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# Multidisciplinary perspectives on attention and the development of self-regulation

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**Abstract**

During infancy and early childhood, children develop their ability to regulate their own emotions and behavior. This development of self-regulatory mechanisms has been considered to be the crucial link between genetic predisposition, early experience, and later adult functioning in society. This paper brings together the updated empirical findings related to the role of attention and the maturation of brain frontal areas in self-regulation. It reviews viewpoints and evidence of disciplines such as developmental psychology, cognitive neuroscience, social psychology, and neurobiology. It examines the *causes* of individual differences in self-regulation and the *effects* of those differences on the social and academic functioning of the individual. The consequences of failure in self-regulation are illustrated by focusing on the attention deficit/hyperactivity disorder (ADHD), including a detailed review of the animal models related to this disorder. Finally, some initial evidence suggesting the possibility of fostering self-regulation through training of attention is presented.


*Keywords:* Self-regulation; Attention; Development; ADHD; Animal models

**Contents**



*Abbreviations:* 5-CSRT, five-choice serial reaction time; 5-HT, 5-hydroxytryptamine; 6-OHDA, 6-hydroxydopamine; ACC, anterior cingulate cortex; ACh, acetylcholine; ADHD, attention deficit/hyperactivity disorder; AMPH, amphetamine; ANT, attention network test; ATP, adenosine triphosphate; BOLD, blood oxygen level-dependent; CPT, continuous performance task; D2, dopamine-2; DA, dopaminergic; DAT, dopamine transporter; DG, deoxyglucose; DCCS, dimensional change card sorting; DLPFC, dorsolateral prefrontal cortex; DRL, differential reinforcement of low rate; DTI, diffusion tensor imaging; EEG, electroencephalogram; EF, executive function; ERP, event-related potential; ERT, empathy response task; FCN, fixed consecutive number; fMRI, functional magnetic resonance imaging; g, general intelligence; GABA, gamma aminobutyric acid; GLAST, glutamate aspartate transporter; GLT, glutamate transporter; IL, infra limbic; IQ, intelligence quotient; ITI, inter-trial interval; KO, knock out; LPFC, lateral prefrontal cortex; MR, magnetic resonance; MPH, methylphenidate; MS, maternal separation; NAC, nucleus accumbens; NET, noradrenergic transporter; OFC, orbito frontal cortex; PATHS, promoting alternative thinking strategies; PFC, prefrontal cortex; RT, reaction time; SFG, superior frontal gyrus; SHR, spontaneously hypertensive rat; SMA, supplementary motor area; SOA, stimulus onset asynchrony; SSRI, specific serotonin reuptake inhibitors; VLPFC, ventrolateral prefrontal cortex; VPC, visual paired comparison; VTA, ventral tegmental area; WKY, Wister–Kyoto strain

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## 1. Introduction

### 1.1. What is self-regulation?

The concept of self-regulation has received many different definitions within the literature, depending on the different theoretical perspectives under which it has been studied. It can be used to refer to the ability to comply with a request, to initiate and/or cease behavior according to situational demands, to modulate the intensity, frequency, and duration of verbal and motor acts in social and educational settings, to postpone acting upon a desired object or goal, to generate socially approved behavior in the absence of external monitoring, to modulate emotional reactivity, etc. (e.g., Fonagy and Target, 2002; Kopp, 1992; Thompson, 1994; Vaughn et al., 1984, and others). The broader definition would be that self-regulation refers to the ability *to monitor and modulate cognition, emotion and behavior, to accomplish one's goal and/or to adapt to the cognitive and social demands of specific situations*. When referring to emotional regulation, one usually refers to intensity and temporal characteristics of the emotional response (Thompson, 1994), and one of the working definitions that has been recently proposed is that it refers to "the process of initiating, avoiding, inhibiting, maintaining, or modulating the occurrence, form, intensity, or duration of internal feeling states, emotion-related physiological, attentional processes, motivational states and/or the behavioral concomitants of emotion in the service of accomplishing affect-related biological or social adaptation or achieving individual goals" (Eisenberg and Spinrad, 2004).

### 1.2. What is being self-regulated?

Most probably, the definition above does not refer to a single process, but to a group of monitoring mechanisms underlying the ability to self-regulate. First, self-regulation of emotion can be distinguished from self-regulation of cognition, which might or might not include regulation of overt behavior. These processes have been studied separately, and seem to be challenged in somewhat different situations. However, as will be described in detail in Section 2, some interesting links can be found between these broad categories of regulation. These links seem to indicate that there is one common underlying factor behind all forms of self-regulation. This factor seems to be the executive aspect of attention (Fonagy and Target, 2002; Kopp, 1982; Posner and Rothbart, 1998; Ruff and Rothbart, 1996). According to this view, attention is the key aspect of the larger construct of self-regulation, and is the basis of inhibitory control, strategies of problem solving, and self-monitoring.

### *1.3. How does self-regulation develop? Developmental phases during infancy and early childhood*

The milestones in the process of developing self-regulation from early infancy have been described by Kopp (1982, 1989). Some initial form of self-regulation can already be observed in the first months of life. At this stage, neuro-physiological modulatory mechanisms protect an infant from too much arousal or stimulation. Infants are able to reduce the level of stimulation to some extent, by turning away from the source of stimulation (i.e., closing their eyes) and/or engaging self-soothing activities such as sucking. According to Kopp, the next stage begins when an infant begins to show clearly defined cycles of wakefulness that are relatively congruent with social definitions of day and night. Gradually, during a period that continues until the age of 9–12 months, infants become capable of responding to external control. They become aware and capable of intentional means-end actions (e.g., reaching for a pacifier and putting it into the mouth) and they begin to comply with external signals and commands (e.g., complying with a parental requirement such as ''don't touch this''). The type of self-regulation in this phase is called sensory-motor modulation, as infants' increasing mobility and improving motor control become progressively more self-directed. They use their sensory-motor repertoire to modulate their interaction with the environment. As mentioned, one of the important mechanisms that helps infants to modulate the level of arousal is the orienting of attention. Indeed, Johnson et al. (1991) found that the probability of disengaging attention from a central attractor to process a peripheral target increased very dramatically within the first 4 months of life. Moreover, Harman et al. (1997) showed the interaction between attention and soothing in 3- to 6-month-old infants. They found that infants, who were first distressed by visuo-auditory stimulation, could orient to an alternative interesting stimulus that was presented to them. While the infants re-oriented to this new stimulus, their facial and vocal signs of distress disappeared. Their finding is consistent with caregivers' reports of how attention is used to regulate the state of an infant: while before the age of 3 months, caregivers mainly hold and rock an infant in order to sooth him, at about the age of 3 months they report trying to distract an infant by orienting their attention toward alternative stimuli. Toward the end of the first year of life, infants begin to show the first simple forms of compliance with external control. They begin to respond to warning signals and perform one-step simple commands (Kopp, 1982). During toddlerhood children develop a sense of autonomy and awareness of self. Their emotional repertoire becomes more sophisticated and begins to include secondary emotions related to self-consciousness and self-awareness, such as shame and pride (Lewis, 1992; Sroufe, 1995). This emotional development parallels achievements in cognitive abilities as have been described by Piaget (1926, 1952) and a growing sense of self (Lewis, 1997, 1998). The relevant cognitive achievements include the ability to plan and perform a means-end sequence of action, the ability to hold in mind a mental representation, the development of language, etc. These, together with the growing sense of self, enable children at this age to begin carrying out their own intentions and to comply with external requests to control physical actions, communications and emotional expressions (Bronson, 2000). The type of monitoring at this stage has been called by Kopp ''self-control'', instead of ''self-regulation'', meaning that the child still has limited flexibility in adapting acts to meet new situational demands and a limited capacity for delay and waiting. As pointed out by Kopp (1992), children at this stage are not yet fully skilled in managing their emotions. They tend to react with physical aggression and have emotional outbursts such as crying or temper tantrums, if frustrated. They still depend heavily on their caregivers to help them maintain control in the face of stress, fatigue, or challenge. Adults must set and maintain the standards for behavior, anticipate difficult or frustrating situations, and assist a child who is losing control (Sroufe, 1995). Vaughn et al. (1984) studied two main aspects of self-control in children between the ages 18 and 30 months—delay/response inhibition in the presence of an attractive toy and compliance with maternal directives in a cleanup task. In addition to age differences and an increase in coherence of compliance measures with age, significant positive correlations were found between self-control and the cognitive-developmental status of the toddlers. Recent studies provide supporting evidence that some preliminary signs of self-control can be found already at the age of 2–2.5 years (Carlson, 2005; Diamond et al., 2005; Hughes and Ensor, 2005). However, as proposed by Kopp (1982, 1989), it seems that it is not until preschool ages that children actually enter a stage of real self-regulation, becoming increasingly able to use rules, strategies and plans to guide their behavior. Toddlers begin to succeed in challenges such as not peeking during the gift delay–bow task (Carlson, 2005). In this situation, the experimenter tells the child that he is going to receive a present and is shown a large gift bag with a wrapped gift inside. Then the experimenter says he forgot to put a bow on the gift and asks the child to wait until he returns with a bow before opening the present. The experimenter leaves the room for 3 min and returns with a bow, and invites the child to open the gift (if the child has not done so already). Peeking is scored as a fail. About 70% of 24-month-old children can cope with this challenge and pass this test successfully (Carlson, 2005). If the situation is made more challenging, such as in the gift delay–wrap task (Carlson, 2005; Kochanska et al., 1996), it is not until the age of 5 years old that children begin to succeed and reach the 70% probability level of passing the test. Here, the child is told he is going to receive a prize. However, the experimenter ''forgot'' to wrap their present. The experimenter asks the child to turn around in his seat until the present is wrapped so it will be a big surprise. The experimenter then wraps a gift noisily (rifling through a paper bag, cutting wrapping paper with scissors, folding the paper around the box, and tearing off tape) for 60 s. As in the easier version, peeking behavior is recorded.

As will be explained in more detail in Section 2.2, between the ages of 3 and 5 years there is a gradual progression in the ability of children to deal with conflict. A variety of tasks have been designed to measure and study these changes, for example, the dimensional change card sorting (DCCS) task (Carlson, 2005; Diamond, 2002, 2006; Frye et al., 1995; Zelazo et al., 2003). In this task, after sorting cards according to a certain dimension (e.g., color), the child is required to begin

sorting by a different dimension (e.g., shape). Three-year-olds seem to still have 'attentional inertia'. Having focused their attention on a particular dimension, their attention gets stuck there, and they have extreme difficulty redirecting it. In other words, children's difficulty lies in disengaging from a mindset (a way of thinking about the stimuli) that is no longer relevant. Older children seem to acquire the ability to inhibit this tendency and succeed in switching from one sorting dimension to another (Kirkham et al., 2003).

Between the ages of 3 and 5 years old children begin to succeed in a variety of tasks designed to tap frontal functions, including working memory, inhibition, planning, and set switching. Most importantly, these changes occur in parallel to the changes in self- and social-understanding (Carlson and Moses, 2001). As pointed out by Bronson (2000), at preschool age children begin to use speech as a technique for controlling actions and thoughts (Berk and Winsler, 1995; Luria, 1961; Vygotsky, 1962). One of the best documented transitions is in the improved ability to withhold a response or to make an incompatible response, as demonstrated in experimental tasks designed by Luria (Beiswenger, 1968; Diamond and Taylor, 1996; Luria, 1966; Miller et al., 1970). Generally, there appears to be a dramatic increase between 3 and 5 years of age in children's ability to switch between two incompatible rules (Kirkham et al., 2003; Zelazo and Jacques, 1996), and to deal with conflict where children must override a prepotent response and substitute a conflicting response (Gerardi-Caulton, 2000; Reed et al., 1984).

Still, the developmental process of self-regulation is by no means finished at preschool years. Self-regulating abilities continue to develop throughout childhood and adolescence (Barkley, 1997; Bronson, 2000; Davidson et al., 2006; Welsh, 2001).

The whole process of developing self-regulation that has been described above can be conceptualized as a gradual transition from external control to internal or self-control (Bronson, 2000; Schore, 1994; Sroufe, 1995). This development of self-regulatory mechanisms has been considered to be the crucial link between genetic predisposition, early experience, and later adult functioning in society (Eisenberg et al., 1995, 2001; Fonagy and Target, 2002).

According to the model proposed by Posner and Rothbart, the time-schedule of this ontogenic process seems to be dictated by the unfolding of higher order cognitive capacities such as executive aspects of attention (Posner and Rothbart, 1998, 2000) and language acquisition. In the next section, we will clarify the meaning of executive attention and its relation to self-regulation. It should be mentioned at this point that although in this review we focus on the importance of executive attention for the development of self-regulation, there are alternative theoretical approaches in the literature that emphasize the importance of executive functions (EFs, e.g., the ability to formulate and hold in mind problem-solving strategies), which are mostly dependent on increasing working memory capacities (Davidson et al., 2006; Espy and Bull, 2005) and on increasing the hierarchical complexity of the rules that children can formulate and use when solving problems (Zelazo et al., in press; Zelazo et al., 2003, etc.). For example, recent findings reported by Espy and Bull (2005) suggest that children' performance in tasks requiring attention control might be related to differences in working memory.

Not all children develop the same degree of self-regulation and there are many individual differences in the development of these capacities. Several factors affect these individual differences. On one hand, temperamental differences between babies are relevant. Section 3.1 is dedicated to temperament and its relevance to self-regulation. On the other hand, the environment has a great impact on the development of self-regulation. Children do not develop this capacity in isolation. Regarding regulation of emotions, for example, Sroufe (1983, 1995) has suggested that the roots of self-regulation are the dyadic regulation within the relationship with the attachment figure. Moreover, the social and physical environment provides the goals and constraints for the adaptive modulation of behavior and emotion (Bronson, 2000; Denham, 1998; Sroufe, 1995; Thompson, 1994). Section 3.2 is dedicated to the environmental influences affecting the development of self-regulation.

In addition, this paper deals with the effects of self-regulation, from differences in children's social functioning (Section 4.1) to the consequences of anomalous self-regulation, one example of which is seen in attention deficit/hyperactivity disorder (ADHD). Section 4.3 focuses on this syndrome, and includes a review of the evidence based on animal models. To conclude, in our final section, we refer to the link between self-regulation and motivation and we review preliminary evidences for the possibility of training and enhancement of self-regulation.

## 2. Attention

In everyday life there are constantly competing demands on our cognitive and emotional systems by the outside world as well as from internally generated goals. The need for mechanisms to arbitrate between these competing demands is straightforward—so that they can be integrated, prioritized, or selected among to provide coherent and adaptive behavior. Many agree that the attention system of the brain is centrally involved in providing such adaptive behavior. Research suggests that attention involves different mechanisms subserved by separate brain areas. In particular, attention encompasses three sub-systems; orienting, alertness, and selection-executive function.

### 2.1. Attention networks

#### 2.1.1. Orienting

Orienting of visual attention to a point of interest is commonly accompanied by overt movements of the head, eyes, or body. Attending may originate at will, as when we decide to look at a particular location where something of interest is expected, or it may originate reflexively without intention when something captures our attention, as when we orient to a flash of light in the dark or to a movement in the periphery of our vision.

Michael Posner developed a paradigm widely employed to study visual spatial attention (Posner, 1980). Orienting to a

specific location in space facilitates responding to targets appearing at that location. Research has suggested that brain injuries, especially in posterior areas of the brain, damage the orienting system. In particular, damage to the temporal-parietal junction and the parietal lobe produce a syndrome called neglect or extinction (Friedrich et al., 1998; Karnath et al., 2001). Neglect is characterized by difficulty in responding to stimuli presented in the contralesional field and extinction is the inability to disengage from stimuli presented in the intact field. Damage to the midbrain superior colliculus (Sapir et al., 1999) and to the frontal eye fields (Henik et al., 1994) also incurs deficiency in performance of the orienting system. Neuroimaging studies are in line with patient studies and suggest that the superior parietal lobe is involved in voluntary shifts of attention (Corbetta et al., 2000). Pharmacological studies (e.g., Davidson and Marrocco, 2000; see also Posner and Fan, in press) relate the orienting system to the neurotransmitter acetylcholine (ACh).

As will be explained in more detail in following sections, the ability to orient attention is important for self-regulation early in infancy.

#### 2.1.2. Alertness

Many situations require high sensitivity to stimuli, for example, a situation characterized by weak or infrequent stimuli. What is involved in achieving such sensitivity? One way to study this system is by manipulating parameters of warning signals that precede targets (Posner and Boies, 1971) and measuring the transient alerting effects of these signals. It has been suggested (Posner and Petersen, 1990) that this system involves right frontal and right parietal structures and that modulation of alertness is achieved by the neurotransmitter norepinephrine (NE) (Marrocco and Davidson, 1998). This same system seems to be involved in maintaining the state of alertness over time, a function often referred to as sustained attention. To study this ability, a long and boring task is presented and fluctuations in performance over time are measured. An example of a task of this sort is the continuous performance task (CPT).

#### 2.1.3. Selective attention and executive attention

In order to study selective attention psychologists create a conflict situation in which the subject has to respond to one stimulus or to one aspect of the stimulus and ignore another stimulus or another aspect of the stimulus. In these situations the subject needs to focus on the target (a stimulus or an aspect of a stimulus) and ignore all the rest of the display. The two most widely used paradigms for studying this type of selection are *Stroop color naming* (MacLeod, 1991; Stroop, 1935) and *the flanker paradigm* (Eriksen and Eriksen, 1974). For example, in the Stroop task color-words are presented in color and subjects are asked to name the color of the ink and ignore the meaning of the word. The ink color and word meaning can be congruent (e.g., red in red), neutral (e.g., xxx in red) or incongruent (e.g., blue in red).

Another way to look at interactions within and between attributes is to present the relevant and irrelevant attributes in separate locations (Cohen and Shoup, 1997; Eriksen and Eriksen, 1974; Miller, 1991), for example, have subjects focus on a color patch at the center of a screen and ignore a flanking word. In order to look not only at the effect of the word on the color, but also at the effect of color on color (interaction within an attribute), one can present the word in color (Henik et al., 1999). Again, the attributes of the target and the flanker can be congruent, neutral or incongruent. Failures in attention are commonly revealed in two ways: (1) reduction in efficiency of responding to the target when the irrelevant features of the display are present and (2) indications for processing of the irrelevant material (i.e., word meaning) especially when it clearly interferes with processing of the target.

Throughout the years many variations of these tasks were created. Patient studies and neuroimaging studies suggested that two frontal areas are involved in such conflict situations; the anterior cingulate cortex (ACC) and the lateral prefrontal cortex (LPFC, including the dorsolateral PFC, BA 9 and 46—DLPFC, and the ventrolateral PFC, BA 44, 45, 47—VLPFC). Note that Rushworth et al. (2004) have suggested that a medial superior frontal gyrus (SFG) region centered on the pre-supplementary motor area (pre-SMA) is involved in the function of selection (for example, selecting a specific dimension of a stimulus) and that activations that originated in this region might have been erroneously attributed to the ACC. The ACC and other medial PFC areas project to the ventromedial striatum, including the nucleus accumbens (Alexander et al., 1990; Haber, 2003) and the DLPFC projects mainly to the rostral head of the caudate (Haber, 2003), but projections also extend in a rostro-caudal direction to the tail (Alexander et al., 1990). Both striatal regions receive input from midbrain dopaminergic (DA) neurons. The ventromedial striatum receives input primarily from the ventral tegmental area (VTA), whereas the dorsal striatum is innervated by widespread input from the ventral and lateral DA cells, including the pars compacta of the substantia nigra (Haber, 2003).

It was suggested that the medial structure (ACC) is responsible for conflict monitoring whereas the lateral structure (LPFC) maintains task requirements and is responsible for inhibition of irrelevant responses (Bunge, 2004; Bunge et al., 2002b; Bunge et al., 2001; McDonald et al., 2000). Activity at the head of caudate, as indicated by the Magnetic resonance blood oxygen level-dependent (MR BOLD) signal, has also been shown to correlate with successful inhibition in go/no-go tasks (Durston et al., 2002). As will be explained in more detail in following sections, this is the type of attention that seems to be the most relevant for further advances in self-regulation during childhood.

### 2.2. The frontal system and self-regulation

The ability to focus on a task and to ignore irrelevant information is important for continuous performance of demanding tasks, decision making and inhibiting automatic response tendencies. As mentioned earlier, it has been suggested that the ACC is responsible for error detection and conflict monitoring. The LPFC may be involved in maintenance of context or task instructions. The latter may be related to the involvement of this structure in working memory.

Whatever roles are ascribed to these structures, it seems that the orchestrated work of the ACC and the LPFC is central for efficient performance under these situations. Brain imaging studies have linked these areas to a variety of specific functions in attention (Posner and Fan, in press), such as monitoring for conflict (Botvinick et al., 2001) and error (Holroyd and Coles, 2002). A combined functional magnetic resonance imaging (fMRI) and event-related potential (ERP) study found that the ACC was critical in monitoring infrequent signals and in generating the ERP waves associated with oddity (N2b) and attention (P3). Moreover, the ACC was shown to send feedback to the modality-specific sensory cortex, which detected the infrequent signals. In simple tasks such as the oddball task, the DLPFC and other lateral prefrontal areas were not activated with the ACC, suggesting that the LPFC regions may only be involved in higher levels of conflict, such as those involved in the Stroop task (Crottaz-Herbette and Menon, 2006).

In addition, the ACC and LPFC have been linked to working memory (Duncan et al., 2000), emotion (Bush et al., 2000), and pain (Rainville et al., 1997). Moreover, research suggests that these frontal structures are recruited under diverse tasks that seem to be related to general intelligence. Duncan and his colleagues (Duncan et al., 2000) studied the neural basis of general intelligence (g) and showed that tasks characterized as high g tasks recruited the lateral prefrontal cortex (LPFC) and the ACC. The LPFC was activated regardless of whether the task was verbal or spatial in nature. Despite the evidence for involvement of the ACC in cognitive control from neuroimaging studies, the evidence from lesion studies is equivocal. Although Swick and Jovanovic (2002) reported deficits in performance of the Stroop task in two patients with unilateral ACC damage, Fellows and Farah (2005) found intact response modulation to different conditions and instructions on the Stroop and go/no-go tasks in four patients, including one with an extensive bilateral medial prefrontal lesion. It is, therefore, critical to further explore the role of the ACC in cognitive control in patients with lesions, with attention to the side of the lesion.

#### 2.2.1. Cognitive control of emotion

A recent review paper (Ochsner and Gross, 2005) suggested that the ability to control emotion involves frontal structures. Studies have examined control of emotion through selective attention or attention distraction, and by cognitively changing the meaning of the emotional stimuli. Selective attention can be manipulated by changing the task. For example, it is possible to ask participants to evaluate the emotional features of the stimuli or to attend to their perceptual characteristics (Hariri et al., 2000). Another way to change the amount of attention devoted to the emotional stimuli is by presenting distracting stimuli or by employing a high load secondary task (Pessoa et al., 2002).

Ochsner and Gross (2005) suggested that both forms of emotion regulation depend upon interactions between prefrontal and cingulate structures, and cortical and subcortical emotion-generative systems. This view is consistent with the relation between the control of cognition and emotion suggested by Posner and Rothbart (1998, 2000). Evidence for the interactions between neocortical, cingulate and subcortical regions in the regulation of emotion was recently demonstrated by Etkin et al. (2006) using a Stroop-like emotional task. Words depicting an emotion (happy or angry) written in color were printed across a picture of a face that displayed either the same (congruent) emotion as the word, or the opposite emotion (incongruent). Color naming in incongruent trials was slower than in congruent trials; however, if an incongruent trial followed another incongruent trial, the reaction times were faster and accuracy better than if the incongruent trial followed a congruent trial. This suggested that resolving the conflict in one incongruent trial enabled the participant to more easily resolve the conflict in a subsequent trial (termed high conflict resolution). In contrast, if an incongruent trial followed a congruent trial, the condition was deemed to have low conflict resolution. The level of conflict (low conflict resolution > high conflict resolution) was reflected by changes in the BOLD signal in the DLPFC bilaterally and midline dorsomedial PFC. The level of resolution (high > low) was reflected in activation of the rostral ACC. These data suggest that the rostral ACC is involved in resolution, but not in monitoring of conflict, whereas the DLPFC is involved in monitoring, but not in resolution of conflict. This argues against a strict functional division of the cingulate/dorsomedial prefrontal cortex into a ventral affective and a dorsal cognitive component (Bush et al., 2000).

Moreover, ACC activity was associated with dampening of amygdala activity in trials with high conflict resolution and better improvement in reaction times between low and high conflict resolution trials. Moreover, the improvement in behavioral performance was associated with dampening of the sympathetic skin conductance response. Thus, the rostral ACC was shown to be critical for reducing amygdala activity and consequently both autonomic and behavioral manifestations of conflict (Etkin et al., 2006).

#### 2.2.2. Development

While the orienting and alerting systems seem to be active very early in life, the more anterior network develops gradually throughout childhood and begins to control attention. The first primitive form of executive control seems to mature by the end of the first year. Studies of reaching behavior in human infants and monkeys suggest that development of such behavior involves both the ability to plan and execute sequences of action and the ability to inhibit certain reflexive actions or dominant response tendencies. Reaching behavior of infants has been studied by Adele Diamond and her colleagues using several paradigms. A detailed understanding of the gradual development occurring during the second half of the first year of life was obtained in Diamond's studies (Diamond, 1991; Diamond et al., 1994) of "detour reaching" in the Object Retrieval task. In this task, a toy is positioned inside a small transparent box placed in front of the child. The box has an opening only on one side. Since the top of the box is transparent, the initial tendency of the child is to reach straight down toward the toy, following his line of sight. Infants aged 6.5–7 months show a strong

tendency to reach only to the side of the box through which they see the toy. That means that if the opening is at the front side, and they can see the toy through it, they would be able to reach for the toy through this opening instead of the useless reaching toward the top of the box. Diamond describes a gradual progression in the emerging ability to inhibit the tendency to reach straight ahead with the line of sight, until the age of 12 months. At this age, the child is able to retrieve the toy even when the opening is on the side, and he does not need to adjust his line of sight to match this reaching trajectory (see details in Diamond, 1991; Diamond et al., 1994).

In addition, Diamond used the classic A-not-B task, suggested by Piaget, to further examine the early development of control (Diamond et al., 1994). In this task, children are trained to reach for a hidden object at location A. After this response is well-trained, they are then tested on their ability to search for the hidden object at a new location B. Children younger than 12 months of age tend to look in the previous location A, even though they see the object disappear behind location B. After the first year, children develop the ability to inhibit the prepotent response toward the trained location A, and successfully reach for the new location B (for review of this line of evidence see Marcovitch and Zelazo, 1999). Success in the A–not-B task seems to reflect two abilities: first, the ability to inhibit a previously reinforced response, that is, the tendency to reach toward location A where the object had been located in prior trials; second, the ability to hold the location in working memory during the delay after which the infant is allowed to reach for the object. While at 8 months of age, infants make the A-not-B error even when a 2–3 s delay is used, at 12 months, infants can withstand delays of 10 s and still succeed in the task (Diamond et al., 1994). Evidence from lesion studies and single-cell recordings in monkeys suggests that this increase in control is achieved mainly through the maturation of the DLPFC (Diamond, 1991).

However, those are only the first primitive signs of the ability to inhibit, to deal with cognitive conflict, to hold information in working memory, etc. The consolidation of executive attention functions is considered to begin only after the second year of life (Clohessy et al., 2001; Posner and Rothbart, 2000; Ruff and Rothbart, 1996). After this age, children begin to be able to solve simple cognitive conflicts. A combination of the Stroop and Simon tasks has been designed to be appropriate for conflict testing in young children. The task involves presenting a simple visual object on one side of a screen in front of the child and requiring the child to respond by pressing a button that matches the target identity (Berger and Posner, 2000; Gerardi, 1997). The appropriate button can be either on the side of the target stimulus (congruent trial) or on the side opposite the target stimulus (incongruent trial). The prepotent response is to press the button on the side of the target stimulus, irrespective of its identity. However, the task requires the child to inhibit that prepotent response and to base their actions on identity instead. The ability to resolve this conflict is measured by the accuracy and speed of their key press responses. Data strongly suggests that executive attention undergoes dramatic change during the third year of life. Performance by toddlers at the very beginning of this period is dominated by a tendency to repeat the previous response (Gerardi, 1997). Perseveration is associated with frontal dysfunction and this finding is consistent with the idea that executive attention is still very immature in a child at 24 months of age.

An even more difficult type of conflict is introduced by a task requiring executing instructions from one source while inhibiting those from another (Posner and Rothbart, 1998). This conflict task is the basis of the Simon Says game. Several studies employed a simplified puppet version of this game and indicate that the ability to perform this task emerged at the age of 4 years (Carlson, 1997; Jones et al., 2003; Reed et al., 1984). The impressive developmental change in attentional control at this age is supported by additional studies with tasks involving conflict (Gerstadt et al., 1994; Jerger et al., 1988; Zelazo et al., 1995), which showed that in this type of task, there is little evidence of successful performance before 3 years of age (Posner and Rothbart, 2000) (although, as mentioned above, there are some EF tasks which 2–2.5-year olds can pass (Carlson, 2005; Hughes and Ensor, 2005). These age-related changes in EF (see Section 1.3) seem to be consistent across a range of testing procedures. As described by Diamond et al. (2005), ‘‘At the same age that children fail to switch sorting dimensions on a standard DCCS task (3 years), they also fail an array of other tasks that similarly require holding two things in mind and inhibiting a prepotent response (Diamond, 2002). At the same age that children first succeed on the DCCS task (4–5 years), they likewise first succeed on those other tasks as well’’.

The development through childhood in the ability to deal with conflict was studied using the computerized attention network test (ANT) (Rueda et al., 2004). Dramatic improvements were found in the conflict (flanker) effect from the age of 4 to 7 years. Interestingly, after 7 years of age no further improvements were found (Posner and Rothbart, 2007). In contrast, in a recent study by Davidson et al. (2006) that employed variations of the Simon task, inhibition and working memory were found to continue developing gradually after early adolescence until reaching their mature levels only at adulthood.

Error detection seems to develop before the development of error correction. In the context of the Simon Says game, children of 36–38 months of age showed no slowing of their responses following an error, but did so at 39–41 months (Jones et al., 2003). Despite these behavioral findings, there is recent evidence for changes in ERP activity that reflect error detection in infants as young as 6–9 months. Hence, error detection seems to develop before the development of the ability to exert motor control for error correction (Berger et al., 2006). As mentioned above, monitoring of errors is one important function that has been traced to the anterior cingulate (Bush et al., 2000; Luu et al., 2000).

### 2.3. *Maturation of the frontal lobe and its role in attention and self-regulation*

The size of newly evolved areas of the brain has been found to be correlated with the length of time required to reach

maturity. In keeping with this finding, the relative size of the human frontal lobe is larger than in other species, and its prolonged development between infancy to adulthood allows it to be molded by experience (Johnson, 2003). It has been known for some time that although certain cortical areas are predestined to subserve particular functions, experience is critical in the postnatal stages of development. The sequence of development of the cortex is based largely on research in non-human primates, and to some degree on post-mortem studies in humans (Luciana, 2003). In humans, the processes of cell proliferation, differentiation into neurons and glial cells, migration of neurons to their cortical destination and differentiation occur between the 10th to 18th weeks of gestation. Thereafter, the two major developmental events are related to connectivity: (a) synaptogenesis, which involves two stages—proliferation and pruning of the dendritic and axonal processes and (b) myelination. The full-term infant has a laminated cortex whose volume is about a third that of an adult cortex (Huttenlocher, 1994). The initial stages of proliferation, migration and differentiation are complete at term; however, the maturational stages of synaptogenesis and myelination begin toward the end of the second and beginning of the third trimester of pregnancy and continue throughout infancy to adolescence. Sowell, Toga and their colleagues mapped developmental changes in thickness of different cortical regions during childhood and described two developmental patterns: (1) increasing thickness of the gray matter, which might be associated with either proliferation of dendrites or enlargement of somata and (2) increased myelination, which in structural neuroimaging appears to be progressive 'thinning' of cortical gray matter. This ''thinning'' in childhood should not be confused with cortical degeneration seen in late adulthood (Sowell et al., 2004; Toga et al., 2006). These processes will be the focus of the next sections.

### 2.3.1. Synaptogenesis

In rodents and non-human primates the dendritic tree and axonal collaterals are initially over-developed, reaching about 150% of adult levels. Thereafter, redundant connections are reduced in a process called pruning. Huttenlocher and Dabholkar (1997) found that the prefrontal cortex (middle frontal gyrus) had a later time course of synaptogenesis and pruning than did the primary auditory cortex in humans. The peak synaptic density in the primary auditory cortex was at 3 months of age, whereas in the middle frontal gyrus, synaptic density peaked at 3.5 years.

The evidence that the processes shaping growth of dendrites and axons can be influenced by environmental factors stems from two sources: environmental enrichment and sensory deprivation studies in laboratory animals. Cortical thickness and dendritic branching were enhanced when rats were raised in an enriched environment (compared to the standard impoverished laboratory conditions), providing the first evidence that sensorimotor stimulation affects cortical architecture (Diamond et al., 1964, 1966). Increased basal dendritic branching was found in pyramidal neurons of layers 4 and 5 of the temporal cortex, but not the frontal cortex, in animals reared in a complex environment (Greengough et al., 1973). Furthermore, Hebb (1947) showed that rats raised in an enriched environment were better at learning mazes compared to rats raised in a standard laboratory, suggesting that sensorimotor stimulation can have long-lasting effects on learning. The beneficial effects of environmental enrichment have been confirmed in many studies (Kolb et al., 2003; van Praag et al., 2000). The overproduction of synapses is regulated at critical periods by pruning of redundant connections. The classic study of Hubel and Wiesel (1965) demonstrated that unilateral occlusion of an eye during a critical period resulted in wider ocular dominance columns for the unobstructed eye in the primary visual cortex. Redundancy of geniculo-striate projections representing both eyes is normally eliminated by competition between strong and weak connections; however, unilateral sensory deprivation diminishes the activity from the stronger connections such that the weaker connections prevail, even after sight is restored to the eye. Brief amounts of binocular exposure can offset the effects of longer periods of monocular deprivation (Schwarzkopf et al., 2007). In the retino-geniculate pathway, synaptic input is sculpted in early stages by spontaneous ganglion cell activity that can occur even before visual input. However, in later stages of development, visual experience is critical (Hooks and Chen, 2006; Katz and Shatz, 1996). Thus, development of the visual system depends on spontaneous activity at an early stage, even before sensory input is possible, but is influenced by sensory stimulation at a later age. Evidence for this was also found in studies of infants born with cataracts, who were functionally blind in one eye. Infants with patterned visual deprivation up to 9 months of age, showed improved visual acuity as early as one hour following removal of the cataracts and being fitted with contact lenses. Acuity improved up to 1 month in monocularly deprived eyes, whether or not the contralateral eye had been patched. However, the authors reported that at later ages, competition from the non-deprived eye resulted in poorer acuity in the eye that was recovering (Maurer et al., 1999). Kolb and Whishaw (2001) suggested that the over-abundance of synaptic connections in childhood allows for plasticity and potential recovery from brain damage if it occurs before pruning in that particular region has taken place. This research suggests that disruption of normal sensorimotor stimulation can have critical behavioral consequences, even after the state of deprivation is rectified.

Since the prefrontal cortex is a critical region for regulation of attention and emotion, the time course of synaptogenesis and pruning of this region can shed light on self-regulatory functions. Huttenlocher and Dabholkar (1997) found that in children, pruning of synapses in the primary auditory cortex is complete by 12 years of age, compared with mid-adolescence for the middle frontal gyrus. The rise and fall of synaptic density is paralleled by changes in cerebral glucose metabolism, which show low levels at birth except in sensorimotor regions, increases in parietal, occipital and temporal areas at 3 months of age, and increases in the PFC only at about 8 months (Chugani and Phelps, 1986). Increasing gray matter thickness with age, which may be associated with dendritic proliferation, was prominent over the perisylvian language areas, particularly

Broca's and Wernicke's areas in the left hemisphere and correlated with improvement in phonological skills over a period of approximately 2 years (Lu et al., 2007).

It has been suggested that the increased activity of the frontal lobe in the second half of the first year coincides with the infant's ability to learn to inhibit a prepotent response in the A not B task (Bell and Fox, 1994; Luciana, 2003). Although it is difficult to find precise behavioral correlates between synaptogenesis and self-regulation, neuropsychological studies suggest that between the ages of 10 and 12 years, children attain adult levels of performance on some EF tasks, such as the Tower of Hanoi, verbal fluency and motor sequencing, in parallel with the process of synapse elimination (Luciana, 2003; Welsh, 2001).

In summary, experimental research on animals and children shows that synaptogenesis and pruning are stages of development that can be altered by sensory and motor experience. In humans, there appears to be a later time course for these processes in the PFC, compared to primary sensory areas.

### 2.3.2. Myelination

Developmental changes in myelination have been accurately measured using neuroimaging techniques (Sowell et al., 2004). Myelination in the cerebrum has been shown to commence in the fetus and progress from caudal to rostral areas until late adolescence or early adulthood (Giedd et al., 1999; Paus et al., 1999; Sowell et al., 1999). Thinning of the grey matter, associated with myelination, was concurrent with brain growth between ages 5 and 11 years. Progressive thinning (i.e., myelination) was first observed between ages 4 and 8 years in primary sensory and motor areas, then in parietal regions involved in spatial orientation and language at age 11–13 years, and finally in the prefrontal cortex in late adolescence. In the left lateral dorsal, frontal and parietal regions, thinning was correlated with changes in scores on the Vocabulary subtest of the Woodcock Johnson test, which is indicative of general verbal ability (Sowell et al., 2004) and in the hand area of the left precentral gyrus, progressive thinning was correlated with improved motor skills (Lu et al., 2007).

In summary, neuroimaging studies confirm the earlier findings from post-mortem research, suggesting that there is a progressive increase in myelination from posterior to rostral regions, which culminates in the prefrontal cortex during late adolescence or early adulthood. A higher correlation between the developmental trajectory of the cortex was found in monozygotic compared to dizygotic twins in prefrontal, but not posterior regions of cortex. This suggests that the development of the prefrontal areas is predominantly determined by genetic factors, whereas parietal and temporal regions may be more influenced by environmental factors (Toga et al., 2006). Individual differences in developmental trajectories can be correlated with cognitive function. Superior intelligence (>120 intelligence quotient (IQ)), as measured by estimated IQ scores, was associated with a delayed peak of cortical thickness at approximately 11 years of age in the superior medial prefrontal gyrus bilaterally and the left middle temporal gyrus. This was followed by a more rapid decline in thickness in late adolescence. In contrast, children of average intelligence showed a gradual increase in thickness, peaking at around 5–6 years and more gradual thinning, whereas children with high IQ (100–120) were in between the average and superior group (Shaw et al., 2006).

### 2.3.3. Connectivity

Connectionist models of development (Johnson, 1999, 2003) suggest that behavior develops as a consequence of maturation of connections between brain regions. In support of this model, studies show that in infants and children, certain tasks might involve widespread activation of different cortical regions, which then become more spatially restricted as intra-cortical pathways develop. This pattern of activation has been shown for verbal tasks in children, which initially activate widespread cortical areas, but become more focused over left temporal regions as vocabulary develops (Neville and Bavelier, 2002). Finally, Johnson points out that acquisition of behaviors in children parallels skill-learning in adults, such that frontal areas that are active in the initial effortful learning stages become less active as the skill becomes more automatic. For instance, increased ability to suppress interference from irrelevant flanker stimuli in adults, compared to children (8–12 years old), was associated with a switch in the primary areas of activation from the left PFC and insula in children, and a right frontal-parietal-basal ganglia network in adults. Moreover, children who performed better on response inhibition than other children of the same age showed less activation of the left PFC. In children aged 5.3–16 years there is a significant correlation between the volume of the area of the right anterior cingulate and the ability to perform tasks relying upon focal attentional control (Casey et al., 1997). These data suggest that maturation of self-regulation involves a shift in the locus of frontal lobe control, which might be mediated by a change in strategy, that is, a reduced need for mental verbalization (Bunge et al., 2002a,b). Increased levels of myelination of fronto-striatal axons, as measured by restricted diffusion in diffusion tensor imaging (DTI), were associated with faster reaction times in the go trials of a go/no-go task in children and adults. Children, but not adults, showed slowing in trials that had a high level of conflict, and the slowing was positively correlated with diffusivity and negatively correlated with accuracy on no-go trials. Thus, increased fronto-striatal connectivity during development led to ameliorated performance of high conflict trials and inhibition of prepotent go responses (Liston et al., 2006).

Thus, self-regulation can be viewed as a capacity that depends on maturation and integration of the PFC with other cortical and sub-cortical structures. Consistent with this idea are the findings about power and coherence changes in frontal and parietal electroencephalogram (EEG) alpha in infants during the first years of life and their relation with emotional self-regulation when faced with maternal facial emotional expressions, maternal separation, etc. (Bell and Fox, 1994; Dawson, 1994).

### 2.3.4. Role of neurotransmitters in cortical development

Numerous studies have found that the classical modulating neurotransmitters are more abundant in the foetal brain than in

the adult brain of rodents and are critical for many of the developmental processes mentioned above (Benes et al., 2000; Gu, 2002; Hohmann, 2003). Thus, gestational exposure to drugs, stress and malnutrition can have profound effects on the foetal brain. Acetylcholine (ACh) and acetylcholinesterase play major roles in the maintenance and growth of neurons and in synaptogenesis (reviewed in Hohmann, 2003). Basal forebrain cholinergic projections influence dendritic arborization (Villabos et al., 2000) and the development of normal cytoarchitecture (Nishimura et al., 2002; Zhu et al., 2002).

Reciprocal effects of serotonin (5 hydroxytryptamine (5-HT)) and DA on innervation of the cortex have been found. Neurotoxic lesions of 5-HT neurons in the raphe nuclei increased the number of midbrain DA neurons and dopaminergic innervation of the cortex, suggesting that 5-HT and DA neurons interact competitively (Benes et al., 2000). 5-HT, but not catecholamine neurons, also affected the morphology and delayed the appearance of gamma aminobutyric acid (GABA) interneurons in the cortex (Durig and Hornung, 2000). 5-HT was shown to be necessary for neurogenesis, migration, synaptic remodeling and dendritic growth (Whitaker-Azmitia, 2001). Noradrenaline was shown to be critical for synaptic plasticity in the monocular deprivation model mentioned above (reviewed in Gu, 2002). Glutamate was also found to be critical for cortical development. Double knock-out mice for two glutamate transporters, glutamate aspartate transporter (GLAST) and glutamate transporter (GLT), showed disrupted neurogenesis, poor orientation of radial glial cells essential for migration of neurons and other abnormalities, which were partially reversed by glutamate receptor antagonists (Matsugami et al., 2006). In conclusion, the development of neurotransmitter systems is critical not only for their synaptic actions, but because of their role in regulating early developmental processes that occur in gestation and postnatally.

## 3. The *causes* of individual differences in self-regulation

### 3.1. Temperament

The concept of temperament refers to those core individual differences around which the personality of the child will eventually develop. This is an intuitive definition. However, beyond it, researchers markedly differ regarding the exact conceptualization of this construct (Bates, 1989). Most researchers agree that temperament refers to those innate individual differences in behavioral tendencies and style, which appear early in life and remain relatively stable across situations and time (Goldsmith et al., 1987). Researchers disagree, for example, with regard to the question of whether those behavioral tendencies must be genetic and are present early after birth (Buss and Plomin, 1984) or some aspects of it emerge during childhood, and develop as a function of brain maturation (Posner and Rothbart, 1998). The methods for measuring temperament vary from the common parental report (Rothbart et al., 2001), to direct observations of child behavior within systematic laboratory batteries (Lab-Tab, Goldsmith and Rothbart, 1996). In all these measures, children are rated along different temperamental dimensions, such as the tendency to display positive emotionality, the tendency to approach toward novel stimuli, etc.

From the different models of temperament, the most relevant to the topic of self-regulation being discussed in this paper is Rothbart's model (Rothbart, 1989; Rothbart and Bates, 1998). Her approach defines temperament as individual differences in: (a) reactivity; meaning the speed, style and intensity of the initial behavioral and/or emotional response and (b) self-regulation; meaning the capacity to modify this reaction by engaging behavioral strategies and exerting effortful self-control. The dimensions belonging to the reactivity factor are innate and include positive and negative reactions. These are expressed via somatic, autonomic, cognitive, and neuro-endocrine reactions (Rothbart, 1989). Individuals differ in the thresholds of these reactions, their intensity, temporal characteristics, etc. In addition, there are individual differences in self-regulatory capability. Children differ already at infancy in the initial self-soothing behaviors, such as, finger-sucking (Rothbart et al., 1992). Most important, children differ in the more effortful self-regulatory and self-monitoring processes that begin to develop at preschool age. This means that there are individual differences in self-monitoring capacities that include selective orientation toward or away from the stimuli and inhibition of a dominant response. This temperamental factor is called effortful control and it heavily depends on executive aspects of attention (Posner and Rothbart, 2000; Rueda et al., 2005a) and EFs (Rueda et al., 2005b). Therefore, effortful control develops relatively late and continues to develop during childhood.

Negative correlations between the temperamental factors of effortful control and reactivity, are found both in parent reports of the temperament of their children and in laboratory observations. For example, as mentioned previously, research on the tendency to display anger shows that children high in effortful control are low in their tendency to react with anger or other negative emotions. This finding is also consistent with the notion that attentional skills may help attenuate negative affect (Gerardi-Caulton, 2000; Rothbart et al., 2001). As mentioned in Section 2, this type of correlation has also been found in adults.

Moreover, there are indications for some degree of heritability in the individual characteristics of self-regulation, based on greater similarity between identical twins than between fraternal twins. This has been demonstrated both in measures of emotional regulation (Goldsmith et al., 1997; Goldsmith and Davidson, 2004) and, executive aspects of attention (Fan et al., 2001).

#### 3.1.1. Stability of individual differences in effortful control

Significant stability has been found repeatedly in individual characteristics of effortful control both across measurements, and across time. Longitudinal studies show that sustained attention at the age of 9 months predicts effortful control at the age of 22 months (Kochanska et al., 1998, 2000). Moreover, in these longitudinal studies, children perform consistently across different tasks within the battery designed for assessing

effortful control. Children were also stable in their performance across time. Further evidence for the stability of effortful control can be found in the studies of Mischel (1993) and Shoda et al. (1990), who found that the length of the delay that preschoolers successfully waited for a reward predicted their parent-reported attentiveness, ability to concentrate and control over negative affect when these children were adolescents. Moreover, individual differences in performance of EF task were found to be stable in toddlers between ages 24 and 39 months (Carlson et al., 2004). Stability in performance in tasks requiring working memory and inhibitory control have also been reported by Diamond et al. (1997) in their longitudinal study on children treated for phenylketonuria and a comparison group of siblings.

#### 3.1.2. Temperamental differences in self-regulation and left-right frontal EEG asymmetries

Developmental evidence suggests a relation between electrophysiological left-right frontal asymmetry and regulatory aspects of temperament and affective styles. This relation has been observed as early as the first year of life (Bell and Wolfe, 2004; Wolfe and Bell, 2004). For example, infants who cry at maternal separation are more likely to show right frontal brain electrical activation at rest (Fox, 1994; Fox et al., 1994). Moreover, infants who display more negative affect and more motor activity at the age of 4 months tend to show right frontal activation at the age of 9 months and inhibited behavior at 14 months (Calkins et al., 1996). Individual differences in temperament and frontal asymmetry in their brain activity are likely to be relatively stable throughout the preschool years (Fox et al., 2001; see a more detailed review of the evidence connecting electroencephalogram (EEG) asymmetry and temperament in Fox and Calkins, 2003 and Bell and Wolfe, 2004). Evidence based on EEG asymmetry also supports the suggested relation between attention and emotional regulation. For example, Perez-Edgar and Fox (2000) found that children having greater attentional focus and lower distractibility showed greater self-control of emotion and increased left-right frontal EEG asymmetry.

### 3.2. Environmental influences

#### 3.2.1. Influences of attachment

In addition to the individual characteristics emanating from a child's own genetic endowment, the environment heavily influences the development of self-regulation. Early sensitive caregiving and the quality of the attachment that the child develops toward his caregiver seem to have long-lasting effects in the mental representational model of adult attachment relationships (Bowlby, 1973, 1980), as well as for the self-regulatory mechanisms for coping with stress (Goldberg, 2000; Schore, 1994) that the child develops.

Based on his studies with rodents, Hofer (1996) asserts that the mother–infant relationship regulates the infant's neuronal system, and its loss or dysfunction implies poor modulation and coordination of physiological function, affect, and behavior. Staying close to and interacting with the mother seems to be not only important for the infant's survival but offers many opportunities to regulate the infant's physiological and behavioral system (Hofer, 1995; Polan and Hofer, 1999). Meaney's group showed that in rats, low levels of maternal behavior, such as licking and nursing, impaired spatial learning in the water maze and reduced hippocampal synaptogenesis compared to offspring of dams showing better maternal care (Liu et al., 2000). The offspring of poor mothers showed less inhibitory regulation of the stress-induced hormonal response of hypothalamic–pituitary–adrenal axis and greater behavioral signs of anxiety in response to novel or aversive stimuli (Caldji et al., 2000).

There is also evidence that long-term influences of attachment on the regulation of affect and social competence are related to serotonergic and dopaminergic neurotransmitter systems in primates (Suomi, 2000). Just as in rat pups and baby monkeys, there is an increasing awareness in the literature that in humans too, the mother–infant unit ensures the ontogenetic development of biological regulators (Fonagy and Target, 2002). Several studies by Kochanska (2001) and Kochanska et al. (1996, 1997, 2000) are relevant for testing the hypothesis that effortful control is influenced by the context of the mother–infant relationship, that is, influenced by attachment processes. The pioneering studies of attachment in infants conducted by Ainsworth et al. (1978) were based on a laboratory procedure known as ''the strange situation''. This procedure tests the reaction of the infant to his mother in the presence of a stranger. The infant is observed when his/her mother leaves the room and when she is reunited with him/her, and the attachment style is classified as secure, resistant, avoidant, or disorganized (Main and Solomon, 1990).

Kochanska (2001) demonstrated that infants' attachment classification in the strange situation at 14 months of age predicts their emotional regulation almost 2 years later, at the age of 33 months. They found that insecure children were resistant, avoidant, and disorganized, had difficulties in regulating their affect, and showed more fear and anger in situations designed to elicit these emotions and more distress in situations designed to elicit joy, than did secure children. In animal studies, maternal separation (MS) during the first 3 weeks of life (before weaning) when synaptogenesis is taking place, increased anxiety behaviors (Parfitt et al., 2004; Romeo et al., 2003) and led to either a blunted (Mirescu et al., 2004) or exaggerated (Parfitt et al., 2004) release of corticosterone by the adrenal glands in response to stress. In addition, MS reduced stress-induced neurogenesis, a critical process in neural plasticity (Mirescu et al., 2004).

There is also empirical evidence that mother-infant affect-synchrony affects the emergence of self-control. Feldman et al. (1999) found that maternal synchrony with infant affect at 3 months of age (infant-leads-mother-follows relation) and mutual synchrony at 9 months (cross-dependence between maternal and infant affect) were each related to self-control at 2 years of age when temperament, IQ, and maternal style were partialled out. Infant temperament moderated the relations of synchrony and self-control, and closer associations were found between mutual synchrony and self-control for difficult infants.

Based on these findings, they suggested that mutual regulation of affect in infancy, as moderated by temperament, is important to the emergence of self-regulation.

*3.2.2. Parenting strategies and styles*

Parents adopt different strategies and styles toward their offspring. An authoritative, rather than alternative style supports the child's internalization of social guidelines. A balance of warmth and firm guidance that is appropriate to the child's age and understanding and supports in developing inner control, leads to both independence and sociability (Baumrind, 1972; Baumrind and Black, 1967). Children of authoritative parents tend to be able to control behavior in accordance with adults' expectations, and exhibit little anti-social behavior. In addition, they are self-assured and competent in their social skills. These characteristics have been found not only in childhood but also in adolescence, where a low incidence of drug abuse has also been documented (Baumrind, 1991a,b,c). Another aspect of parental behavior that has been studied is the degree of intrusiveness. For example, Nachmias et al. (1996) found that children of mothers who were more intrusive with their wary children in a novel situation had more regulatory difficulties. Results of such studies suggest that parents who allow autonomy, facilitate their children's ability to regulate their own behavior. According to this view, children will most likely be able to internalize aspects of their social surroundings when there are opportunities for them to autonomously initiate and maintain behavior. Thus, while recognizing the importance of parents' responding to children's distress and structuring their environments to facilitate adaptation, parents who are too active and do not provide opportunities for autonomous regulation will likely undermine children's capacity to self-regulate. Studies employing laboratory tasks in which the self-regulation of the child is measured in parallel to the behavior of the mother seem to support these ideas (Calkins and Johnson, 1998; Silverman and Ragusa, 1990; Spinrad et al., 2004).

## 4. The *effects* of individual differences in self-regulation

Individual differences in effortful control are related to some aspects of meta-cognitive knowledge, such as theory of mind (i.e., knowing that people's behavior is guided by their beliefs, desires, and other mental states Carlson and Moses, 2001). Moreover, tasks that require the inhibition of a prepotent response correlate with theory of mind tasks even when other factors such as age, intelligence, and working memory are factored out (Carlson and Moses, 2001; Hughes and Ensor, 2005). Inhibitory control and theory of mind share a similar developmental time-course, with advances in both areas between the ages of 2 and 5 years of age. In addition, Kochanska et al. (1996) have identified developmental links between effortful control and the development of conscience.

Negative correlations have been found between effortful control and aggression, and positive correlations between aggression and surgency, and aggression and negative affect, especially anger (Rothbart et al., 1994). Since effortful control was not found to have a unique contribution to aggression, Posner and Rothbart (2000) suggested that effortful control regulates aggression indirectly by controlling reactive tendencies underlying surgency and negative affect. For example, children high in effortful control may be more able than others to direct attention away from the rewarding aspects of aggression by shifting attention away from negative cues related to anger. Supporting evidence for this relation can also be found in additional studies (Calkins and Dedmon, 2000; see a review of this line of evidence in Fox and Calkins, 2003). Also, individual performance on the spatial Stroop task has been found to be negatively correlated with the individual tendency to express negative affect (Gerardi, 1997). In Gerardi's study, the temperamental characteristics of the infants were measured using temperament questionnaires filled out by the parent. Infants showing high performance in the Stroop task were rated by the parents as having better regulation of their negative emotionality.

### *4.1. Self-regulation and the child's social functioning*

An increasing body of empirical evidence supports the idea that self-regulation, especially regulation of negative emotional reactivity, affects the children's functioning, both at school and within their peer groups. For example, Eisenberg et al. (1993, 1994) examined the relations between frequency and intensity of negative emotion, attentional control and coping behavior, with preschool and kindergarten children's socio-metric status and social behavior. They studied this relation, by employing direct socio-metric scales and adults' estimations (parents and teachers) of socio-metric status. They found that emotional intensity and aggressive coping behavior, as reported by teachers at school, were related in boys to their socio-metric status. That is, high emotional intensity and aggressive coping behavior (as opposed to more constructive coping strategies) were associated with low levels of social functioning and with low socio-metric status. In contrast, high attentional control and constructive coping strategies were associated with positive social functioning. Also, Denham et al. (2003) found evidence in preschoolers of a strong influence of emotional self-regulation on a child's academic and social competence.

Although the actual relationship between emotional regulation and social functioning turns out to be more complex than the above schema, children who are better able to inhibit inappropriate behaviors, delay gratification, and use cognitive methods of controlling their emotion and behavior tend to be socially competent overall, liked by their peers, and well-adjusted (Calkins and Dedmon, 2000; Eisenberg et al., 1996, 1997, 2001; Gilliom et al., 2002; Lemery et al., 2002; Lengua, 2002). In contrast, intense, emotionally negative children are less popular with peers (Stocker and Dunn, 1990).

A similar relationship between weak self-regulation of negative affect and behavioral problems, such as aggressive behavior toward peers, has also been found beyond childhood, and seems to be relevant at adolescence also (Caspi et al., 1995). Longitudinal studies found supporting evidence for a prospective, predictive relation between emotional regulation

at infancy and toddler years, and social functioning at school age (Eisenberg et al., 1997, 2000).

Regarding the mechanisms that connect self-regulation and adjustment, a study by Eisenberg et al. (2001) suggests that non-optimal self-regulation and control are intimately related to externalizing and internalizing behavioral problems. Their data supported the view that internalizing and externalizing children differ from each other, as well as from normal children, with regard to some types of regulation: (1) children classified as internalizing scored lower on impulsivity than those classified as externalizing; (2) children with both internalizing and externalizing symptoms were found to be lower than normal children in attentional regulation/effortful control; (3) internalizing children were somewhat higher in inhibitory control than externalizing children; (4) externalizing children displayed more negative emotionality in a disappointing situation than internalizing children. Overall, children rated high in internalizing behavioral problems were over controlled (high in involuntary control), and appeared to lack spontaneity and flexibility of control that is seen in children with healthy adjustment. In contrast, children with externalizing behavioral problems were under controlled (low both in effortful control and in involuntary control).

### 4.2. Self-regulation and compliance

Compliance to caregivers' instructions and requirements is a crucial and challenging developmental achievement during the process of socialization (Kaler and Kopp, 1990). Compliance refers to the ability of the child to cooperate with daily requirements and to accept behavioral standards imposed by the caregiving environment. Kochanska and Aksan (1995) distinguish between compliance within ''do'' requirements and compliance within ''don't'' requirements. ''Don't'' situations include inhibition or avoidance of a pleasant, but forbidden behavior. In contrast, ''do'' requirements involve the initiation of a new behavior according to the parent/educator instruction. These two types of requirements impose different challenges to the self-regulation ability of the child and follow different developmental stages. In most situations, it seems that compliance to ''do'' requirements is more challenging than to ''don't'' ones and develops later. Moreover, the percentage of compliance to ''don't'' requirements is usually higher than the percentage of compliance to ''do'' requirements, both in toddlers and preschoolers (Kochanska et al., 1998, 2001). One plausible explanation for this difference is that, whereas ''don't'' requires stopping or inhibiting a current behavior, ''do'' requires both, a) stopping a current behavior, and b) initiating a new one according to the request (Kochanska and Aksan, 1995).

According to Kochanska (1993), the development of compliance depends on the one hand on the quality of the mother–child interaction and the socialization process, and on the other hand, on the temperamental individual characteristics, especially in terms of self-regulation. This relation between self-regulation and compliance has been explored by Kochanska et al. (2001) in toddlers and preschoolers. In their study, inhibitory control was assessed in a battery of tasks designed for toddlers and preschoolers, including delayed response to a candy, motor control when moving a toy animal (turtle/bunny) on a track, a turn-taking game, etc. Compliance to a ''don't'' requirement made by the mother was assessed in a situation in which attractive toys were placed in a laboratory room while the child was forbidden to touch them and was given boring/broken toys to play with instead. Children who received high scores in inhibitory control showed higher compliance to parental requirements.

Compliance of toddlers to their parents has been found to correlate with parental sensitivity and rearing philosophies. Moreover, maternal sensitivity and discipline strategy predicted compliance to other caregivers (Feldman and Klein, 2003). These and similar findings are consistent with the idea of generalization of socialization from the mother to non-maternal agents.

It should be mentioned that from the preschool years and onward, gender differences have been documented in compliance, with girls showing more compliant behavior than boys to the requests and demands of parents and adults in general (Eaton and Enns, 1986; Feingold, 1994; Maccoby and Jacklin, 1974; Ruble and Martin, 1998).

So far, we have described the typical developmental trajectory of self-regulation with respect to brain development and the interaction between environmental factors and individual differences. In addition, we stressed the importance of self-regulation for social adjustment. In the following sections, we will illustrate the anomalous development of self-regulation. Although there are several developmental syndromes related to failures of self-regulation (e.g., obsessive compulsive disorder), we chose to focus on ADHD because of its prevalence and the fact that it can be associated with both internalizing and externalizing problems. Moreover, there is a large body of research on animal models of ADHD that shed light on some of the neuronal mechanisms of this disorder.

### 4.3. Developmental pathologies in self-regulation—the case of ADHD

ADHD is one of the most common disorders of childhood, having a prevalence of at least 3–5% (American Psychiatric Association, 1994). The disorder is more common in boys than in girls, both in epidemiological and in clinical populations (American Psychiatric Association, 1994; Breton et al., 1999). Evidence suggests that the disorder has both genetic and environmental underpinnings. First-degree relatives of children with ADHD are 7.6 times more likely to have the disorder than are relatives of normal children (Biederman et al., 1992). Furthermore, 60% of children having a parent with ADHD are likely to be diagnosed as ADHD (Biederman et al., 1995). The high heritability estimates (75–90%) for ADHD in twin studies support a strong genetic contribution (Goodman and Stevenson, 1989; Larsson et al., 2004; Levy et al., 1997; Rietveld et al., 2004), and recent evidence from molecular genetics further attests to a genetic basis of the disorder. A number of studies have found the dopamine D4 receptor gene (DRD4) (Faraone

and Biederman, 1998; LaHoste et al., 1996; Smalley et al., 1998) and the dopamine transporter gene (DAT1) (Cook et al., 1995; Gill et al., 1997) to be associated with ADHD.

Environmental factors seem to also have some contribution to the syndrome: for instance, family relationships, parent–child interaction, and family adversity are associated with the development and severity of the disorder (Biederman et al., 1995; Cunningham and Barkley, 1979; Jacobvitz and Sroufe, 1987).

For over 20 years, ADHD has been viewed as comprising three primary symptoms, namely poor sustained attention, impulsiveness, and hyperactivity (American Psychiatric Association, 1994; Barkley, 1981; Douglas, 1972, 1983). These behavioral deficits arise relatively early in childhood, typically before the age of 7 years of age, and are fairly persistent over development (Barkley, 1990; Hinshaw, 1994; Weiss and Hechtman, 1993). The three major impairments have currently been reduced to two, with hyperactivity and impulsivity constituting a single impairment. As a result, three subtypes of the disorder have been proposed in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV; American Psychiatric Association, 1994): the predominantly inattentive type, the predominantly hyperactive–impulsive type and, most frequent, the combined type.

Children with ADHD place heavy demands on clinical, educational, and social services (Loeber, 1990). During development, ADHD is associated with greater risks for low academic achievement, poor school performance, retention in grade, school suspensions and expulsions (Barkley, 1990, 1997), poor peer and family relations, anxiety and depression, aggression, conduct problems and delinquency, early substance experimentation and abuse (Biederman et al., 1992), driving accidents and speeding violations (Barkley et al., 1993, 1996; Murphy and Barkley, 1996), as well as difficulties in adult social relationships, marriage, and employment (Barkley et al., 1990; Hinshaw, 1994; Murphy and Barkley, 1996; Nadeau, 1995; Weiss and Hechtman, 1993). Most of these developmental risks may be exacerbated by the presence of comorbid aggression-conduct problems (Barkley et al., 1990, 1993; Hinshaw, 1987, 1992, 1994). Treatments for ADHD often include parent, family, and teacher counseling about the disorder; parent and teacher training in behavior management techniques, special education resources, and psychoactive medications (Barkley, 1997).

Most of the children with ADHD are diagnosed at the age of 7–8 years old, when they enter elementary school. However, symptoms might be found much early. One of such early indices seems to be problems with emotional self-regulation. This was demonstrated by Nigg et al. (2004), who found correlations between early measures of emotional regulation and later symptoms of attention deficits.

In laboratory cognitive testing, ADHD subjects do especially poorly in tasks requiring inhibitory control, either motor (i.e., go/no-go stop-signal, and anti-saccade tasks) or cognitive (i.e., Stroop and flanker tasks), although there are some inconsistencies regarding some of these task (see review of empirical evidence related to failures in inhibition in Nigg, 2001). They also do poorly in tasks requiring sustained attention over time, such as the continuous performance tasks (e.g., Chae et al., 2001; Epstein et al., 1997; Weyandt et al., 2002) and show no RT adjustment after making an error (Sergeant and van der Meere, 1988). There is some evidence regarding impairment in tasks requiring reaction toward punishments and rewards, at behavioral and physiological levels. For example, children with ADHD showed attenuated heart rate reactions to changes in reward contingencies, such as extinction and reinstatement of reward, and showed faster habituation to reward, but they did not have elevated reward thresholds on an attentional operant task of Iaboni et al. (1997).

#### *4.3.1. Alternative models for explaining ADHD*

For many years, the most dominant theory of ADHD was that of Barkley (1990, 1997). According to his view, a deficit in inhibitory control is the core symptom underlying the development of broader deficits in EF, accounting for the wide range of dysfunctional behavior in ADHD. This model proposes a link between response inhibition and four EFs that depend on such inhibition for their own effective performance. These four functions serve to bring behavior under the control of internally represented information and self-directed actions. By doing so, the four functions permit greater goal-directed action and task persistence. The four executive neuropsychological functions are: (a) working memory, (b) self-regulation of affect-motivation arousal, (c) internalization of speech, and (d) behavioral analysis and synthesis. According to Barkley, the deficit in inhibitory control explains cognitive difficulties and causes problems in self-regulation of affect. His model predicts that children with ADHD will show also: (a) decreased empathy, (b) increased emotional responsivity to provoking situations, (c) diminished ability to anticipate emotional reactions to future events, (d) decreased capacity to regulate emotional states during goal-directed behavior, and (e) a greater reliance on externally based stimuli to provide the motivation and arousal needed to persist during goal-directed actions. Braaten and Rosen (2000) examined one of the hypotheses that emanated from Barkley's predictions—that boys with ADHD have a decreased ability to act empathically relative to those without ADHD. Empathy was measured by an empathy response task (ERT) and through self- and parent-reports of emotion. On the ERT, children responded verbally to fictitious stories. Results revealed that boys with ADHD were less empathic than boys without ADHD. Boys with ADHD less frequently matched the emotion they identified in the character with the one identified in themselves and gave fewer character-centered interpretations in their descriptions of the character's emotion. Parent-report data revealed that boys with ADHD exhibited more behavioral manifestations of sadness, anger, and guilt than did boys without ADHD. Their results suggested that children with ADHD may be able to self-regulate their positive emotions but not their negative emotions, relative to the control group, which was comparable in variables such as age, verbal intelligence, and socio-economic background.

However, not all the predictions of Barkely's model have been empirically confirmed and today his model is considered

by many researchers as being too unidimensional. When reviewing the data regarding inhibition and ADHD, Nigg (2001) summarized that ''For the ADHD combined type, data support a deficit in executive motor control. However, data are mixed with regard to interference control and are too limited to draw conclusions about cognitive inhibition''. In addition to the lack of support regarding a generalized inhibitory deficit in ADHD, those deficits that are found tend not to be exclusive to ADHD, raising the possibility that an inhibitory deficit is *secondary* instead of *primary*, or at least not sufficient for explaining the complex range of symptoms and findings in this disorder.

Although there is convincing evidence for inhibition deficits in ADHD (Nigg, 2001), this might not characterize all, but only a portion of children with ADHD. For example, Nigg et al. (2005) have estimated that 35–50% of cases of attention deficit hyperactivity disorder-combined type have this kind of deficit.

#### 4.3.2. Motivational theories of ADHD

An additional type of deficit that might help to explain ADHD is a motivational deficit, specifically, an anomalous reaction to rewards and punishments. The basic logic in this line of explanation for ADHD is that these children do not have a normal response to cues for the consequences of their behavior, leading to impulsive, poorly regulated and socially inappropriate behavior (Douglas, 1985; Douglas and Parry, 1994; McBurnett, 1992; Newman, 1998; Nigg, 2000; Quay, 1997; Sonuga-Barke, 2002, 2003, 2005; Sonuga-Barke et al., 1992). In other words, a motivational deficit explanation for ADHD implies that for children with this syndrome, threatening events, contextual cues for punishment, etc., do not trigger the same motivational cascade as in other children, which in turn produces a failure to regulate normal social learning. In this context, it has been suggested that children with ADHD have a primary motivational deficit, with more rapid habituation to repeated positive reinforcement (Iaboni et al., 1997), less arousal or behavioral response to punishment (Crone et al., 2003; Iaboni et al., 1997; Toplak et al., 2005), and ''delay aversion'' (Kuntsi et al., 2001; Sonuga-Barke et al., 1992).

The motivational hypothesis has to a large extent been based on the temporal discounting model which implies that children with ADHD will have a lower equivalence value when given a choice between immediate small rewards and larger delayed rewards. The equivalence point refers to the reward size and delay value for which a subject prefers/does not prefer the larger reward over the smaller reward. The findings in this area with respect to children and adolescents with ADHD are equivocal. When adolescents with ADHD were asked to make a hypothetical choice between a delayed (1 month–10 years) fixed reward of US$ 100 or an immediate reward ranging from US$ 1–100, they had steeper temporal discounting than controls, but this effect was not replicated when the delayed amount was set at US$ 1000 and the varying immediate amounts ranged from US$ 10–1000 in intervals of US$ 100. This suggested that the group effect depended on the reward magnitude (Barkley et al., 2001). In contrast to Barkley et al.'s (2001) study, which partially supports the notion of steeper temporal discounting in ADHD children, Sonuga-Barke et al. (1992) implied that the immediacy preference seen in impulsive children is a result of aversion from all delays, pre- or post-reward. An elegant task design enabled Sonuga-Barke et al. to distinguish between three alternative sources of the impulsive preference bias. Interestingly, it was found that impulsive and control children are equally good reward maximizers, as they both shifted their preference to the bigger delayed reward when a post reward delay was added to the immediate reward condition. When the task duration was fixed, both groups tended to prefer the immediate reward, that is, all children preferred many small reinforcements to fewer large reinforcements. However, when the number of responses was fixed, so that rewards could be maximized only by choosing the large delayed reward, the children with attention deficits chose the smaller immediate reward more often. This result, replicated by Kuntsi et al. (2001), emphasizes the idea that children with ADHD have a delay aversion, regardless of whether the delay is pre- or post-reinforcement. In accordance with this view, Scheres et al. (2006) did not find evidence for a steeper discounting rate in ADHD. However, in a signal detection task, where equally-sized immediate or delayed rewards were given after correct response to two similar stimuli, the response bias toward the stimulus associated with the immediate reward was stronger among ADHD children (Tripp and Alsop, 2001). This result suggests that ADHD children do show higher preference for immediate reward, but implies that its manifestation might be too subtle to be revealed in the explicit reward discounting procedure. Delay periods, whether pre- or post-reinforcement, are likely to be filled by fidgeting and other off-task behavior, typical of children with ADHD (Sonuga-Barke, 2003). It is interesting to note that in some studies reporting motivational deficits, the deficits emerged only in later phases, as the experiment progressed. For instance, in the gambling task, Toplak et al. (2005) found that the adolescents with ADHD chose more cards from the disadvantageous deck than adolescents in the control group in the last 50 trials, but not in first blocks of the session. Similarly, in the arrow flanker go/no-go task, Crone et al. (2003) noted deterioration in accuracy in the ADHD group in later phases, compared to the first phase. In that study, punishment was introduced in the later phases of the experiment, revealing a more attenuated physiological and behavioral response in the children with ADHD. Iaboni et al. (1997) found that children with ADHD habituated faster to reward and had an attenuated heart rate and skin conductance response to extinction and reinstatement of reward, which were introduced in later phases of the experiment. Thus, it is plausible that the alleged motivational deficit in the children with ADHD is a manifestation of fatigue and effort.

Sonuga-Barke (2005) proposed that what are usually regarded as competing, traditional approaches to ADHD, should be seen as complimentary accounts of the subtypes of ADHD. According to this proposal, each sub-type includes a different psychophysio-pathology, with different developmental pathways, underpinned by different cortico-striatal circuits and modulated by different branches of the dopamine system. One is the neuro-cognitive aspect of ADHD, which is an

executive dysfunction underpinned by disturbances in the fronto-dorsal striatal circuit and associated dopaminergic branches (e.g., mesocortical, Casey, 2001). The other is the motivational aspect of ADHD, which is an altered reward process and delay aversion that implicates fronto-ventral striatal reward circuits and mesolimbic branches that terminate in the ventral striatum, especially the nucleus accumbens (Sonuga-Barke, 2003).

#### 4.3.3. The energetic model of ADHD

In addition to the inhibitory and motivational deficits, there is a third type of explanation to the deficits in ADHD, namely the energetic approach (Sergeant, 1995, 1996, 2005; Sergeant et al., 1999, 2003; Sergeant and van der Meere, 1990; van der Meere and Stemerdink, 1999). According to this approach, a deficit in arousal and activation could explain the findings mentioned above—that children with ADHD perform poorly in tasks requiring sustained attention over a long period of time and that their reaction times are usually longer than controls—a type of finding that, at first sight, seems contradictory with their impulsivity (see reviews in Berger and Posner, 2000; Sergeant et al., 2003). Moreover, since the right frontal brain regions are involved both in alertness/vigilance and in executive aspects of attention, the energetic model is also consistent with the neuro-anatomical and functional evidence cited in the next section indicating abnormalities in this brain region in children with ADHD.

Deficits in vigilance *per se* are difficult to isolate from the executive aspects that govern attention in older children and adults. However, a recent study in our lab provides initial evidence that in 1-year-old infants, who do not yet have a developed executive attention, a deficit in vigilance might distinguish between those at risk for ADHD and their comparison group (Berger et al., submitted).

A new and provocative, but still very speculative, energetic approach has been recently proposed by Russell et al. (2006). They proposed a metabolic deficit in glia cells. Specifically, they hypothesize that in ADHD, astrocyte function is insufficient, particularly in terms of its formation and supply of lactate. This insufficiency has implications both for performance and development: (1) in rapidly firing neurons there is deficient adenosine triphosphate (ATP) production, slow restoration of ionic gradients across neuronal membranes and delayed neuronal firing and (2) in oligodendrocytes, insufficient lactate supply impairs fatty acid synthesis and myelination of axons during development. These effects are hypothesized to manifest behaviorally as inefficient and inconsistent performance (variable response times across the lifespan, especially during activities that require sustained speeded responses and complex information processing).

#### 4.3.4. The ADHD inattentive subtype

Most of the empirical research and theoretical models described so far relate to the combined type of ADHD (Nigg, 2001). It has been suggested that the inattentive ADHD group suffers from dysfunction in cognitive but not behavioral suppression, and exhibits poor interference control; however, studies providing empirical data on this subtype to support this claim are lacking (Nigg, 2001). Recently, an additional model has been suggested by Diamond (2005) for explaining this subtype. According to this view, while the core problem in the combined type may lay in response inhibition; the core problem in the truly inattentive type of ADHD is in working memory. Moreover, Diamond suggests that ''children with the truly inattentive type of ADHD, rather than being distractible, may instead be easily bored, their problem being more in motivation (under-arousal) than in inhibitory control''. In other words, Diamond suggests that the motivational and energetic deficits presented above are involved in the inattentive subtype, without involvement of the neuro-cognitive deficit of inhibition. According to this view, the combined and the inattentive subtypes are not two different types of ADHD, but two different disorders with different cognitive and behavioral profiles, different patterns of comorbidities, different responses to medication, and different neurological substrates.

#### 4.3.5. Evidence of brain abnormalities of frontal areas in ADHD

Pathologies of the brain frontal areas related to inhibitory control, executive attention and vigilance have been extensively found in ADHD (Berger and Posner, 2000). Volumetric differences between children with ADHD and controls have been found mainly in those brain areas involved in inhibitory control of motor responses, such as the dorsolateral prefrontal cortex and the caudate nucleus of the basal ganglia (Aylward et al., 1996; Filipek et al., 1997). Children with ADHD, have smaller frontal lobe grey and white matter volumes than age-matched controls (Mostofsky et al., 2002). Other studies have shown additional volume reductions in parietal, temporal, anterior cingulate and cerebellar regions (Carmona et al., 2005) in children with this syndrome. Right midbrain dopa decarboxylase activity, inferred from binding of radioactive fluoradopa, was found to be higher in boys with ADHD than in controls and positively correlated with symptom severity (Ernst et al., 1999). Left lateral and midline prefrontal dopa decarboxylase, on the other hand, was reduced in adults with ADHD by approximately 50% compared to matched controls.

There are discrepant findings regarding DAT binding in ADHD, with many studies reporting increased binding and others reporting no change in striatal DAT binding (reviewed in Spencer et al., 2005). A single study, using a different ligand than previous studies, found a decrease in midbrain DAT and D2 receptors in adolescents with ADHD compared to control adults (Jucaite et al., 2005).

Functional abnormalities have been found with imaging techniques such as fMRI, during performance of tasks demanding inhibitory control, such as the stop-signal and go/no-go tasks (Bush et al., 1999; Casey et al., 1997; Casey, 2001; Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998). For example, Vaidya et al. showed that children with ADHD had higher frontal activation and lower striatal activation than control children during response inhibition. Moreover, administration of methylphenidate led to improved performance associated with increased frontal activation for

both groups and an increase in striatal activation for the children with ADHD. Durston et al. (2003), in part, replicated these findings in younger children with ADHD, showing that the striatum was the most robust region of difference between children with and without the disorder. Functional abnormalities have also been found in the electrophysiological brain functioning of children with ADHD in these types of tasks, by studies employing EEG/ERP techniques (Dimoska et al., 2003; Overtoom et al., 2003; Pliszka et al., 1997, 2000). This literature suggests local abnormalities in cerebral activation in ADHD, with a hypo-perfusion of prefrontal and possibly striatal areas. Functional studies using cognitive control paradigms show deficits in frontal and striatal function, further implicating this circuitry. These results confirm the evidence from the developmental fMRI literature that the development of cognitive control is supported by the maturation of fronto-striatal circuitry, and that poor cognitive control in ADHD is related to changes in this circuitry (Durston and Casey, 2006).

Overall, the volumetric and functional abnormalities found in ADHD tend to support mainly the neuro-cognitive account; however, there is recent evidence of lower levels of DAT in the nucleus accumbens of adults with ADHD (Volkow et al., 2007). More direct research on neuro-imaging deficits in motivation in ADHD is required.

As mentioned above, there is also genetic evidence that gives further support for the involvement of the dopamine systems in the frontal lobe in ADHD. Recent findings indicate that ADHD may involve a mutation of the D4 dopamine receptor gene, which is largely expressed in the cortex and thalamus, but not the basal ganglia (Meador-Woodruff et al., 1996; Mrzljak et al., 1996). Overall, the neuroimaging and genetic evidence support the involvement in ADHD of all the brain areas included in the executive attention network, that is, the basal ganglia, PFC and the cerebellum.

#### *4.3.6. Contribution of animal models to the understanding of self-control and impulsive behavior*

Self-control can be modeled in controlled laboratory situations, thereby facilitating the investigation of underlying neural mechanisms. In the following section, several animal tests of self-control and attention, such as reward discounting, and premature or preservative responding on a vigilance task, will be reviewed in light of parallel behaviors in children with attention or conduct disorders. Evenden (1999) reviewed the conceptualization of impulsivity in personality through psychiatric studies and concluded that impulsivity is a multifactorial behavior with independent and varied manifestations in healthy and impaired human behavior. In particular, various nosologies distinguish among aggressiveness, venturesomeness, disinhibition, and a variety of other dimensions. In the animal literature, the most common approaches to evaluate self-control are based on reward discounting, or control of response rate or timing. However, as pointed out by Evenden (1999), these paradigms may not capture certain facets of impulsivity, such as lack of persistence. In a meticulous analysis of the relation between several behavioral tests of impulsive behavior and locomotor activity, reward discounting appeared to be dissociated from other operant indices of impulsivity, and locomotor activity was not correlated with other operant measures of impulsivity (Dellu-Hagedorn, 2006). Our review in this section will be limited to reward discounting, auto-shaping and the five-choice serial reaction time (5-CSRT) paradigms, which have been extensively studied in the context of animal tests of self-control. Specific attention will be focused on animal models of ADHD that have used these paradigms in addition to measuring increased locomotor activity.

The most direct approach to evaluate self-control relies on the observation that the subjective value of a delayed reward is reduced compared to the subjective value of an immediate reward, a phenomenon usually referred to as temporal discounting. Mazur (1988, 2000) was the first to demonstrate that the subjective value of a delayed reward is best described by a hyperbolic, rather than an exponential function. Whereas the exponential temporal discount function postulates a fixed discount proportion per time, the hyperbolic discounting function predicts increased discounting at short delays and less discounting as the delay progresses in fixed increments. The hyperbolic function predicts that there is a point at which the relative value of two different alternatives can switch, whereas the exponential function predicts that one of the choices will be consistently preferred over the other. The hyperbolic function was validated empirically by Richards et al. (1997) who found that the function accounted for 98% of the variance of delayed reward preferences in a group of eight rats. Discounting steepness is usually regarded as an index for impulsivity and can be described by a single impulsivity factor derived from the hyperbolic function. Moreover, discount functions can be modeled to account for changes in temporal delay, reward magnitude and reward probability, and can be used to predict motivational effects and neural substrates of impulsive behavior (Ho et al., 1999).

Other approaches designated to model impulsive behavior, such as differential reinforcement of low rate (DRL) and autoshaping procedures, can be formulated in accordance with discounting principles (Monterosso and Ainslie, 1999). In the DRL behavioral test, an operant response is rewarded only if it occurs after a fixed interval of time has expired. The degree to which an organism responds prematurely is used as a measure of impulsivity. Likewise, the autoshaping procedure is considered to be a measure of impulsivity because the response is executed even though it is not required and even delays the primary reward. A variation of these procedures, developed by Evenden (1999) is the paced fixed consecutive number (FCN) operant procedure, which allows better control for confounding motor effects of drugs. In contrast to the DRL, in which the animal is required to execute at least one operant after a fixed interval (e.g., DRL 72 s), the FCN requires the execution of a predetermined number of responses on one lever, before responding on another lever in order to obtain a reward. The animal is required to switch levers after executing the FCN, controlling for the possibility of stereotyped behavior, and is required to make a minimal number of consecutive responses, controlling for sedative effects. However, pharmacological studies of this procedure are ambiguous. Both haloperidol and

amphetamine increased impulsivity, whereas specific serotonin reuptake inhibitors (SSRIs) decreased impulsivity. Thus far, the FCN procedure has not been explored with respect to lesion or genetic animal models of attention deficits.

In summary, various operant procedures have been developed to test self-control in laboratory rodents. Despite procedural differences, Monterosso and Ainslie (1999) claim that temporal discounting is a key underlying property in DRL and autoshaping, as premature responses in DRL and autoshaped responses are intrinsically rewarding. Because temporal discounting has also been used in neuroimaging studies of healthy subjects (McClure et al., 2004) and in numerous studies on children and adolescents with attention deficits (see above), this paradigm will be reviewed in more detail in the following sections.

#### 4.3.7. Temporal discounting

Several studies have demonstrated that when humans face the choice between a small and immediate monetary reward and a delayed or probabilistic larger reward, they act according to a hyperbolic discounting function (e.g., Myerson et al., 2003). However, the range of delays used in human and animal studies is hardly congruent (ranging from several seconds to 2 min in animals compared to minutes to years for humans), and the rewards are fundamentally different in their nature (symbolic or real money in humans compared to food for an animal under food deprivation). Yet, the view that a common behavioral mechanism controls preference shift in humans and other species is reinforced by the findings of an identical discounting pattern. In order for temporal discounting in animal studies to be considered as a model for ADHD that has face validity, there must be an a priori assumption that steeper discounting rates will be found in children and adolescents with ADHD.

The concept of temporal discounting of reward has become a central theme in the development of animal models of ADHD; however, as reviewed above, most of the data in this population suggests a more generalized delay aversion, which is not limited to the response-reinforcement interval (Luman et al., 2005).

Another crucial issue for developing a valid animal test is its predictive validity. The critical question is whether drugs that reduce symptoms of ADHD improve temporal discounting. Psychopharmacological studies in rodents have focused mainly on the DA drug effects on temporal discounting, since impulsive ADHD children are successfully treated with drugs that raise dopamine and norepinepherine levels, such as methylphenidate (MPH) and amphetamine (AMPH) (Biederman and Faraone, 2005; Madras et al., 2005). Increased value of delayed reward following treatment with stimulant drugs (e.g., Pietras et al., 2003; Richards et al., 1997; Winstanley et al., 2005) serves to strengthen the pharmacological validity of the reward discounting procedure, as it confirms a drug effect that is effective in children with ADHD (Evenden and Ko, 2005). Both AMPH and MPH regulate catecholamines by several complex and different mechanisms; however, both raise extracellular DA levels in the striatum and nucleus accumbens (NAC) and DA and NA levels in the frontal lobe (reviewed in Madras et al., 2005; Sullivan and Brake, 2003). DAT density in the PFC is sparse; however, MPH may raise DA levels by its activity on the noradrenergic transporter (NET), which has a high affinity for DA (Madras et al., 2005).

Serotonin (5-HT) is known to affect impulsive behavior, probably via interactions with cortical catecholamine systems. 5-HT depletion attenuates the ability of AMPH to reduce impulsivity although it has no direct effect on temporal discounting or on amphetamine-induced hyperactivity (Winstanley et al., 2003). While several studies did not find altered discounting functions after tryptophan depletion in human subjects (Anderson et al., 2003; Crean et al., 2002), tryptophan depletion did lead to a disinhibited response style in a continuous performance test (CPT) (Walderhaug et al., 2002) and to less optimal decision making in a reward-probability task (Rogers et al., 1999). Interactions between amphetamine and serotonergic drugs in humans remain to be tested. Considering the evidence mentioned above, it becomes clear that regulation of self-control is likely to involve complex interactions between DA, NA and 5-HT systems and that the pharmacological interactions revealed in animal studies must be further investigated in humans.

#### 4.3.8. The five-choice serial reaction time (5-CSRT)

While self-control deficits are a core feature of various psychiatric disorders, their manifestations can be fundamentally different from one disorder to another (Evenden, 1999). Keeping this in mind, it would seem inadequate to solely evaluate self-control capacities in any given animal model, because in the absence of any other disorder-related contextual variables, attribution of a self-control deficit finding to a specific disorder, is somewhat arbitrary. An elegant solution to this problem is provided by the five-choice serial reaction time (5-CSRT) test, which enables simultaneous evaluation of spatial attention, impulsivity, and activity variables. The 5-CSRT test has been used to study various aspects of attentional performance and to mimic attention deficits in animal models of ADHD and schizophrenia (Le Pen et al., 2003).

The test apparatus consists of a concave wall with an array of five–nine illuminable apertures and a food magazine on the opposite wall. Successful nose-poking of an aperture following its brief illumination leads to the release of a food pellet from the food magazine. The task primarily tests sustained spatial attention, which can be deduced from the *accuracy* of responding to the stimuli. Additional response dimensions such as vigilance, motor activity, motivation and inhibitory control can be derived from the task. Measurements of *response latencies* are usually indicators of decision processes; however, slower response and magazine latencies (time to pick up food) would be more suggestive of motor or motivational factors. Similarly, errors of *omission* in the absence of changes in response latency may be related to attentional, rather than motor, sensory or motivational causes. Responses occurring during the inter-trial interval (ITI) are punished by a brief time-out and can be divided into two types. Firstly, *premature responses*, occurring during the period in which the rat presumably anticipates the illumination of one of the lights, are

regarded as impulsive, as they represent a maladaptive form of behavior. Secondly, *perseverative* behavior, in which the rat continues to respond even following the stimuli presentation, are regarded as compulsive because they represent lost of inhibitory control and can be compared to autoshaped responses (see Robbins, 2002, for an excellent review).

The fact that the 5-CSRT test includes various independent performance variables has revealed dissociations between underlying neuronal substrates of various aspects of attention. This impressive achievement has been accomplished by Robbins and his colleagues in rats in over a decade of systematic analysis of the task, using lesion, metabolic and pharmacological methods (Robbins, 2002). To summarize, lesion studies have shown dissociations between response accuracy and inhibition of inappropriate responses in different neural systems. For example, medial PFC lesions dramatically reduced accuracy without affecting premature response rate, while ACC lesions enhanced premature response rate without affecting accuracy (Chudasama et al., 2003; Muir et al., 1996). In addition, infra limbic (IL) cortex lesions increased the rate of premature responses, while orbitofrontal cortex (OFC) lesions resulted in inappropriate perseverative responses, suggesting that impulsiveness and compulsiveness can be anatomically distinguished (Chudasama et al., 2003).

Systematic administration of SKF 38393, a partial D1 agonist, affected the accuracy of performance, but had no effect on inhibitory control. In contrast, ketanserin, a 5-$HT_{2A}$ antagonist, reduced the number of premature responses, but had no effect on accuracy of performance (Passetti et al., 2003). The 5-CSRT test has led to the construction of a screening test for animal models of ADHD, by using cut-off criteria to select poor performers on this task. Puumala et al. (1996) compared the effect of methylphenidate on poor performers and good performers and a third group of good performers whose performance was impaired by reducing the duration of the stimulus. Accuracy was negatively correlated with the percent of premature responses. Premature response rates (impulsivity) were positively correlated with activity and rearing in the open field in the first, but not second session. These findings support the construct validity of the 5-CSRT paradigm. Methylphenidate resulted in a slight increase in accuracy rates but had no effect on premature responses in the poor performers, and had no effect in the controls.

Poor 5-CSRT test performers have also been shown to have distinct brain activation patterns compared to controls, as revealed by [$^{14}$C] deoxyglucose (DG) metabolism. A positive correlation between accuracy rates and metabolic activity was found in most cortical regions, including the prefrontal cortex, and in the hippocampus, substantia nigra and substantia innominata. Conversely, a negative correlation was found between premature response rates and DG uptake in the cingulate and ventrolateral orbital cortex. Group differences between good and poor performers were found only in the areas allegedly related to premature responses—the cingulate and ventrolateral orbital cortex—a finding which parallels the reduction in activity in these regions in children with ADHD (Barbelivien et al., 2001).

Using a simplified version of the 5-CSRT test with only one aperture instead of five, involvement of the PFC, 5-HT and DA was determined by in vivo microdialysis and ex vivo HPLC (high performance liquid chromatography). Premature responding was associated with increased baseline and task-related 5-HT, but not DA levels in the PFC, as determined by microdialysis (Dalley et al., 2002a). A comparison of two subpopulations with low and high rates of premature responding revealed higher turnover of DA in the ACC in high impulsive rats compared to low impulsive rats, supporting the view that abnormal cingulate functioning may be a trait marker for impulsive behavior. Interestingly, this study contrasts with other studies linking decreased frontal 5-HT to increased impulsivity (Adriani et al., 2003), and suggests that interactions between 5-HT and DA in the PFC, and in particular in the ACC, control impulsive behavior.

In summary, several behavioral tests have been developed to try to evaluate self-control and attention deficits in rodents. On the one hand, temporal discounting was found to have some predictive pharmacological validity, in that drugs that improve performance in this task are also effective in the treatment of ADHD. On the other hand, there are few studies that clearly demonstrate temporal discounting in children or adolescents with ADHD and other explanations such as delay aversion cannot be ruled out. The 5-CSRT test includes measures of vigilance, impulsiveness and perseveration, which is somewhat akin to continuous performance tests that reveal poor performance in children with ADHD (Pennington, 1997; Shallice et al., 2002; Willcutt et al., 2005). Thus, the 5-CSRT test has face validity as a measure of attention impairment in children with attention deficits and it has predictive validity, since performance in a subgroup of poor performers was improved by methylphenidate (Puumala et al., 1996). However, the face validity of the self-control parameters (e.g., premature response) is still to be demonstrated. Construct validity as a test for attention is supported by the fact that manipulations that impair performance on attention tests in humans, such as distracting stimuli (white noise bursts), unpredictability (variable ITI) and degraded stimuli (short stimulus duration), have similar effects in the 5-CSRT test (Dalley et al., 2002a,b; Robbins, 2002).

#### 4.3.9. Rodent models of ADHD

Several models of ADHD have been established in mice and rats, and described in recent reviews (Davids et al., 2003; Viggiano et al., 2003). In order for a rodent model to provide insight into neural mechanisms of a behavioral disorder, it should reflect the developmental aspect of ADHD, and show deficits in the area of attention as well as activity.

*4.3.9.1. Lesion models of self-control deficits: prefrontal cortex and nucleus accumbens.* Lesion models may enable us to explore the neuroanatomical basis of self-control. Problematically, essential differences in self-control abilities of humans and rodents can be attributed, at least to some extent, to the dramatic difference in the size of their frontal lobe.

Nonetheless, preclinical and clinical studies converge to suggest that attention deficits are associated with hypofunctioning of PFC DA circuits and hyperfunctioning of striatal DA circuits (Sullivan and Brake, 2003). In humans, it has been proposed that competition between two separate neural systems, representing immediate and delayed reward, underlie choice processes. fMRI brain scans of subjects performing the delayed discounting task indicated that choosing the delayed reward was associated with greater activation of the lateral prefrontal cortex and the posterior parietal cortex, while activation in the limbic areas was associated with bias toward the immediate reward (McClure et al., 2004). This result suggests that frontal lobe activity is necessary for conceiving the subjective value of delayed reward—a central ability for self-control. Surprisingly, animal studies suggest that choice preference in animals is determined by an equivalent neural process. Single-unit recording of the presumed pigeon analog of the human prefrontal cortex revealed increased frontal activity with the increase of the delay to reward. In addition, pigeon frontal activity was also correlated with the expected reward amount, suggesting that, in accord with human findings, pigeon frontal activity represents the subjective value of a reward (Kalenscher et al., 2005). Moreover, patients with OFC lesions commonly exhibit behavior patterns often described as impulsive, (Damasio and Anderson, 2003), leading to the prediction that rats with analogous lesions would choose small immediate rewards over larger delayed rewards. Children with ADHD are known to have reductions in gray matter volume of prefrontal areas (Kates et al., 2002; Krain and Castellanos, 2006) and altered asymmetry of the basal ganglia (Castellanos et al., 1994), supporting the face validity of the lesion models.

Although a steeper reward discounting function was indeed reported after OFC lesions (Mobini et al., 2002), paradoxically, some studies found increased tolerance to delay in an odds discounting paradigm following OFC lesions (Winstanley et al., 2004). This issue was resolved by systematically examining the effects of excitotoxic and 6-hydroxydopamine (6-OHDA) OFC lesions on functions that manipulated reward magnitude or probability. Kheramin et al. (2003, 2004) concluded that the apparent decreased sensitivity to temporal delay can be offset by an increase in sensitivity to difference in reward magnitude or reward probability induced by OFC lesions. Indeed, this was elegantly demonstrated in a study by Rudebeck et al. (2006) that found that OFC-lesioned rats could be taught to prefer a large delayed reward after being trained to reverse their tendency to prefer the small immediate reward. Thus, the OFC was critical for evaluating different parameters of rewards; however, neuronal activity encoding delay to reward and reward magnitude was not correlated, suggesting that in the OFC these two parameters are dissociable (Roesch et al., 2006).

Medial PFC lesions (within 0.5 mm of the midline) had no effect on temporal discounting (Cardinal et al., 2001), even though, as described above, this region was critically involved in the 5-CSRT task (Dalley et al., 2002a,b; Muir et al., 1996). These studies suggest that the different neural substrates of self-control subserve performance on vigilance and reward evaluation tasks. On the other hand, ACC lesions did impair effort discounting in rats that were given the choice between a large reward that had to be obtained by climbing a barrier or a small reward that was easily obtained (Rudebeck et al., 2006). This finding is consistent with the motivational models of ADHD (Sergeant et al., 1999) and inattentive attention deficit disorder (Diamond, 2005). The dissociation between performance of OFC- and ACC-lesioned rats is consistent with the view that impulsive and inattentive behavior are mediated by different substrates.

Reward discounting was also affected by neurotoxin lesions in the nucleus accumbens, a structure critical for evaluation of reward in human and other species (Pagnoni et al., 2002; Schultz, 2004). Excitotoxic (Cardinal et al., 2001) and specific 6-hydroxydopamine lesions both enhance locomotor activity, but lead to different effects on reward discounting. Whereas excitotoxic lesions led to less tolerance to a delayed reward, 6-OHDA lesions had no effect on temporal discounting (Winstanley et al., 2005) and did not reduce the ability of amphetamine to reduce impulsive reward choice. However, 6-OHDA lesions of the NAC reduced the ability of a 5-$HT_{1A}$ receptor agonist to increase the rate of impulsive choices. The series of studies by Winstanley and her colleagues reveal that hyperactivity and reward discounting are dissociated with respect to the underlying dopaminergic circuitry. The lesion models reveal intricate interactions between dopaminergic and serotonergic systems in controlling different facets of the ADHD syndrome (Winstanley et al., 2006).

Neonatal lesion models may have more promise for revealing developmental impairments in self-control. 6-OHDA lesions of PFC dopamine pathways result in transient hyperactivity that responds to stimulant drugs. Rats with these lesions also showed a decrease in the number of D2 autoreceptors and in DAT, increased sensitivity of post-synaptic D1 receptors and an increase in D4 receptors. Operant and spatial learning deficits were also reversible by stimulant drugs, but show less resemblance to the ADHD syndrome than do tests of impulsivity (reviewed in Davids et al., 2003). Future studies should validate the neonatal lesion model by investigating effects on reward discounting and the 5-CSRT tasks.

*4.3.9.2. An animal model for ADHD—the spontaneously hypertensive rat (SHR).* The spontaneously hypertensive rat is commonly portrayed as a valid genetic model for ADHD, as it expresses to some extent hyperactivity, attention deficit and impulsivity, the three main symptoms of ADHD (Adriani et al., 2003; Sagvolden, 2000). The SHR strain has been extensively tested with respect to locomotor activity, sensitivity to delayed rewards, vigilance and impulsivity, using the 5-CSRT test. Analysis of the dopamine circuitry in this strain supports the construct validity of this model. SHR rats were reported to have less dopamine release, impaired vesicular storage of dopamine and increased number of D1/D5 receptors with lower affinity. Male SHR rats have five-fold greater turnover of D1 and D2 receptors in basal ganglia and limbic terminal areas compared to females (Sagvolden and Sergeant, 1998). Higher extra-

cellular DA was found in the shell of the NAC, whereas lower levels were found in the striatum. Developmental studies revealed lower tyrosine hydroxylase mRNA expression in the striata of SHR rats in early postnatal development and lower DAT mRNA and DAT function in the postweanling stage (Leo et al., 2003). In addition, SHR rats have small brain volumes in the PFC, occipital lobe and hippocampus (Russell et al., 2005). The above pharmacological and behavioral findings suggested that the SHR strain would be a useful model for revealing the neural mechanisms of attention deficits. However, the validity of the model has been challenged by several findings.

One of the prevailing criticisms of the SHR model is that it is usually compared to the WKY (Wister–Kyoto) strain, a strain with abnormally low activity levels, which is considered to be an animal model of depression (Braw et al., 2006). When compared to Wistar rats, SHR rats do not consistently show increased activity (van den Bergh et al., 2006). Moreover, the alleged hyperactivity is not reduced by psychostimulants, reducing its predictive validity (van den Bergh et al., 2006). Examination of operant behavior only partially supports the SHR model of ADHD. SHR rats were found to have more inappropriate responding on DRL, during extinction, and in high FI (fixed interval) ratios (Sagvolden et al., 1992; van den Bergh et al., 2006), suggestive of impulsive behavior. However, psychostimulants did not reduce responding or increase the number of rewards obtained in the DRL, although there was a trend to a reduction in burst responding with methylphenidate.

Reward discounting was tested indirectly by comparing performance on two FI schedules using the matching law. Comparing performance on FI 60 and FI 120 schedules, SHR rats had a higher rate of responding but maintained a steeper FI scallop than WKY rats even after treatment with psychostimulants (Sagvolden et al., 1992). In contrast, the shape of the scallop in the WKY rats was disrupted by amphetamine and methylphenidate, leading to responses being equally distributed throughout the FI interval. The slope of the FI scallop was interpreted by Sagvolden et al. (1992) as representing the reinforcement decay gradient; however, in a recent study, a high rate of pressing in the FI interval was found to be unrelated to reward discounting (Dellu-Hagedorn, 2006). The flat scallop in the WKY strain following treatment with psychostimulants may reflect stereotyped responding or disrupted timing. Moreover, a shorter reinforcement decay gradient, as posited by Sagvolden, would be expected to result in faster extinction in SHR rats. In fact, the SHR strain showed slower extinction compared to the WKY strain. Dellu-Hagedorn (2006) found that high rates of bar-pressing during extinction were associated with more errors on a spatial working memory task but not with the reward discounting gradient.

In another study, the temporal discounting curves of SHR and WKY rats were identical. A median split of each group yielded differences only in the SHR strain, creating one subgroup with a stable preference for the large delayed reward and another subgroup with a steep discounting curve showing a switch to the small reward with increasing delays (Adriani et al., 2003). Although the finding that half the rats consistently preferred the large *delayed* reward to the immediate reward is inconsistent with the assertion that these rats have a steep reward decay gradient, the subgroup that was sensitive to delay did show a steeper reward decay gradient than the parallel WKY group. This subgroup also had lower 5-HT turnover, and lower NE levels and lower cannibinoid 1 receptor binding in the medial frontal cortex than the non-impulsive group, with no change in dopamine. In another operant conditioning task, the decay gradient, K, of SHR rats was not different than that of the control WKY rats, even though the SHR rats showed more sensitivity to the immediate reward (Johansen et al., 2005). To conclude, SHR rats do not consistently show a steep reward gradient or impulsive behavior; however, a subgroup of SHR rats shows that these traits may be associated with neurochemical changes in the PFC.

In a modified version of the 5-CSRT test, SHR rats did not have longer acquisition times or more impulsivity than Wistar rats, suggesting that they do not have an attention deficit. Moreover, methylphenidate affected anticipatory responding in Wistar, but not SHR rats (van den Bergh et al., 2006). In conclusion, SHR performance in the 5-CSRT test, reward discounting and open field paradigms fundamentally challenges the view that SHR rats exhibit an impulsive and inattentive behavior profile. In support of the SHR model, they did exhibit a methylphenidate-reversible impulsive pattern of behavior on the DRL test.

#### *4.3.10. Genetic models of ADHD in mice*

While the genetic basis for self-control is not known, it has been established that heredity makes a significant contribution to disorders of self-control, such as ADHD. The 7-allele variant of the gene encoding the D4 receptor has been linked to novelty seeking in adults (Ebstein et al., 1996) and impaired emotional regulation in infants (Auerbach et al., 1999). D4 antagonists alleviate ADHD symptoms and D4 receptor changes were found to contribute to the hyperactivity seen in juvenile mice following neonatal forebrain 6-OHDA lesions (Davids et al., 2003). The *Dat1* gene, coding for the DAT, was found to distinguish SHR from WKY mice (Mill et al., 2005). In parallel, certain polymorphisms of the gene are more common in children with ADHD (Gill et al., 1997).

How accurately do genetic models in mice portray self-control deficits in children? While it is beyond the scope of this article to describe genetic models, recent reviews have examined this issue comprehensively (Davids et al., 2003; Viggiano et al., 2003). Knock out (KO) and transgenic mice often have different phenotypes on different genetic backgrounds, and may have stunted growth or impaired sensorimotor functions that are not characteristic of the syndrome in children. DAT-KO mice are hyperactive in a novel environment, but also show stunted growth, skeletal abnormalities and pituitary hypoplasia that are not characteristic of ADHD (Madras et al., 2005). The hyperactivity is reversed by the psychostimulants amphetamine, cocaine and methylphenidate, and by specific serotonin reuptake blockers, but not by specific noradrenergic transport blockers (Gainetdinov et al., 1999). In parallel, children with ADHD are successfully treated with

psychostimulants, but also with the specific NET inhibitor atomoxetine (Spencer and Biederman, 2002). The DAT-KO mice also had deficits in spatial working memory and more perseverative errors (Gainetdinov et al., 1999), which is analogous to spatial working memory deficits reported in children with ADHD (Willcutt et al., 2005). Paradigms such as reward discounting, and the 5-CSRT task have not been tested in DAT-KO mice, or in fact, in any of the other dopamine-related genetic deletions. The reward discounting paradigm has been adapted effectively to mice. The degree of impulsive choice was positively correlated with activity (Isles et al., 2004). Moreover, amphetamine had a biphasic effect on impulsivity, reducing preference for small rewards at low doses and increasing small reward preference at high doses (Isles et al., 2003). Future research should extend the phenotype mapping of genetic models of ADHD to include the self-control paradigms developed in rats. Viggiano et al. (2003) reviewed the effects of deletions of DA receptors, D1-D5, most of which result in reduced exploratory activity. One might, therefore, expect a different pattern of self-control deficits in these genotypes, perhaps leading to a distinction between ''inattentive'' and ''hyperactive'' sub-types. Another area that remains to be explored more carefully is the interaction of anxiety with self-control. Sustained attention deficits have been reported in mice with genetic alterations of neuropeptide Y Y2 receptors (Greco and Carli, 2006) and glucocorticoid receptors (Steckler et al., 2000), both of which are involved in regulating emotional behavior.

In summary, emotional and cognitive self-control deficits represent a wide range of behaviors that can be simulated in sophisticated operant conditioning procedures. Fastidious neuropharmacological analysis of a single paradigm that yields multiple dependent variables is one approach that has led to a greater understanding of the different components of the 5-CSRT task (Robbins, 2002). It is equally important to compare different paradigms in a single laboratory in order to better delineate how different behavioral patterns are related to one another (Dellu-Hagedorn, 2006; van den Bergh et al., 2006). The genetic pieces of the puzzle have yet to fall into place, but promising mutation models will provide further insight into the neural basis of self-control.

## 5. Final words

In this paper we have focused on the development of self-regulation, tracing its roots to the mutual influence of innate temperament on the one hand, and caregiver influences at early stages of life on the other. Specifically, we focused on the key role of attention in the development of self-regulation. Neurobiological studies emphasize the interactions of prefrontal monoamine systems in regulating sustained attention and impulsive behavior, which is consistent with current medical treatment of attention deficits. An intriguing question for future research is how medication and attentional training can interact to improve self-regulation. There is some initial evidence that attentional training is beneficial in typically-developing preschoolers (Posner and Rothbart, 2007; Rueda et al., 2005a,b) and in people who suffered a brain injury affecting their attention (Sohlberg and Mateer, 1987, 2001). There are also reports of some preliminary findings in a double-blind placebo-controlled study of attention training with ADHD children (deBeus et al., 2004). There is also some evidence for the efficacy of training programs within educational settings, designed to promote emotional self-regulation, which focus on social skills, aggression control and conflict management, such as the PATHS (Bierman and Erath, 2004; Kam et al., 2004; Riggs et al., 2006) and the ''Tools of the Mind'' (Diamond et al., 2007) intervention programs.

Furthermore, consistently with what was presented above in the section about effects of parenting strategies and styles, there is recent evidence concerning impressive efficacy of interventions based on the training of parents, on the attentional skills of their children (Neville, 2007). Although it is still too early to conclude whether it is feasible to foster self-regulation by means of attention training, this is certainly an interesting and provocative possibility that deserves further exploration.

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