathway presumably facilitates thalamo-cortically mediated behavior, while the indirect pathway is thought to inhibit thalamo-cortically mediated behavior.

As the prefrontal cortex projects directly to the basal ganglia and cerebellum and as both project back to the prefrontal cortex via the thalamus, an account of suppression of competing actions may be described here in somewhat more mechanistic terms. That is, the basal ganglia and cerebellum have been implicated in monitoring the frequency and/or timing of events (Davidson et al., 2003; Hayes et al., 1998; Ivry and Keele, 1989; McClure et al., 2003; Spencer et al., 2003; Van Mier and Petersen, 2002). The ability to predict what and when an event will occur is an essential component of cognitive control, in planning and maintaining appropriate thoughts and actions in different contexts over time. Maintaining representations of such events and information is critical in suppressing competing ones.

Thus, frontocerebellar and frontostriatal circuits may provide neural mechanisms for the maintenance of representations of events over time. In contrast, detecting violations in such predictions (which presumably allows the system to attend to and learn new information) may be linked to intrinsic inhibitory functions of GABA-related functions of the basal ganglia and cerebellum in the absence of frontally driven planned thoughts and actions. Accordingly, the basal ganglia and cerebellum do not generate planned or voluntary movements or behaviors *per se*, but rather the prefrontal cortex generates these voluntary actions. They do, however, detect violations in the timing and nature of events, providing the system with a way to shift out of prefrontally driven behavior when highly salient events occur. The basal ganglia and cerebellum then act broadly to inhibit competing thoughts and behaviors that would otherwise interfere with the prefrontally driven goal or behavior (Casey, 2000; Mink, 1996).

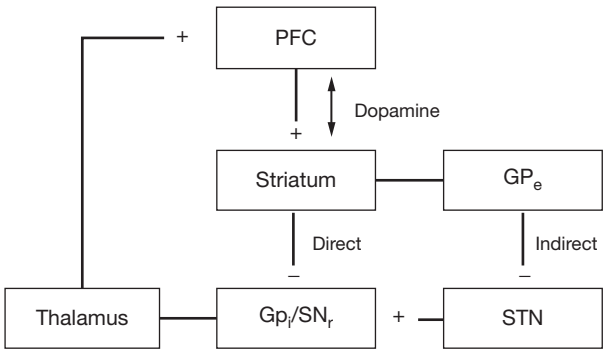

FIGURE 39.3 Direct and indirect pathways of the basal ganglia corticosubcortical circuit involved in cognitive control.

39.6 DISRUPTION OF COGNITIVE CONTROL CIRCUITRY

How does the previously described circuitry contribute to the symptoms and behaviors observed in the childhood disorders of cognitive control? First, the typical assumption made when a child presents with a cognitive control problem is that it is due to top-down prefrontal dysfunction or inefficiency. For example, disruption of the prefrontally mediated direct pathway within the basal ganglia corticosubcortical circuit described can result in constantly interrupted behaviors such as those observed in ADHD or constantly interrupted thoughts observed in schizophrenia. In contrast, if the basal ganglia and cerebellum are involved in shifting out of prefrontally driven thoughts or behaviors (Redgrave et al., 1999), then their disruption may result in irrepressible repetitive behaviors and thoughts similar to those observed in OCD and Tourette syndrome. Likewise, disruption in cortical signaling from the posterior parietal and anterior cingulate cortex of perceptual or

response conflict may result in failure of prefrontal systems to bias appropriate signals in favor of goal-directed behavior. As such, inappropriate attentional or behavioral responses (i.e., distractibility and impulsivity) as observed in ADHD may result (Bush et al., 1999; Tamm et al., 2006). Finally, neuromodulatory (e.g., dopamine) imbalances or deficiency in prefrontal circuitry can lead to problems in cognitive control resulting in constantly interrupted behaviors and thoughts as seen in ADHD and schizophrenia. Several psychiatric and neurologic disorders have been linked to disruptions in specific frontostriatal (Alexander et al., 1986, 1991), frontocerebellar (Dum and Strick, 2003; Middleton and Strick, 2002), and corticocortical loops (Bush et al., 2005; Casey et al., 2007b).

The theoretical framework distinguishing between signaling and implementation of control suggests that information is maintained in an active state over time in the prefrontal cortex by means of recurrent excitatory connectivity (Cohen et al., 1992). The prefrontal 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, as evidenced in ADHD. The basal ganglia and cerebellum, which consist primarily of inhibitory projections (GABA), are involved in switching or shifting attention elsewhere when there is a lack of sufficient prefrontal input to drive the behavior in an organized way. Disruption to these brain regions (basal ganglia and cerebellum) or their development may therefore result in cognitive control deficits related to an inability to shift out of particular behavioral sets (Hayes et al., 1998), as evidenced in OCD and schizophrenia. Likewise, disruption in cortical signaling from the posterior parietal and anterior cingulate cortex of perceptual or response conflict may result in failure of prefrontal systems to bias appropriate signals in favor of goal-directed behavior, as observed in ADHD (Bush et al., 1999; Tamm et al., 2006).

39.7 SUMMARY

A key feature of cognitive development is the gradual increase in the ability to suppress competing thoughts and actions in favor of goal-oriented ones, referred to as cognitive control. This ability is disrupted in several neurodevelopmental disorders including ADHD, OCD, Tourette syndrome, and schizophrenia. The protracted development of the prefrontal cortex has made this region a primary candidate in the study of the development of cognitive control. Further, the neuropsychological literature showing that frontal lobe damage impairs the ability to regulate behavior and suppress inappropriate thoughts or actions has driven the focus of clinical studies.

Recent theoretical and empirical studies suggest that the function of the prefrontal cortex in cognitive control relates to the active maintenance of patterns of activity that represent goals and the means to achieve them. The implementation of control requires signaling of the prefrontal cortex to bias relevant sensory and motor systems for goal-directed behavior. These signals may arise from cortical or subcortical regions. Cortical regions include the posterior parietal cortex and anterior cingulate cortex, which have been implicated in detecting perceptual and response conflict and signaling the prefrontal cortex to implement control. Subcortical signaling regions include the basal ganglia and cerebellum. These regions have been implicated in detecting violations in the expected nature and timing of events, providing the system with a way to shift out of prefrontal-driven behavior when highly salient or novel events occur.

Each region is thus unique and part of an interactive circuitry that project both to and from the prefrontal cortex, thus providing a means for signaling prefrontal regions to help impose top-down control of attention and behavior by biasing signals relevant to goal-related behavior. Immaturity, developmental delay, or dysfunction within these circuits can lead to cognitive control problems. Ineffective signaling of control systems by any one of these regions can lead to poor regulation of attention or behavior, but with subtle differences depending on the system impacted. Ineffective biasing of circuits by control systems can likewise lead to poor regulation of attention or behavior, though in a more general way.

In sum, basic learning and attention systems are important in signaling top-down control systems to adjust attention and behavior when predicted outcomes are violated (Botvinick et al., 1999; Casey et al., 2000). The basic assumption is that learning where, when, or what contexts to expect an event is critical for goal-directed behavior across different contexts over time. Deficits in learning to detect regularities in the environment can lead to less signaling of control systems to help alter or adjust behavior when these expectations are violated. Such deficits can mimic those observed when top-down control systems themselves are impaired.

SEE ALSO

Circuit Development: Cerebellar Circuits. **Cognitive Development**: Developing Attention and Self Regulation in Infancy and Childhood; Statistical Learning Mechanisms in Infancy; Structural Brain Development: Birth Through Adolescence; The Effects of Stress on Early Brain and Behavioral Development. **Diseases**: Neurodevelopmental Genomics of Autism, Schizophrenia and Related Disorders.

Glossary

ADHD Characterized by both distractibility and impulsivity, with frequent overlap of these behaviors; symptoms usually start before 7 years of age.

Anterior cingulate cortex The frontal part of the cingulate cortex with connections to the prefrontal cortex; implicated in response conflict detection and its resolution.

Basal ganglia A group of nuclei situated at the base of the forebrain with strong connections to the prefrontal cortex and thalamus; implicated in learning about the frequency of events.

Cerebellum It is tucked underneath the cerebral hemispheres at the posterior ventral portion of the brain with connections to the prefrontal cortex and thalamus; implicated in learning about the timing of events.

Cognitive control The ability to override or suppress inappropriate thoughts and behaviors in favor of appropriate ones.

Diffusion tensor imaging (DTI) An imaging technique that enables the measurement of the restricted diffusion of water in tissue in order to produce images of neural tracts in the brain.

Direct pathway Involves an inhibitory projection from the striatum to the internal capsule of the globus pallidus (GPi) and substantia nigra (SNr) resulting in the dampening of an inhibitory projection to the thalamus (i.e., disinhibition); implicated in facilitation of thalamo-cortically mediated behavior.

Dopamine A catecholamine neurotransmitter produced in the substantia nigra and ventral tegmental area; acts as a neuromodulator of the frontostriatal and frontocerebellar loops and is implicated in controlling the flow of information from other areas of the brain to the prefrontal cortex in the service of gating and maintaining information.

Functional magnetic resonance imaging (fMRI) A specialized type of MRI that measures the hemodynamic response (change in blood flow) related to neural activity in the brain or spinal cord of humans or other animals.

Glutamate The most abundant excitatory neurotransmitter in the nervous system with high concentrations in the prefrontal cortex and thalamus; implicated in maintenance of information for action.

Go/No-go task A task assessing cognitive control in which a subject presses a button to each target stimulus and must withhold a response when a rare nontarget stimulus appears on screen.

Indirect pathway Consists of an inhibitory GABA projection from the striatum to the external capsule of the globus pallidus (GPe) that dampens the inhibitory projection to the subthalamic nuclei (STN) resulting in excitation of the internal capsule of the globus pallidus and substantia nigra, leading to inhibition of the thalamus; implicated in the inhibition of thalamo-cortically mediated behavior.

Magnetic resonance imaging (MRI) A noninvasive medical imaging technique used in radiology to visualize the detailed internal structure of the body and brain.

N-back working memory task A task assessing cognitive control in which the participant sees stimuli one at a time and must respond whether the stimulus they see is the same stimulus as they saw a predetermined number of trials back.

OCD An anxiety disorder characterized by intrusive thoughts and ritualistic behaviors; age of onset is seen earlier in men, ranges from childhood to young adulthood, and is often before 15 years of age.

Phenylketonuria (PKU) An autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase, which ultimately results in decreased levels of tyrosine, a precursor of dopamine, in the central nervous system.

Piaget's A-not-B task A classic task demonstrating a child's developing ability to resolve behavioral conflict in which an infant reaches for a hidden toy in one location and is then required to find the toy in a new location hidden in full view.

Positron emission tomography (PET) A nuclear medicine imaging technique which produces a three-dimensional image of functional processes in the body through the detection of gamma rays emitted indirectly by a positron-emitting tracer, which is introduced into the body on a biologically active molecule.

Posterior parietal cortex The posterior section of the parietal cortex with connections to the prefrontal cortex; implicated in the generation of motor plans via transformations of sensory inputs from multiple modalities in the service of perceptual decision-making and detecting and resolving perceptual conflict.

Prefrontal cortex Located in the anterior part of the frontal lobes of the brain with widespread connections to many areas of the brain, including the anterior cingulate cortex, the posterior parietal cortex, the basal ganglia, and the cerebellum; implicated in cognitive control capabilities and biasing relevant signals; development is protracted and maturity is not reached until young adulthood.

Schizophrenia A mental illness characterized by disorganized thoughts, delusions, or hallucinations and difficulty suppressing them; symptom onset typically occurs in young adulthood.

Tourette syndrome Characterized by difficulty suppressing repetitive movements and vocalizations that may be complex, emotionally provocative, and exacerbated by stressful situations; disease onset is usually seen in childhood.

Wisconsin card sorting task A task assessing cognitive control in which the participant sorts cards according to rules that change over the course of the experiment.

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