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A dynamic developmental theory of Attention-Deficit /Hyperactivity Disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes

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Abstract: ADHD is currently defined as a cognitive/behavioral developmental disorder where all clinical criteria are behavioral. Inattentiveness, overactivity, and impulsiveness are presently regarded as the main clinical symptoms.

The dynamic developmental behavioral theory is based on the hypothesis that altered dopaminergic function plays a pivotal role by failing to modulate non-dopaminergic (primarily glutamate and GABA) signal transmission appropriately.

A hypofunctioning mesolimbic dopamine branch produces altered reinforcement of behavior and deficient extinction of previously reinforced behavior. This gives rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioral variability, and failure to "inhibit" responses ("disinhibition").

A hypofunctioning mesocortical dopamine branch will cause attention response deficiencies: deficient orienting responses, impaired saccadic eye movements, and poorer attention responses towards a target) and poor behavioral planning (poor executive functions).

A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficient nondeclarative habit learning and memory. These impairments will give rise to apparent developmental delay, clumsiness, neurological "soft signs", and a "failure to inhibit" responses when quick reactions are required.

Hypofunctioning dopamine branches represent the main individual predispositions in the present theory. The theory predicts that behavior and symptoms in ADHD result from the interplay between individual predispositions and the surroundings. The exact ADHD symptoms at a particular time in life will vary and be influenced by factors having positive or negative effects on symptom development. Altered or deficient learning and motor functions will produce special needs for optimal parenting and societal styles. Medication will to some degree normalize the underlying dopamine dysfunction and reduce the special needs of these children. The theory describes how individual predispositions interact with these conditions and produce behavioral, emotional, and cognitive effects that can turn into relatively stable behavioral patterns.

Keywords: catecholamine; dopamine; clumsiness; hyperkinesis; hyperkinetic disorder; impulsivity; monoamine; neuromodulator; overactivity; pollutants; reinforcement; reward; verbally-governed; behavior; soft signs; variability

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) (American Psychiatric Association, 1994) is a seemingly heterogeneous group of behavioral disorders affecting between 2% and 12% of grade-school children (Swanson et al., 1998; Taylor, 1998; Taylor et al., 1998; American Academy of Pediatrics, 2000). The disorder usually, but not always, manifests itself before the child is 7 years old (Applegate et al., 1997). Of children diagnosed with ADHD, 50-70% will have problems related to social adjustment and functioning, and/or psychiatric problems as adolescents and young adults (Cantwell, 1996). Of these, 20-30% will continue to suffer from ADHD during late adolescence and adulthood (Muglia, Jain, Macciardi, & Kennedy, 2000), while the full ADHD syndrome is found in only 4% of the adult population (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). However, the persistence of ADHD into adolescence and young adulthood varies according to who is being interviewed and the criteria used to define the disorder (Barkley, 2002). The finding by Mannuzza and coworkers (Mannuzza et al., 1998) is based exclusively on self-report and is probably an underestimation. In addition, remission rates can either be defined as syndromatic (less than full syndrome), symptomatic (less than subthreshold diagnosis), or functional (full recovery) remission; and differences in reported remission rates reflect the definition used rather than the disorder's course (Biederman, Mick, & Faraone, 2000). In childhood, the disorder is more common in boys than in girls. In the general population, ~9% of males and ~3% of females are found to have behaviors consistent with ADHD (American Academy of Pediatrics, 2000). During adolescence and young adulthood relatively more females are affected (Biederman et al., 1994). There might be slight geographic variations in the percentage of children diagnosed as ADHD (Alarcon, Westermeyer, Foulks, & Ruiz, 1999; Meyer, 1998; Taylor, 1998). Some of this variation could be due to different referral practices and different diagnostic criteria (Swanson et al., 1998).

There have been multiple changes in diagnostic criteria for ADHD over the past two decades. Research in this period has sought to identify more homogeneous subtypes. The emphasis has shifted from a unidimensional conceptualization to a model consisting of two factors: hyperactivity/impulsiveness and inattention (for a review of the history see Taylor (Taylor et al., 1998)). The latter model is based on exploratory and confirmatory factor analyses (cf. (Willcutt, Pennington, & DeFries, 2000). Thus, overactivity, impulsiveness, and inattentiveness are presently regarded as the main clinical symptoms of ADHD (American Psychiatric Association, 1994).

The ADHD diagnosis has three subtypes based on two behavioral dimensions: the ADHD predominantly inattentive subtype that is more typical amongst girls than boys (Taylor et al., 1998), the ADHD predominantly hyperactive/impulsive subtype that is more typical amongst boys than girls with a diagnosis of ADHD (Taylor et al., 1998), and the combined subtype. The 'inattention dimension' includes difficulty in sustaining attention, distractibility, lack of persistence, and disorganization. The 'hyperactivity/impulsiveness' dimension includes excessive motor activity and impulsive responding (Lahey et al., 1998). Admittedly, the symptoms are not that well defined and requirements vary somewhat between the ICD and DSM taxonomies (Swanson et al., 1998; Taylor, 1998). According to DSM-IV criteria, it is possible to have "ADHD" without being inattentive. Inattentiveness is, however, a necessary requirement for a hyperkinetic disorder according to ICD-10 criteria (Taylor, 1998).

Disruptive behavioral disorders and internalizing disorders are the most common comorbid disorders in ADHD. The disruptive behavioral disorders, Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), coexist with ADHD in ~35% of children. Internalizing disorders like anxiety and mood/depressive disorders coexist with ADHD in ~25% and ~18%, respectively (American Psychiatric Association, 1994; American Academy of Pediatrics, 2000). Finally, learning disabilities (e.g. reading disorder (RD), dyslexia, dyscalculia, problems with writing) are common (~25%), especially in boys with ADHD (Biederman et al., 2002c; Seidman, Biederman, Monuteaux, Doyle, & Faraone, 2001). Estimates of comorbid learning disabilities vary between 7%-92% depending on the definitions used (DuPaul & Stoner, 1994).

1.1. A dynamic developmental theory of ADHD

1.1.1. Behavioral foundations of ADHD symptoms

The search for a pivotal behavioral deficit in the behaviorally-defined ADHD and its corresponding neurobiological correlates has proven particularly challenging. A comprehensive neuropsychological model of ADHD has yet to be proposed although models of other psychopathologies have been suggested previously e.g. by Gray (Gray, 1982; Gray, Feldon, Rawlins, Hemsley, & Smith, 1991).

We will offer a novel behavioral theory of ADHD that to a large extent is inspired by behavioral analysis (see Catania's precommentary accompanying this article). In parallel we will suggest how this theory may be related to neurobiological factors. There is increasing agreement that dysregulation of fronto-striatal circuits may underlie many of the behavioral symptoms of ADHD (Biederman & Faraone, 2002a; Castellanos & Tannock, 2002b; Castellanos, 1997; Grace, 2001; Grace, 2002; Johansen, Aase, Meyer, & Sagvolden, 2002; Sagvolden & Sergeant, 1998b; Solanto, Arnsten, & Castellanos, 2001b). We will explore behavioral predictions from the point of view of interactions between dysregulated fronto-striatal circuits and hypofunctioning dopamine systems. We realize that many other changes besides hypofunctioning dopamine systems necessarily will be present in ADHD, including upregulation of parts of these systems. We suggest that explanations and predictions derived from hypofunctional dopamine system branches should be explored to the fullest before aiming research at other neurotransmitter systems. By ignoring other possible changes, we hope to be more concrete in the theoretical issues involved. It might also facilitate the design of future studies.

In a dynamic developmental theory we will argue that there might be two main behavioral processes causing ADHD: altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior. These processes may primarily be associated with a hypofunctioning mesolimbic dopamine system (Johansen et al., 2002) and will probably interact with effects of other hypofunctioning dopamine systems: a hypofunctioning mesocortical dopamine system associated with deficient attention and poor behavioral organization; and a hypofunctioning nigrostriatal dopaminergic system impairing motor functions and causing poor nondeclarative habit learning (Fig. 1). The stunted dopamine responses might be due to a combination of insufficient glutamate input from the prefrontal cortex to dopamine neurons and a faulty regulation of dopamine release (below).

The main behavioral selection mechanisms, reinforcement and extinction, are associated with dopamine neuron activity, which at a neurobiological level may have the function of constantly reprogramming neuronal connections by strengthening (reinforce, or potentiate) connections associated with reinforced (usually adaptive) behavior, while at the same time weakening (extinguish, or depress) other neuronal connections associated with non-reinforced (usually maladaptive) behavior. Reinforcement operates within a limited time window from

the occurrence of the behavior to the perception of the consequences of this behavior (for more details see later).

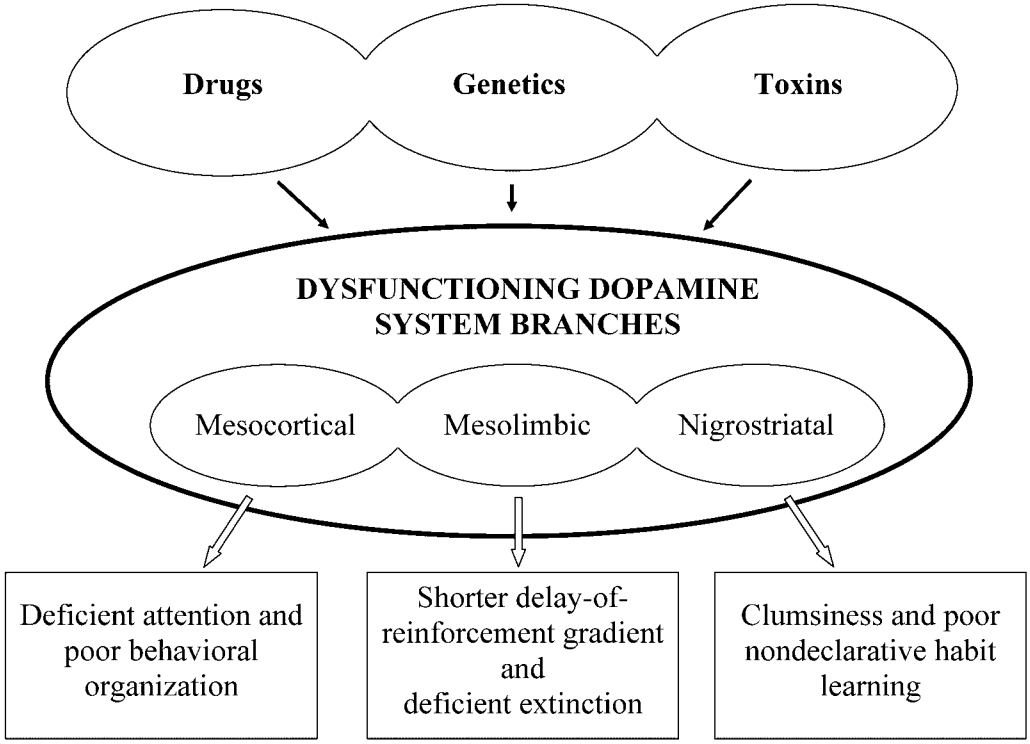

Figure 1. Dysfunction of dopaminergic systems resulting from drug abuse, genetic transmission, or environmental pollutants may cause ADHD symptoms by interacting with fronto-striatal circuits (not shown).

We argue that the time available for associating behavior with its consequences will be shorter in ADHD than in normal children if dopamine systems are hypofunctioning. A narrower time window in ADHD will restrict the stimuli controlling their behavior and therefore explain some of the attentional problems seen in ADHD. Such a narrower time window will also preferentially select short sequences of behavior giving rise to motor impulsiveness. In addition, we suggest that hypofunctioning dopamine systems lead to a deficient behavioral extinction process. This will cause excessive behavior usually labeled hyperactivity and increased behavioral variability frequently interpreted as “failure to inhibit responses”. We argue that response disinhibition is at best misleading and usually a misinterpretation.

The dynamic developmental theory disentangles aspects of various deficient "executive functions" in ADHD into impulsiveness caused by inefficient reinforcement, deficient extinction of previously acquired behavior, and impaired motor control. The concept of impulsiveness has both a motor and a cognitive component. "Motor impulsiveness" is presently defined as bursts of responses with short inter-response times (IRTs). This behavior has been shown to emerge in children with ADHD (Sagvolden, Aase, Zeiner, & Berger, 1998a) as well as in the best-validated animal model of ADHD (Sagvolden, 2000). "Cognitive impulsiveness" implies that private events like thoughts and plans are dealt with for short sequences of time with rapid shifts, resulting in problems with generating and following plans, problems with organizing own behavior, forgetfulness, and inefficient use of time. Although some aspects of cognitive impulsiveness may fit the notion of response “disinhibition” (Barkley, 1997), we will argue that these aspects may be explained as due to slower acquisition of long sequences of behavior and deficient extinction of previously reinforced behavior.

ADHD behaviors such as increased reaction times and speed variability (Oosterlaan & Sergeant, 1998; Rubia, Oosterlaan, Sergeant, Brandeis, & van Leeuwen, 1998) have been described as evidence of impaired executive functions by some authors (Kooijmans, Scheres, & Oosterlaan, 2000) and as response “disinhibition” by others (Sonuga-Barke, 2002; Pliszka, Liotti, & Woldorff, 2000). These behaviors will be explained as more fundamental, simpler motor problems: impaired timing of starting and stopping of responses; impaired acquisition, retrieval, and relearning of programs for sequential motor tasks; and deficient nondeclarative habit learning and memory.

1.1.2. ADHD in a developmental perspective

Behavior and symptoms in ADHD result from the interplay between individual predispositions and the surroundings. Thus, the dynamic developmental theory predicts that the exact ADHD symptoms at a particular time in life will vary and be influenced by factors having positive or negative effects on symptom development (Fig. 2).

The theory describes how individual variations in dopamine functioning may affect learning processes and motor functions thereby producing ADHD behavior: attentional problems, hyperactivity, and impulsiveness. The theory also predicts increased behavioral variability.

Altered, or deficient, learning and motor functions will produce special needs for optimal parenting and societal styles. Medication will to some degree normalize the underlying dopamine dysfunction and reduce the special needs of these children. The theory describes how individual predispositions interact with these conditions and produce behavioral, emotional, and cognitive effects that can turn into relatively stable behavioral patterns.

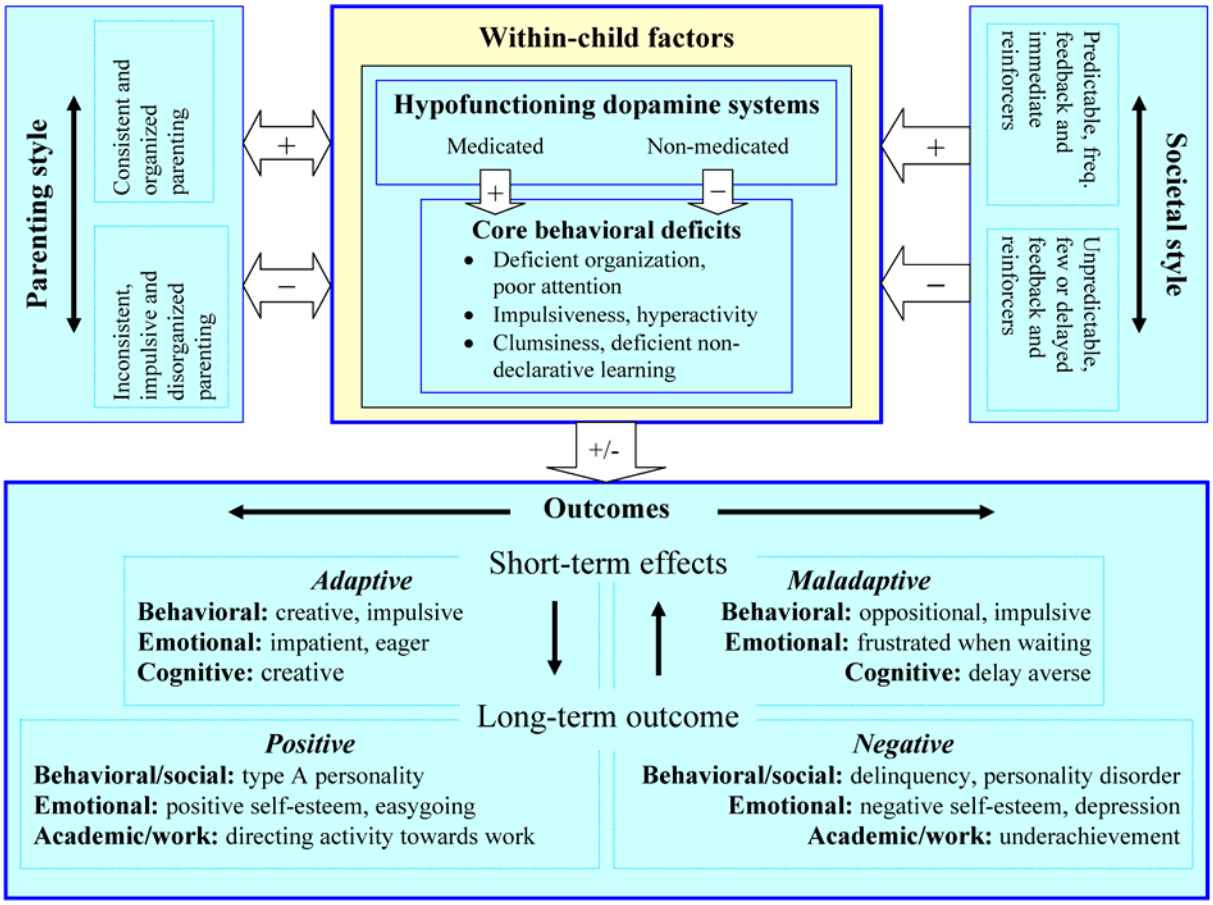

Figure 2. The dynamic developmental theory predicts adaptive as well as maladaptive behavioral outcomes of the core deficits in interaction with medication, parenting, and societal styles. A +- sign within an arrow means a beneficial interaction or influence, a --sign denotes an unfavorable interaction or influence. Parenting and societal styles, and the behavioral outcomes are regarded as vectors, not as discrete categories in order to stress the dynamic and developmental aspects of ADHD behavior.

1.2. Symptoms of ADHD

Inattention, hyperactivity, and impulsiveness are regarded as the main clinical symptoms. These symptoms are frequently explained as caused by faulty executive functions and/or deficient behavioral inhibition (below).

1.2.1. Deficient sustained attention

"Attention", in the widest sense, refers to the relationship between behavior and the environment. One is "attending" to a stimulus, or stimulus property, when variation of that stimulus or stimulus property changes behavior (Catania, 1998). Attention is modified by a multitude of psychological factors like sensory and motivational processes. In various forms, inattention is found in most psychiatric disorders except mania (Taylor, 1994) and it could well be that some non-ADHD disorders masquerade as ADHD (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993). Inattentive behavior is poorly operationalized and judgments about inattentiveness are inferred from observed behavior. This means that "inattentive behavior" may be produced by other deficits leading to poor test scores on measures of attention, i.e., behavioral changes may be misinterpreted as inattention.

Functional mapping of brain electrical activity indicates multilevel deficits in sensory processing in children with ADHD (Pliszka et al., 2000). Thus, a combination of cognitive and sensory-processing deficits may be the underlying bases of inattentive behavior observed in ADHD. It is, however, beyond the scope of the present article to review the neuropsychology of attention (for a review see (Posner & Petersen, 1990)).

"Sustained attention" means that a stimulus, or stimulus property, controls behavior over time. The attention problems of ADHD are typically described as trouble with "sustaining attention" usually occurring in situations where stimuli are widely spaced in time (Douglas, 1983). It might be that the attention problems result from changed motivational processes, as they seem to be evident "only when the ability to concentrate is stressed by the task being unwelcome or uninteresting" (Taylor, 1998) p. 15).

1.2.2. Hyperactivity

An excessive level of activity is typically seen in ADHD as restlessness, fidgeting, and a general increase in gross body movements (Porrino et al., 1983; Taylor, 1998; Teicher, Ito, Glod, & Barber, 1996). Ratings of hyperactivity (and of impulsiveness) involve an element of overstepping implicit or explicit social rules and are judged according to situational appropriateness (Taylor, 1998). Although children with ADHD move twice as frequently and cover a fourfold wider area, the ADHD movement pattern is less complex and more linear (side to side) compared to normal controls (Teicher et al., 1996). Overactivity is seen in some situations such as the classroom, but might not be present in others such as play (Porrino et al., 1983). It seems that the ADHD overactivity is absent in novel situations (Sagvolden et al., 1998a; Sleator & Ullman, 1981). Clinical evaluation of hyperactivity statistically often overlaps with impulsiveness (Taylor, 1998).

1.2.3. Impulsiveness and executive functions

ADHD impulsiveness has often been explained as being due to faulty executive functions (EFs). In DSM-IV, impulsiveness is operationalized as blurting out answers before questions have been completed, having difficulty waiting one's turn when this is appropriate; and frequent interruption and intrusion upon activities of other people. In general terms, impulsiveness means acting without reflecting and failure to plan ahead. In the literature, however, impulsiveness is a heterogeneous concept, including terms such as over-rapid responsiveness, sensation seeking, risk taking, novelty seeking, excessive attraction towards immediate reward, boldness, adventuresomeness, accident-proneness, boredom susceptibility, unreliability, and disorderliness. Measures of impulsiveness necessarily become heterogeneous, ranging from motor and cognitive measures to more complex behaviors.

Executive functions denote psychological processes involved in the organization and planning of behavior (Denckla, 1996; Tannock, 1998). Building upon more fundamental cognitive processes, executive functions consist of an assembly of higher-order cognitive functions and is used interchangeably with concepts like self-control. Impulsive behavior has been suggested to be a result of executive dysfunction caused by behavioral disinhibition (Barkley, 1997). However, the concept of behavioral inhibition is an ambiguous term both regarded as one of the executive functions as well as referring to one of the fundamental processes underlying executive functions. In addition,

the concepts of inhibition/disinhibition have multiple meanings and operationalizations (Sergeant, Oosterlaan, & van der Meere, 1999). Also, empirical findings on "disinhibition" as a characteristic of ADHD are inconclusive (Scheres, Oosterlaan, & Sergeant, 2001).

The concept “inhibition” has a variety of meanings and a long history (MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). According to Webster’s New Universal Unabridged Dictionary, the Latin verb “*inhibere*” means to hold back, restrain, or curb. This dictionary lists two main meanings: 1. to prohibit, forbid; and 2. to suppress, withhold, or check. MacLeod lists two main meanings in medicine and behavioral science: on a neuronal and on a behavioral level. He questions the evidence for the cognitive concept of inhibition, but not the neurobiological concept. The main problem is that one cannot derive the concept of inhibition directly from the concept of inhibition at the neural level (MacLeod et al., 2003).

In what is now known as neuroscience, the phenomenon of ‘inhibition’ had its breakthrough in a monograph showing that stimulation of the cut vagus nerve causes temporary cessation of the heart beat (Weber & Weber, 1846). The concept ‘inhibition of responses’ and its relation to limbic areas of the brain has a long history starting with the seminal electrophysiological works of the neurophysiologist Birger R. Kaada (Kaada, 1951). Kaada showed, along with many other observations, that electrical stimulation of the subcallosal-septal area produced inhibition of respiration, spinal reflexes, and cortically-induced movements. Stimulation of the cingulate cortex produced facilitation of these reflexes. These results were generalized from reflexes to more complex behavior by Robert A. McCleary (McCleary, 1966) showing a double dissociation following lesions of these areas: In passive avoidance where the subject has to withhold responding in order to avoid the aversive stimulus, lesions of the septal nuclei produced deficits while there was no change following cingulate lesions. In active avoidance, where the subject is required to perform an active response to avoid the aversive stimulus, septal lesions improved performance while there were impairments following cingulate lesions.

Excitation and inhibition are fundamental synaptic processes that may explain reflexes involving a few synapses (cf. (Kaada, 1951), but as any textbook in neurobiology will point out, even ‘simple’ spinal cord reflexes are highly intricate and multidimensional. Kaada’s and McCleary’s results were generalized into a theory of psychopathology by Jeffrey A. Gray (Gray, 1982) which later was

developed into theories of ADHD by Herbert C. Quay (Quay, 1988), Russell A. Barkley (Barkley, 1997), and others.

Mainly based on Barkley's and Quay's theories, response inhibition is now used extensively as an 'explanation' of ADHD symptoms perhaps without realizing that the neuronal activities behind integrated behavior are the results of extremely complex sequences of excitations and inhibitions, probably involving large numbers of synapses in highly complex neuronal networks making exact predictions from a synaptic level to behavior exceedingly difficult. Further, the response unit that is supposed to be inhibited is hard to define empirically (Catania, 1998). Few studies have addressed empirically whether functional behavioral units are only active responses or include "passive responses", e.g. recordable inactivity in a sequence of active responses. Iversen has argued that units should be based on functional analyses, not *a priori* assumptions regarding behavioral structure. The proper unit is what emerges when a reinforcement contingency is applied (Iversen, 1991). Further, functional response units are unlikely to remain constant even within the same individual e.g. under the influence of drugs when response chains sometimes appear to be truncated (Lyon & Robbins, 1975).

As long as the unit of behavior (in this case the inhibited response) is not identified, the nature of response inhibition and disinhibition remains enigmatic (Johansen et al., 2002; Sagvolden et al., 1998b). Hence, it is unclear whether response inhibition is as basic a mechanism as often suggested e.g. by Barkley (Barkley, 1997). The use of 'response inhibition' as an explanation of ADHD symptoms may be another example of an overly simplistic idea that influences research primarily because of its appeal.

1.2.4. One or two disorders?

The various attention problems associated with the ADHD subtypes are quite different from each other (Barkley, 1997; Johansen et al., 2002; Taylor, 1998). Children with the ADHD inattentive subtype are often non-hyperactive, rather dreamy, and inert children. Their attention problems are non-specific and related to deficient sensory processes; poor focused attention, and less accurate information processing. Such problems lead to reading disorder, learning disability, and may be associated with reduced IQ. Usually, such attention problems are associated with a family history of

learning problems, sluggish cognitive processes, and school failure (Taylor, 1998; Willcutt et al., 2000). Children with ADHD predominantly hyperactive/impulsive subtype do not have general attention problems in the same sense. Their attention problems are more specifically related to distractibility and reduced persistence, and are present after correcting for IQ (Taylor, Sandberg, Thorley, & Giles, 1991). Furthermore, this subtype is associated with memory retrieval problems, disruptive behavior, and peer rejection.

The subtypes may have very different developmental courses both in terms of outcome and comorbidity (Willcutt et al., 2000). While individuals with ADHD predominantly inattentive subtype may be more socially withdrawn, experience greater academic problems, and develop comorbid anxiety or other mood disorders; early hyperactive/impulsive behavior is associated with externalizing problems like aggression, oppositional behavior, adolescent delinquency, and substance abuse (Barkley, 1997).

There is little or no data on medical treatment of ADHD inattentive subtype (NIH Consens Statement, 1998) although there seems to be a common clinical notion that methylphenidate also helps these children. However, response to central stimulant medication is not specific to ADHD and cannot be used as a diagnostic criterion: both methylphenidate and d-amphetamine have been shown to have similar effects in boys with ADHD and healthy boys (Rapoport et al., 1978; Rapoport et al., 1980; Rapoport & Inoff-Germain, 2002; Conners, 2002); d-amphetamine has been shown to decrease impulsive choice in healthy volunteers (de Wit, Enggasser, & Richards, 2002) and methylphenidate to increase the amount of self-control choices in non-ADHD criminals and former substance abusers with or without conduct disorder (Pietras, Cherek, Lane, Tcheremissine, & Steinberg, 2003)

In conclusion, symptoms and developmental course indicate that the present ADHD diagnosis consists of two separate disorders probably with separate etiology: Attention Deficit Disorder predominantly inattentive type without impulsiveness and hyperactivity (ADD in the text below) and the Hyperactive/Impulsive Disorder with hyperactivity, impulsiveness, and problems with sustaining attention developing into ADHD combined type (ADHD in the text below). We suggest that the latter disorder might be named Reinforcement/Extinction Disorder (RED) according to the proposed underlying dysfunctions (cf. (Sagvolden & Archer, 1989).

We acknowledge the likelihood of ADHD subtypes, and also recognize the importance of other neurobiological factors. However, most explanatory models of ADHD address mainly the predominantly hyperactive/impulsive or the combined subtype (Tannock, 1998; Castellanos et al., 2002b). This is also the case with the dynamic developmental theory of ADHD.

2. Etiology

Abnormal dopamine function has been the focus of attention in the search for the neurobiological basis of ADHD because of the assumed dopamine agonistic action of the stimulant drugs (Johansen et al., 2002; Biederman et al., 2002a; Castellanos, 1997; Castellanos et al., 2002b; Rosenkranz & Grace, 2002; Volkow et al., 1998) that for several decades have provided the primary pharmacological treatment for ADHD (Bradley, 1937; Conners, 2002; Rapoport et al., 2002; Solanto, Arnsten, & Castellanos, 2001a).

2.1. Neurobiological bases of ADHD

Dopamine effects on prefrontal functioning are complicated (for reviews of dopamine neuroanatomy and physiology (see (Haber, Fudge, & McFarland, 2000; Grace, 2002; Missale, Nash, Robinson, Jaber, & Caron, 1998; Schultz, 2002). Dopamine exerts a strong regulatory effect on prefrontal cortical pyramidal neuronal activity. These neurons exhibit bistable membrane potentials alternating between a hyperpolarized, non-firing state and a depolarized, action-potential-firing state. The effects of dopamine stimulation on these prefrontal cells depend on this state (Grace, 2002). The glutamatergic output from these neurons projects to the nucleus accumbens and the ventral tegmental area and exerts a strong regulation of the activity in these areas.

We suggest that dopamine ought to be thought of as a neuromodulator rather than as a neurotransmitter (Siegelbaum, Schwartz, & Kandel, 2000). Its effects are relatively long lasting ones acting on metabotropic receptors coupled to G proteins (Missale et al., 1998). The dopamine actions may best be described not in terms of inhibition or excitation, but rather as gating of inputs and modulation of states of neuronal elements (Grace, 2002). Dopamine has potent regulatory control over interactions between neighboring neurons in target areas of the brain (Grace, 2002). At the systems level, dopamine exerts a focusing effect whereby only the strongest signals will pass

through the striatum to the pallidum (Schultz, 2002). On a behavioral level, “the arrival of the dopaminergic input to the striatum is best seen as providing a temporal window permitting change, rather than as providing a direction to that change” (Gray et al., 1991)p. 17).

Dopamine is the predominant catecholamine neuromodulator in the mammalian brain (Missale et al., 1998). There are at least five distinct G protein-coupled dopamine receptor subtypes all with seven transmembrane domains (Missale et al., 1998): Two D1-like receptor subtypes (DRD1 and DRD5) are primarily situated postsynaptically and are coupled to the stimulatory G protein G_s by a short third intracellular loop activating adenylyl cyclase and thereby stimulating cAMP formation (Fig. 3). The D1-like receptors increase intracellular calcium via various mechanisms. Furthermore, there are three D2-like receptor subtypes (DRD2, DRD3, and DRD4) that are coupled to the inhibitory G protein G_i by a long third intracellular loop common to receptors inhibiting adenylyl cyclase and thereby cAMP formation. The D2-like receptors are found both pre- and postsynaptically. Postsynaptically, these receptors activate K+ channels and reduce calcium influx into the cell via various mechanisms.

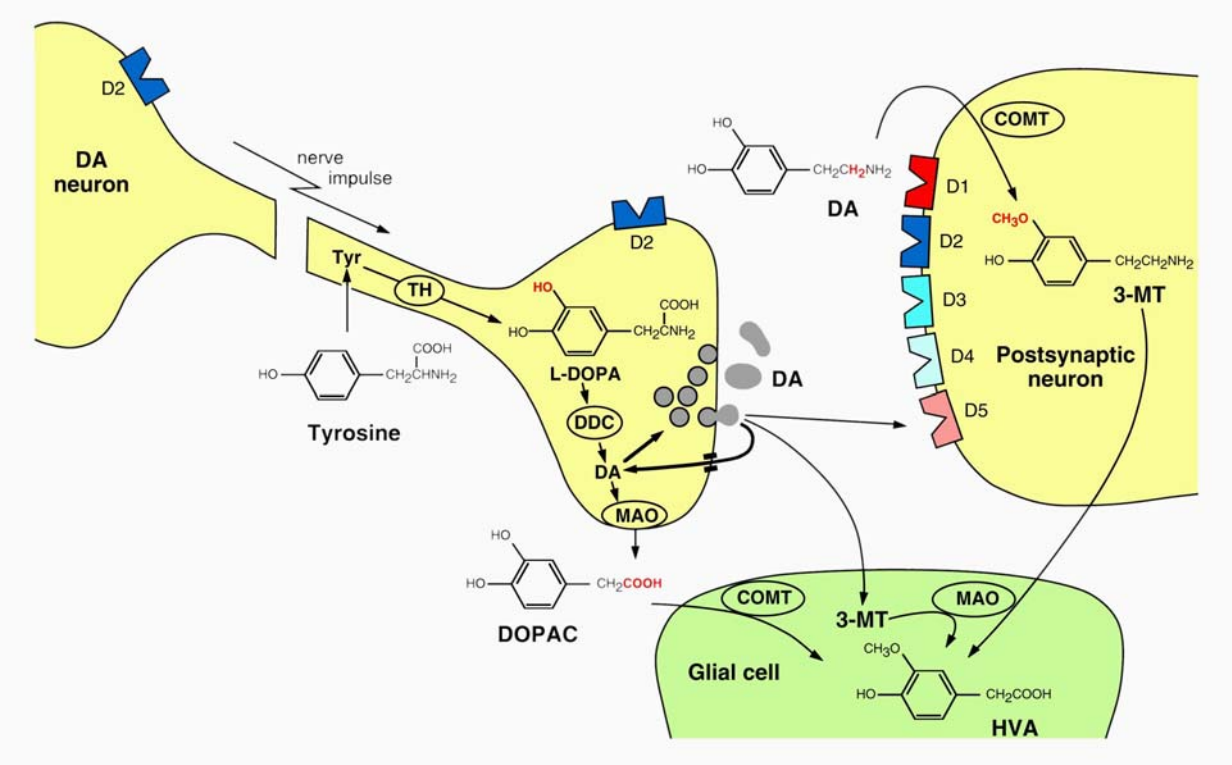

Figure 3. Neurons and glial cell showing dopamine synthesis, metabolism, and typical positions of dopamine receptors. Note that D1/5 and D2/3/4 receptors are not generally colocalized on the same neuron as they have opposite effects. Abbreviations: 3MT = 3-methoxytyramine, COMT = catechol-O-methyl transferase, D1 – D5 = dopamine receptors 1 through 5, DA = dopamine, DDC = DOPA decarboxylase, HVA = homovanillic acid, MAO = monoamine oxidase, TH = tyrosine hydroxylase, Tyr = tyrosine (modified after (Waters, 1995)).

The pharmacological profiles of the D-1-like and D-2-like receptors are different (for a review see (Missale et al., 1998). However, the pharmacological differences within each dopamine receptor subfamily are relatively small and in general related to differences in affinity of various agonists and antagonists.

Dopamine receptors are also found outside of the central nervous system, even in places where there are no dopamine-releasing varicosities such as the cardiovascular system where it is involved in controlling microcirculation (Krimer, Muly, Williams, & Goldman-Rakic, 1998). For instance, the dopamine receptor 4 (DRD4) is found on the heart (Missale et al., 1998). It seems that the function of dopamine receptors within the cardiovascular system control synergistically operating systems reducing or increasing blood pressure. Defective renal dopamine production and/or dopamine

receptor function have been reported in human primary hypertension as well as in genetic models of animal hypertension, suggesting that dopaminergic abnormalities are not a secondary effect of hypertension (Amenta, Ricci, Rossodivita, Avola, & Tayebati, 2001). Dopamine receptors are also found in the renin-angiotensin-aldosterone system (Missale et al., 1998) involved in stress and blood pressure control. This might both suggest an association between ADHD, type-A personality, and hypertension (Whalen & Henker, 1986); and explain why the spontaneously hypertensive rat strain turns out to be a good animal model of ADHD (Sagvolden, 2000). Finally, dopamine controls sodium chloride concentrations in the kidneys (Amenta et al., 2001). It might be that reduced dopamine functions change thirst and micturition in children with ADHD.

2.2. Genetic bases of ADHD

Mental disorders like ADHD are extremely challenging to genetic researchers because they do not stem from errors in single genes, but from polymorphisms that create subtle differences in human behavior and are likely to interact with the environment to create symptoms and functional impairment. In addition, both genes and environment appear to be complexly and interactively involved in the development of mental disorders, perhaps with multiple components of each. Furthermore, a mental disorder such as ADHD probably represents the pathological end of a continuum that includes normal functions.

The genetic basis of ADHD might be rather complicated. No single gene stands out as an obvious candidate. This reflects a polygenetic and multi-determinant etiology of ADHD. Evidence from twin, adoption, and family studies has found heritability to be ~80% in ADHD. However, high heritability does not imply neurobiological determinism; the behavioral result will still heavily depend on interactions with the environment (Biederman et al., 2002a; Taylor et al., 1998). Dopamine genes have been the initial candidates for investigation (Solanto et al., 2001a). Several studies have concentrated on possible links between genes coding for dopamine receptors and ADHD.

Dopaminergic neurons are complicated structures with intricate interactions with other neurons and glial cells (Fig. 3). Even the simplest of behavioral reflexes is controlled by many neurons involving several neuronal signal substances and a multitude of receptors. The various neuromodulators that

have been implicated in ADHD are very tightly linked neuroanatomically such that functional changes in one undoubtedly will affect the functioning of the others (de Villiers et al., 1995). ADHD is most likely a polygenetic disorder (Taylor, 1998) where the polygenetic contribution to the disorder interact with environmental factors in producing the behavioral expression (Taylor et al., 1998). The most frequently found genes linked to ADHD are almost all associated with neuromodulatory functions.

The high heritability of ADHD is likely to be due to multiple genes with small effect size rather than a few genes of major effect. A lot of scientific interest has focused on the human dopamine receptor 4 (DRD4) gene mapped to chromosome 11p15.5. DRD4 is highly expressed in the frontal cortex, the amygdala, the hippocampus, the hypothalamus, and in the mesencephalon and to a lesser extent in the globus pallidus and in the substantia nigra pars reticulata. Finally, the DRD4 is found on the heart and in the retina (Missale et al., 1998). Unlike most G-protein coupled receptors that have no introns interrupting the coding sequence, the DRD4 gene has three such introns.

The human DRD4 gene exhibits extensive polymorphic variations within the coding sequence. There are several insertions in the functionally significant third intracellular loop. A 48-base pair sequence in the third intracellular loop exists either as a single repeat of the sequence or as multiple repeats. The most common form is the 4-repeat form, followed by the 7- and 2-repeat forms (Missale et al., 1998). The 7-repeat allele in exon 3 of the DRD4 gene may be associated with a subsensitive postsynaptic receptor (Missale et al., 1998). Several candidate gene studies have identified an association between a 7-repeat variant in exon 3 of the DRD4 (or a neighboring locus) and ADHD (as well as novelty seeking and Tourette's syndrome) (Barr et al., 2000a; Holmes et al., 2002; Manor et al., 2002) although other studies have failed to replicate this association (Mill et al., 2002; Smith et al., 2003; Fisher et al., 2002; Castellanos et al., 1998). A recent metaanalysis indicates a small, but real association between the DRD4 7-repeat and ADHD (Faraone, Doyle, Mick, & Biederman, 2001).

Although the presence of the DRD4 7-repeat allele may be associated with a modestly increased risk for ADHD, it is not a necessary condition as about half of the ADHD children do not have a 7-repeat allele. Nor is it a sufficient condition since ~ 20% of the unaffected controls have a 7-repeat allele (Swanson et al., 2000a). Surprisingly, in this study the ADHD subgroup defined by the

presence of the 7-repeat allele showed normal response speed and variability in neuropsychological tests designed to probe attention networks with neuroanatomical foci in D4-rich brain regions, whereas the subgroup of ADHD children without the 7-repeat variant of the DRD4 showed the expected abnormality of slow and variable responses. The dopamine receptors are differently distributed across the world and DRD4 7-repeat allele might be associated with novelty seeking, perseverance, and migration (Ding et al., 2002).

Other dopamine receptor genes have also been investigated. The dopamine receptor 1 (DRD1) is the most widespread dopamine receptor in the brain. DRD1 gene polymorphism does not seem to be associated with ADHD (Kuntsi & Stevenson, 2000). The dopamine receptor 2 (DRD2) is mainly expressed in the neostriatum and in the olfactory tubercle. The DRD2 gene is associated with ADHD in some (Comings et al., 1996), but not all studies (Kuntsi et al., 2000; Todd & Lobos, 2002). There might be an association with substance abuse (Blum et al., 1995). The dopamine receptor 3 (DRD3) does not seem to have a role in ADHD (Barr et al., 2000b). The dopamine receptor 5 (DRD5) is found in the hippocampus (where the DRD5 is highly present compared to the DRD1), in the dentate gyrus, in the entorhinal cortex, in the lateral mammillary nucleus, in the diagonal band of Broca, in the prefrontal and premotor cortices, in the lateral thalamus, and in the neostriatum. DRD5 levels are relatively low compared to those of DRD1. In general, the dopamine receptors are found on inhibitory GABA neurons, but the DRD5 are also situated on large cholinergic interneurons (Missale et al., 1998). There might be an association between ADHD and a polymorphism near the DRD5 gene (Tahir et al., 2000) in certain ADHD families(Fisher et al., 2002; Hawi et al., 2003).

The plasma membrane dopamine transporter (DAT1) provides major regulation of synaptic and extra synaptic levels of dopamine and is a principal target of psychostimulant drugs (Missale et al., 1998; Grace, 2002; Volkow et al., 1998). The DAT1 gene has 15 exons, several introns, and several polymorphisms. The 10-repeat allele of the DAT1 gene may be associated with increased re-uptake of dopamine (Swanson et al., 2000b). Allelic variations of the DAT1 gene have been linked to ADHD in some (Comings et al., 1996; Chen et al., 2003; Hawi et al., 2003; Kuntsi et al., 2000), but not in all studies (Palmer et al., 1999; Muglia, Jain, Inkster, & Kennedy, 2002; Fisher et al., 2002). Finally, catechol-O-methyl transferase (COMT), an enzyme metabolizing catecholamines, may be involved in ADHD gender differences in Han Chinese (Qian et al., 2003).

The dopamine systems are linked to the noradrenergic (NE) neuromodulator system originating in the locus coeruleus. Plasma norepinephrine concentrations may be significantly increased in ADHD children with reading disorder and other cognitive disabilities compared to ADHD children without learning disabilities (Halperin et al., 1997). ADHD, especially when associated with learning disabilities and poor grade-school academic performance, has been shown to be associated with the dopamine-beta-hydroxylase (DβH) enzyme converting dopamine into norepinephrine (Comings et al., 1996; Hawi et al., 2003; Smith et al., 2003) and noradrenergic genes: the adrenergic alpha2A receptor (ADRα2A), adrenergic alpha2C receptor (ADRα2C), and DβH genes (Comings et al., 1999). Although the dopamine transporter DAT1 may be involved in ADHD, the gene for the norepinephrine transporter (NET1) does not seem to be a susceptibility factor in ADHD (Barr et al., 2002).

The dopamine systems are also anatomically closely linked to the serotonergic (5-HT) neuromodulator systems originating in the brainstem raphe nuclei. Reduced central serotonergic activity has been implicated in poor impulse regulation and aggressive behaviour. There is evidence for an involvement of 5-HT transporter polymorphism in ADHD (Cadoret et al., 2003; Kent et al., 2002; Fisher et al., 2002). A linkage between polymorphisms in the serotonin HTR2A receptor gene and ADHD has been shown (Quist et al., 2000), but not in all studies (Zoroglu et al., 2003; Levitan et al., 2002). The 5-HT1B receptor, however, may be involved in ADHD (Quist et al., 2003). It could be that norepinephrine and serotonin imbalances contribute to a dopaminergic imbalance, which underlines the possible complex interplay among the neurotransmitter systems in the etiology of ADHD.

In conclusion, it might not be one critical gene associated with ADHD. Instead ADHD could be the result of one of several combinations of genes producing postsynaptic changes of a magnitude exceeding the capacity of normal neuronal or behavioral compensatory mechanisms. This may explain why the same gene allele has not been found to be critical in all studies. Another possibility is that environmental factors (e.g. density of reinforcers, or number and intensity of environmental stimuli) contribute to normalization of synaptic function despite an unfavorable genetic constitution. In addition, it is conceivable that ADHD consists of subgroups that can be differentiated according to the genetic make-up.

2.3. Non-genetic factors in the etiology of ADHD

As reviewed above, dopamine dysfunction seems to play a pivotal role in the neurobiology of ADHD. Reductions in dopaminergic functioning can result from genetic as well as non-genetic factors (Fig. 1). For example, dopamine agonist drugs such as cocaine, crack, and amphetamines produce a down-regulation of dopamine synthesis (Scafidi et al., 1996). The down-regulation and ADHD-like symptoms persist until dopamine functions normalize.

Drug addicts and children exposed to drugs of abuse prenatally exhibit ADHD-like behavior (Vogel, 1997; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). Development of ADHD symptoms is a dynamic process of adaptation to defective neurotransmission in the developing brain. It is important to understand the current status of the nervous system of ADHD children in order to gain insight into the pathogenesis of ADHD. Excitatory inputs to the ventral tegmental area (VTA) dopamine neurons and to the nucleus accumbens are critical for the development of sensitization and addiction to drugs of abuse (Bonci, Bernardi, Grillner, & Mercuri, 2003; Saal, Dong, Bonci, & Malenka, 2003; Thomas, Beurrier, Bonci, & Malenka, 2001; Wolf, 1998; Thomas et al., 2001; Vanacore et al., 2002; Ryu et al., 2002). Sensitization involves incremental adaptations to these drugs.

Chronic *in vivo* administration of cocaine increases dopamine release in the nucleus accumbens and elicits a long-lasting depression of synaptic strength at synapses made by prefrontal cortical afferents onto medium spiny neurons in the shell subdivision of the nucleus accumbens, a change that is required for the maintenance of behavioral sensitization and addiction (Thomas et al., 2001). As a result of the cocaine-induced decrease in synaptic strength of cortical afferent connections, the magnitude of long-term depression (LTD, see below) is reduced in the nucleus accumbens shell (Thomas et al., 2001) thereby impairing extinction.

We suggest that inappropriate overactivity of mesolimbic VTA dopamine neurons at an early stage of development of ADHD could similarly increase excitatory synaptic transmission in the VTA dopamine neurons. This could perhaps result in depolarization block of VTA dopamine neurons and hypoactivity of the mesolimbic dopaminergic system.

Worldwide, more than 3000 chemicals are produced in high volumes (over 500 tons/yr). Few of these have been adequately tested for their effects on the developing brain. It is documented that some environmental toxins cause a wide variety of problems, including impairments in attention, memory, learning, social behavior, and IQ (Stein, Schettler, Wallinga, & Valenti, 2002). Some environmental pollutants cause dopamine dysfunction. Epidemiological studies have linked insecticide, herbicide and fungicide exposure to Parkinson's disease. The concentrations and types of these chemicals vary between countries and regions within a country. Pyrethroid insecticides reduce striatal dopamine function (Pittman, Dodd, & Klein, 2003) and induce anxiety-like behavior in rats (Righi & Palermo-Neto, 2003). The insecticide rotenone causes the death of dopaminergic neurons in vitro and in vivo by mitochondrial chain complex I inhibition, and is widely used to model Parkinson's disease in animals (Beal, 2003; Imam, 2003; Vanacore et al., 2002). The herbicide paraquat and the fungicide maneb enhance sensitivity of the ageing nigrostriatal dopamine pathway resulting in irreversible and progressive neurotoxicity in mice (Thiruchelvam et al., 2003). It is not known whether these chemicals are able to induce ADHD-like symptoms.

Polychlorinated biphenyls (PCBs) constitute a group of halogenated aromatic hydrocarbons that is lipophilic, and consequently, is bioaccumulating (Holene, Nafstad, Skaare, & Sagvolden, 1998). The lipophilic nature of PCBs makes organs like the brain particularly vulnerable. Intake of these pollutants causes developmental abnormalities in human babies including low birth weight, disruptive behavior, and overactivity (see (Seegal, 1996) for references). A series of studies of effects of PCB exposure on behavior and brain chemistry (Holene et al., 1995; Holene et al., 1998) showed that normal male rats exposed to sub-toxic doses of the PCB congener 153 through mother's milk when pups were hyperactive and impulsive after they had grown up. Their behavior was closely similar to that shown by the spontaneously hypertensive rat, the best validated animal model of ADHD (Sagvolden, 2000). Similar behavioral changes are shown by rats either consuming food adulterated with the commercial PCB mixture Aroclor 1248 or PCB-contaminated St. Lawrence River carp (Berger et al., 2001). Although the various PCBs work via different routes, the most likely mode of action of di-ortho-substituted PCB congeners like PCB 153 producing hyperactivity and motor impulsiveness is via monoaminergic pathways. Dopamine and serotonin levels are reduced (Chu et al., 1996) probably by a combination of an inhibition of dopamine synthesis and deficient vesicular storage or release (Chishti, Fisher, & Seegal, 1996).

There is an increasing amount of evidence from prospective studies suggesting a strong linkage between maternal smoking during pregnancy and the development of ADHD, conduct disorder, learning difficulties, and later substance abuse in the offspring (Weissman, Warner, Wickramaratne, & Kandel, 1999). Also, fetal exposure to alcohol is associated with adolescent behavioral and learning problems (Olson et al., 1997; Weinberg, 1997). The direct impact of and neurological mechanisms involved in such exposure on the development of ADHD in the child is not yet established; they are considered to be rather general (but highly increased) risk factors for later behavioral, social, and learning problems.

Finally, children with ADHD are about three times more likely to have been born with low birth weight (LBW) than non-ADHD children. Although birth weight is highly heritable, the increased incidence of LBW among children with ADHD might have other, non-genetic causes. Children with LBW,, however, make up a relatively small proportion of children with ADHD after attending to potential confounders such as prenatal exposure to alcohol and cigarettes, parental ADHD, social class, and comorbid disruptive behavior disorders in parents and offspring (Mick, Biederman, Prince, Fischer, & Faraone, 2002). A recent prospective study following children from birth to mid-adolescence found that small for gestational age status had only modest independent impact on learning, cognition, and attention in adolescence (O'Keeffe, O'Callaghan, Williams, Najman, & Bor, 2003).

2.4. Important neuronal loops

The brain serves behavior by increasing or decreasing activity in neural networks that connect neurons in different anatomical regions of the brain that communicate with each other. The functioning of midbrain dopaminergic neurons and their projection areas, particularly the prefrontal cortex and striatum, has been implicated in ADHD (Castellanos et al., 2002b; Castellanos, 1997; Grace, 2001; Solanto et al., 2001b; Sagvolden et al., 1998b; Teicher et al., 2000). Dopamine and the other neuromodulators exert distinct regulatory actions on the transfer of information through neural circuits that connect, among other structures, frontal cortical areas with the striatum (the nucleus accumbens septi, the caudate nucleus, and the putamen), the pallidum, the thalamus, the substantia nigra, and the ventral tegmental area (Alexander, DeLong, & Strick, 1986).

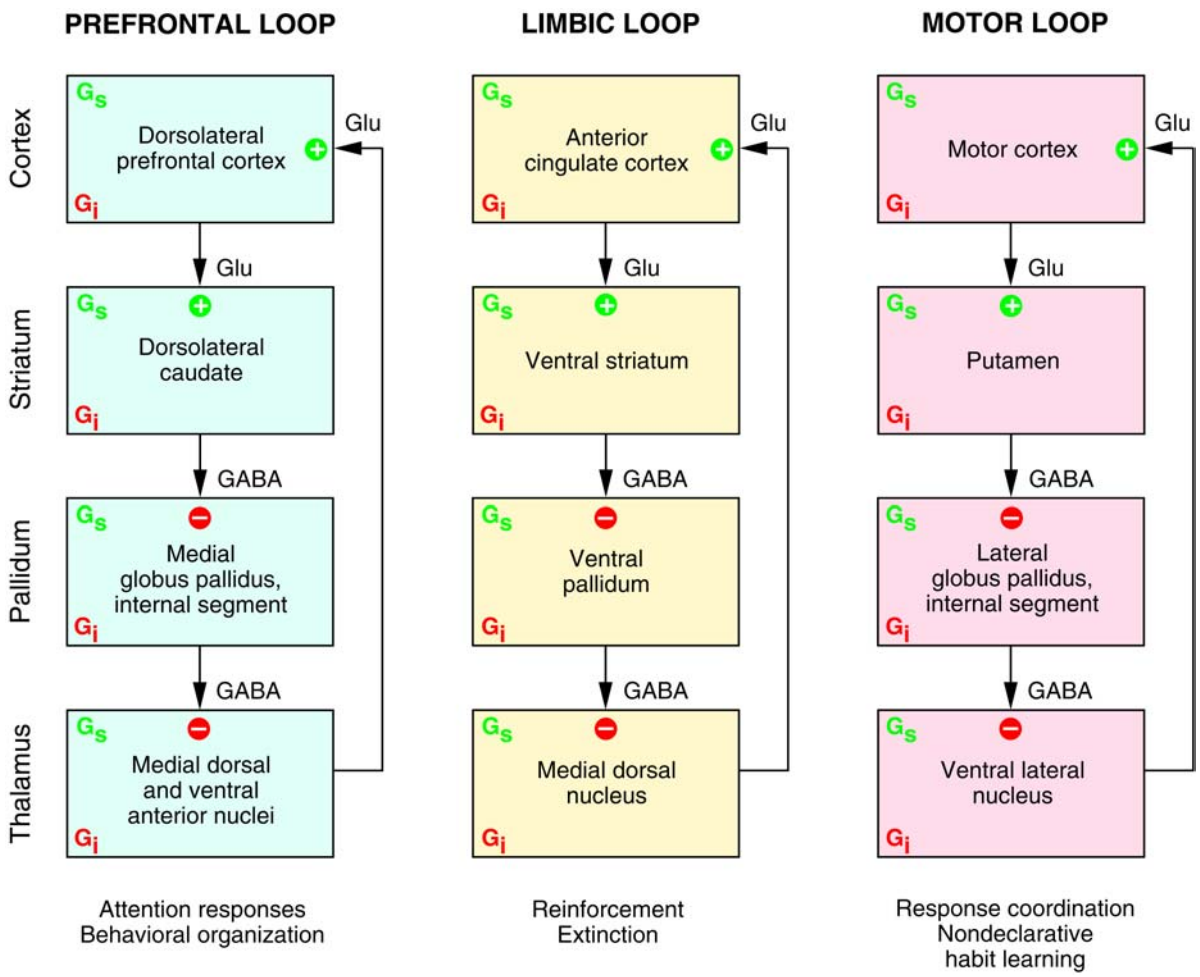

Figure 4. Neurons in the frontal cortical areas send excitatory glutamatergic projections to the striatum. These structures send inhibitory GABAergic projections to the pallidum (and substantia nigra) that inhibit thalamic nuclei through GABAergic connections. Finally, the thalamus completes the circuit by sending excitatory glutamatergic projections to cortical neurons. The figure illustrates that there are several circuits like this probably with distinct functions. On each level, the functioning may be modulated by the actions of stimulatory G proteins, G_s, and inhibitory G proteins, G_i associated with various neuromodulators. Adapted from (Alexander et al., 1986).

In general, neurons in the frontal cortical areas send excitatory glutamatergic projections to the generally silent medium-spiny neurons of the striatum including the nucleus accumbens (ventral striatum). These structures send inhibitory GABAergic projections to the normally active neurons of the pallidum and the substantia nigra that inhibit thalamic nuclei through GABAergic connections. Finally, the thalamus completes the circuit by sending excitatory glutamatergic projections to

cortical neurons (Fig. 4). Figure 4 is a simplification, however, as it omits interactions between the various loops. E.g., dopamine release in the nucleus accumbens shell influences dopamine release in the core which in turn influences dopamine release in the caudate-putamen etc in an ascending spiral (see (Haber et al., 2000)).

There are several circuits like this that may have distinct functions: firstly, a 'prefrontal loop' apparently involved in functions like planning of future behavior, short term memory, and directing attention (cf. (Posner et al., 1990); secondly, a 'limbic loop' involved in reinforcement and extinction of behavior (cf. (Schultz, 2002; Waelti, Dickinson, & Schultz, 2001); and thirdly a 'motor loop' seemingly involved in timing the starting and stopping of responses, in the acquisition, retrieval, and relearning of programs for sequential motor tasks (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999), and nondeclarative habit learning (discriminative stimulus – response – reinforcement relations, (Knowlton, Mangels, & Squire, 1996).

The nucleus accumbens consists mainly of medium-spiny neurons that are surrounded by a "cloud" of glutamate and dopamine from 10 000-15 000 inputs from excitatory glutamatergic neurons and 5 000-6 000 inputs from dopaminergic neurons overlapping the glutamatergic inputs (Grace, 2001). The main inputs are from the prefrontal cortex, the hippocampus subiculum (information about the behavioral context), the amygdala (affective information), and the ventral tegmental area (Grace, 2001; Gray et al., 1991). The medium-spiny accumbens neurons exist in a bi-stable state, either hyperpolarized and non-firing, or at a depolarized plateau where action potentials are generated (Grace, 2001). The hippocampus subiculum controls this bistable state and is, therefore, able to gate information from the prefrontal cortex to pallidum, thalamus, and back to neocortex (Grace, 2001).

As reviewed by Grace (Grace, 2001), there are two functionally distinct, and normally tightly regulated, dopamine components: the phasic and the tonic. Schultz suggests that the phasic component may be subdivided into two subcomponents: a fast (100 to 300 ms) component signaling erroneous 'reward prediction' and an intermediate subcomponent (lasting from seconds to minutes) involved in reinforcement, sex, movement, punishment and stress (Schultz, 2002). The phasic component releases dopamine as a brief pulse in association with an action potential, or "spike". Released dopamine is rapidly removed from the synaptic cleft by the plasma membrane dopamine transporter (DAT1). The tonic dopamine level controls the phasic dopamine release via synthesis-

and release-modulating autoreceptors on the dopamine terminals. Normally, the tonic extracellular dopamine pool is too low in concentration to stimulate postsynaptic dopamine receptors. However, the concentration is sufficient to provide a tonic down-modulation of action-potential-dependent dopamine release by stimulating (presynaptic) release- and synthesis-modulating dopamine autoreceptors on dopamine terminals. This causes a decrease in the action-potential-dependent dopamine release in the synaptic cleft (Grace, 2001; Grace, 2002).

The tonic dopamine level is controlled by two sources: low concentrations of dopamine that has escaped from the synaptic cleft and glutamate released from (mainly prefrontal) cortical afferents in close proximity to the dopamine terminal. This glutamate stimulates close-by presynaptic heteroceptors on the dopamine terminal to release dopamine from an intraterminal pool of vesicles directly into the extrasynaptic space. Normally, a low tonic dopamine level will lead to elevated action-potential-driven phasic dopamine responses (Grace, 2002). An underdeveloped, immature, or hypoactive prefrontal cortex will reduce this glutamatergic input resulting in abnormally low tonic dopamine levels in ADHD (Grace, 2001; Solanto et al., 2001b). We suggest that ADHD is associated with a dysregulation of tonic/phasic dopamine control causing stunted phasic dopamine responses (Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1995) despite low tonic dopamine levels. This might be due to several factors, e.g. genetic mechanisms uncoupling this normally tight regulation.

There are several indications of anatomic and functional changes in the frontal lobes of ADHD (Castellanos, 2001). In a series of studies, Castellanos and collaborators have been using automated methods measuring initial volumes and prospective age-related changes of total cerebrum, cerebellum, gray and white matter for the four major lobes, and caudate nucleus of the brain in patients and controls. Patients with ADHD had significantly smaller brain volumes in all regions. This global difference was reflected in smaller total cerebral volumes and cerebellar volumes. Also previously unmedicated children with ADHD demonstrated significantly smaller total cerebral and cerebellar volumes. Unmedicated children with ADHD also exhibited strikingly smaller total white matter volumes compared with controls and with medicated children with ADHD. Volumetric abnormalities persisted with age in total and regional cerebral measures and in the cerebellum. Caudate nucleus volumes were initially abnormal for patients with ADHD, but diagnostic differences disappeared as caudate volumes decreased for patients and controls during adolescence.

Results were comparable for male and female patients on all measures. Frontal and temporal gray matter, caudate, and cerebellar volumes correlated significantly with parent- and clinician-rated severity measures within the ADHD sample (Castellanos et al., 2002a). Since dopamine is involved in controlling cerebral circulation (Krimer et al., 1998), circulatory changes due to hypofunctioning dopamine systems may be one reason why brain imaging studies have shown relatively global functional and structural differences between subjects with ADHD and controls.

2.5. Roles of dopamine in neuronal processes involved in reinforcement and extinction

The dopaminergic system has several branches: the mesolimbic and mesocortical branches originating in the ventral tegmental area, projecting to the nucleus accumbens septi, the olfactory tubercle (the mesolimbic branch), and to the prefrontal cortex (the mesocortical branch); and the nigrostriatal branch originating in the substantia nigra and projecting mainly to the striatum (Fig. 1). Imbalances in dopamine transmission in these branches will inevitably lead to imbalances in other neurotransmitter systems producing specific behavioral effects related to the different systems and depending on situational fluctuations.

2.5.1. Reinforcement

Reinforcers are required both in acquisition and in maintenance of behavior. Reinforcement describes either a procedure (delivering a reinforcer) or a process ('strengthening' the likelihood that the reinforced response(s) will be repeated later in the same or a similar situation). A stimulus is a positive reinforcer if its presentation increases the probability of future occurrence of the response that produced it. The reinforcement contingencies are the conditions under which a response produces a reinforcer (Catania, 1998).

The concept ‘reinforcer’ is strictly behavioral and makes no reference to subjective or cognitive states. The alternative concept ‘reward’ is more cognitive and connotes several subjective states like ‘pleasure’ as well as ‘reinforcer’ and ‘incentive’ (Robbins & Everitt, 1996). Thus, there is not a perfect overlap between ‘reinforcer’ and ‘reward’. We prefer the more descriptive and less ambiguously defined concept ‘reinforcer’ rather than ‘reward’.

A large body of evidence shows the importance of increased activity of the mesolimbic dopamine system, particularly in the nucleus accumbens, during reinforcement (Di Chiara & Imperato, 1988; Robbins et al., 1996; Schultz, 1998; Schultz, 2002). This does not imply that dopamine activity is only, or always, involved in reinforcement. In general, dopamine is released in the nucleus accumbens, but not necessarily in the dorsal striatum, when novel associations between stimuli, or stimuli and responses can be formed (Datla, Ahier, Young, Gray, & Joseph, 2002). These stimuli may be reinforcers, but also seemingly neutral stimuli without apparent motivational or incentive value, even stressors or aversive stimuli. Only small increases in accumbal dopamine levels are produced by such stimuli when presented alone and out of context, or even by consuming a palatable reinforcer (Datla et al., 2002). Accumbal dopamine release is also seen when associations between two stimuli without apparent motivational value are formed (Young, Ahier, Upton, Joseph, & Gray, 1998).

Dopamine neurons normally fire at a low tonic rate. Following a reinforcer, there is a phasic burst of activity of intermediate duration (Schultz, 2002; Waelti et al., 2001; Schultz, 1998) (Fig. 5). Reinforcement-induced burst firing of dopaminergic neurons produces a global dopamine signal that advances as a parallel wave of activity from the midbrain to the (ventral) striatum and the frontal cortex (Schultz, 1998; Schultz, 2002). Synaptically-released dopamine diffuses out of the synaptic cleft and gives rise to transient peaks of extracellular dopamine concentrations (Schultz, 1998). Thus, in the present theoretical framework, the burst of dopamine neuron activity seems to be linked to stimuli that function behaviorally as reinforcers. These reinforcers may either be primary or secondary (conditioned), scheduled or unscheduled (unpredictable, “free”, (Datla et al., 2002; Schultz, 2002). The phasic burst activity following a reinforcer seems to occur whenever the delivery of this reinforcer deviates from the organism’s acquired behavioral relationships, e.g. reinforcer delivery during acquisition of novel behavior, delivery at an unusual time, or when the reinforcer has a higher-than-usual reinforcing value. The phasic dopamine activity level is gradually transferred to the earliest stimulus predicting future reinforcers. This stimulus is functioning behaviorally as a discriminative stimulus with secondary reinforcer properties (Schultz, 2002). Apparently, there is no change in the tonic dopamine activity when stable-state behavior is established and reinforcer deliveries are according to acquired stimulus-response-reinforcer relations (Schultz, 2002; Waelti et al., 2001; Schultz, 1998) (Fig. 5).

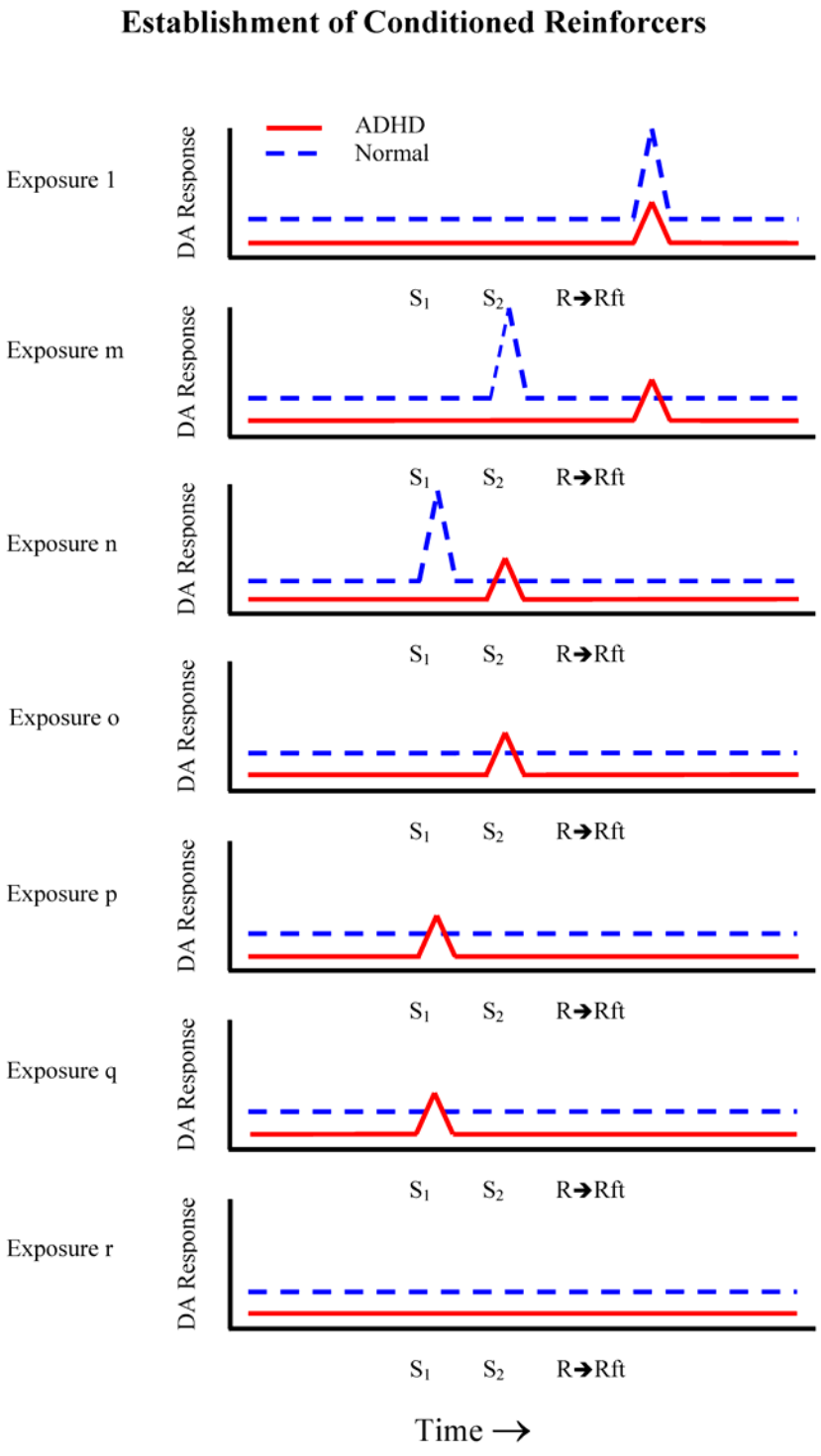

Figure 5. Dopamine neurons normally fire at a low tonic rate. Following a reinforcer, there is a short-lasting, phasic burst of activity. The phasic dopamine activity level is gradually transferred to the earliest stimulus predicting future reinforcers. When stable-state behavior is established and reinforcer deliveries are according to acquired stimulus-response-reinforcer relationships, there is no change in dopamine activity. The predicted hypofunctioning dopamine systems in ADHD slow this process. S_1 and S_2 denote stimuli, R a response that produces the reinforcer (Rft). Adapted from (Schultz, 1998).

Modulation of the long-term increased effectiveness of synaptic transmission, long-term potentiation (LTP) is one of the effects of dopamine release (Pedarzani & Storm, 1995; Stein, Xue, & Belluzzi, 1993). LTP is regarded as a neuronal correlate to learning (Malenka & Nicoll, 1999). It requires interplay between several factors. Among these is coincident glutamate stimulation of NMDA receptors and local membrane depolarization large enough to remove the magnesium ion blocking calcium entry through the ion channel linked to the NMDA receptor. The opening of local excitatory sodium channels like the ones associated with glutamatergic AMPA receptors produces this depolarization. Calcium enters the cell through the NMDA receptor channel and mobilizes "silent" AMPA receptors necessary for LTP to take place (Malenka et al., 1999).

The duration of the time window available for coincidence detection with NMDA receptor stimulation is obviously critical for AMPA receptor mobilization and for subsequent LTP. NMDA-receptor induced excitation necessary for LTP is enhanced by DRD1 receptor activation and attenuated by DRD2 activation (Cepeda, Buchwald, & Levine, 1993; Kerr & Wickens, 2001; Pedarzani et al., 1995). Thus, DRD1-receptor activation may synergistically increase the excitatory actions of glutamate at NMDA receptors by increasing the opening time of NMDA receptors and therefore the time window available for coincidence detection. NMDA receptors are necessary for LTP in the hippocampus (Malenka et al., 1999), in cortico-striatal synapses (Calabresi, De Murtas, & Bernardi, 1997), and in the nucleus accumbens (Kelley, Smith-Roe, & Holahan, 1997). Within the striatum, LTP (and long-term depression, LTD) only occurs in the presence of dopaminergic input (Grace, 2002). Phasic application of dopamine in the prefrontal cortex facilitates LTP (Blond, Crepel, & Otani, 2002).

The dopamine-induced enhancement of synaptic transmission by accelerating LTP of the synapses in these areas is in accordance with a three-factor Hebbian learning rule. Synaptic transmission undergoes plastic changes when presynaptic (glutamatergic) input, postsynaptic activation, and the dopamine signal occur simultaneously at the same neuron. Thus, the homogeneous dopamine signal associated with reinforcement will selectively reinforce the weights of synapses that are active around the time of behavioral reinforcement (Wickens, Begg, & Arbuthnott, 1996). At a systems level, dopamine exerts a focusing effect whereby only coincident inputs are reinforced and subject to LTP, whereas unsynchronized activity has no such LTP-effect. Dopamine probably exerts its

reinforcing effects by acting on D1-like receptors (DRD1 and DRD5; cf., (Schultz, 2002) stimulating adenylyl cyclase to produce cAMP that is essential for activation of PKA (cAMP-dependent protein kinase A). The resultant phosphorylation of CREB (cAMP response element binding protein), activation of gene transcription, mRNA, protein synthesis, and structural changes, are required for memory consolidation (Bailey, Giustetto, Huang, Hawkins, & Kandel, 2000).

Using the hippocampal-slice preparation, it has been shown that the time frames of synaptic plasticity of burst activity in hippocampal CA1 pyramidal cells are closely similar to that of the equivalent behavioral phenomena. The spontaneous bursting of individual CA1 pyramidal neurons may be reinforced with activity-contingent injections of dopamine and cocaine, whereas CA3-bursting responses may be reinforced with contingently-applied dynorphin A (Stein & Belluzzi, 1989; Stein et al., 1993). Burst-contingent injections of the excitatory neurotransmitter glutamate failed to reinforce CA1 bursting. It is likely that dopamine acts as a "neurochemical reinforcer" through D1-like receptors in cellular models (Schultz, 2002).

2.5.2. Extinction

Procedurally and behaviorally, extinction is defined in relation to reinforcement. Discontinuation of reinforcer deliveries (actually, discontinuation of a reinforcement schedule) is termed an extinction procedure. This procedure starts an extinction process. This process has traditionally been understood as part of the process generated by reinforcement: Responding is maintained as long as reinforcers are delivered contingent on the responses and stops, or is reduced to the level prior to reinforcement (the operant level), when this contingency is discontinued (Catania, 1998). Thus, for operant behavior, extinction is the other side of reinforcement. Operant extinction may be the demonstration that the effects of reinforcement are temporary (cf., Catania's commentary this issue of BBS.)

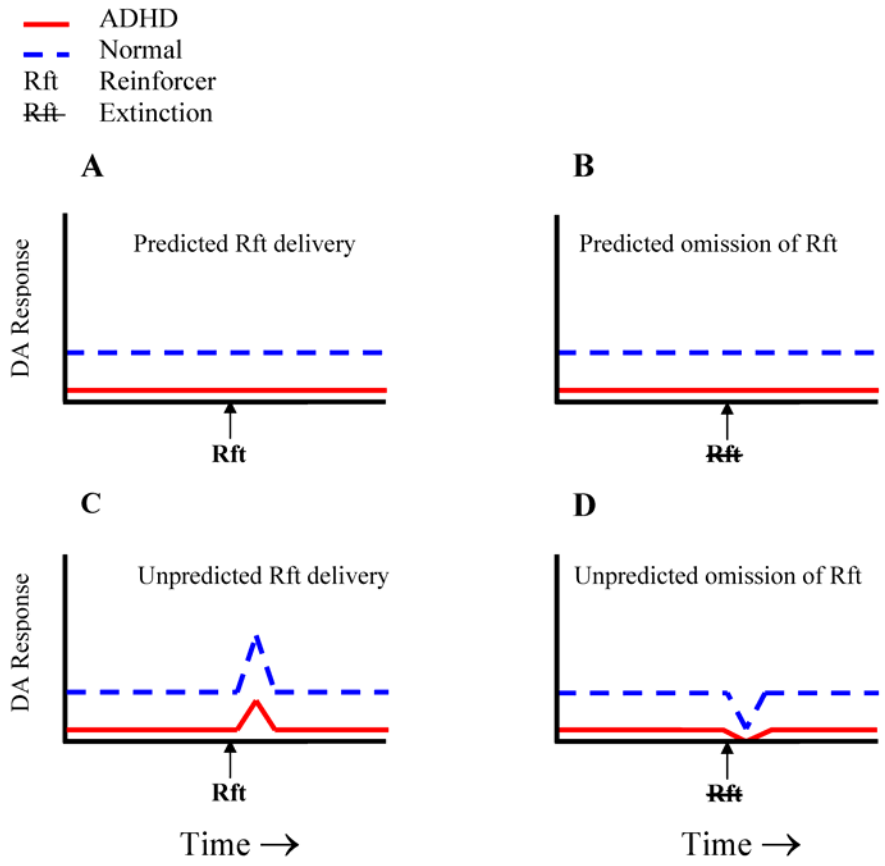

Figure 6. Dopamine neurons normally fire at a low tonic rate. When a reinforcer is delivered according to an established reinforcement schedule, there is no change in dopamine activity either when the reinforcer is delivered (A), or when an omission of a reinforcer is signaled or predicted (B). Phasic changes are observed whenever there are unpredicted deviations in reinforcement schedules. An increased activity takes place when an unpredicted ("free") reinforcer is delivered (C), while a decrease occurs when a predicted reinforcer is not delivered (D). Hypofunctioning dopamine systems in ADHD results in stunted dopamine activity changes. It is predicted that, in particular, the phasic decrease in the dopamine activity (D) is stunted in ADHD due to a "floor" effect. This will cause deficient extinction often manifested as a failure to inhibit responses. Adapted from (Waelti et al., 2001).

Neurobiologically, however, reinforcement and extinction may be separate processes associated with different aspects of dopamine neuronal activity. Depression of dopamine activity seems to occur when, in our terms, previously established stimulus-response-reinforcer relations are discontinued, (cf. (Schultz, 2002; Waelti et al., 2001). Extinction (and reinforcers with lower than previously experienced reinforcer value) is accompanied by a short-lasting (100-300 ms) phasic *decrease* in the tonic level of dopamine activity. There is no depression of dopaminergic neuronal activity, however, when an omission of a reinforcer is signaled (Fig. 6) (Waelti et al., 2001). Thus,

the extinction process depends on phasic depression of the tonic level of dopamine activity. On a synaptic level, it might be predicted that reduced availability of dopamine will start a long-term depression (LTD) process. The open time of the NMDA-receptor associated ion channels will be reduced and less calcium is allowed to enter the cell. The reduced intracellular calcium levels will activate protein phosphatases removing phosphate groups from proteins and start removing the AMPA receptors from the active zone of the synapse (Luscher, Nicoll, Malenka, & Muller, 2000). The associated LTP will no longer be maintained and will therefore gradually be reduced.

3. A dynamic developmental theory of ADHD

ADHD is currently defined as a cognitive/behavioral disorder with no biological marker. We will consequently offer a dynamic behavioral theory. In order to break the potential intrinsic circularity involved in explaining behavior by behavioral principles, we will suggest how this theory may be related to some of the presently less well-established genetic and neurobiological correlates to ADHD reviewed above.

The dynamic developmental theory of ADHD focuses on dopamine hypofunction because the majority of findings from a variety of research fields seem to converge on dopamine in the etiology of ADHD (Biederman et al., 2002a; Sagvolden et al., 1998a; Johansen et al., 2002; Castellanos et al., 2002b; Solanto et al., 2001b; Sagvolden et al., 1998b; Grace, 2001). The importance of other neuromodulators must not be underrated, however, and the present model may be applicable mainly to a subgroup of ADHD linked to dopamine hypofunction. However, in the genetics section we concluded that ADHD should be analyzed on a systems level, not on a single-gene, or a single-synapse level. It might well be that behavioral processes like reinforcement and extinction constitute the most elementary level at which it is possible to identify factors that are universal in a disorder like ADHD. It is likely that the development and severity of symptoms are linked to degree of dysfunction in the various dopaminergic systems.

The neuromodulator dopamine will regulate the processing of the information the brain receives via neurotransmitters like glutamate (Deutch & Roth, 1998). Genetic links to ADHD do not represent mutations, but polymorphisms that create subtle differences between normal and ADHD behavior. The theory offers an explanation of why ADHD is not a pathology that represents a separate entity

with behavior qualitatively distinct from normal behavior, but is a case where functions of the central nervous system occasionally exceeds the limits of normal variation and adaptation.

3.1. Attention deficits

Attention encompasses highly multifaceted functions that are modified by a multitude of psychological factors like sensory and motivation processes. Excellent reviews of attention processes and networks are found elsewhere (Posner et al., 1990) and outside the scope of the present review. It has been established that both dopamine and norepinephrine are important neuromodulators in attention processes (e.g. (Arnsten, 2001). The catecholamines may contribute to different aspects of attention processes. As our focus is on dopamine, we will suggest that both the 'prefrontal loop' and the 'limbic loop' (Fig. 4) are involved in different aspects of attention.

The prefrontal loop is mainly involved in directing attention and selecting the behavior needed to achieve a given goal in a given situation (cf. (Posner et al., 1990). It is suggested that a dysfunctioning mesocortical dopamine branch will cause various attention deficiencies like inefficient orienting responses and abnormal control of eye saccades (Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001) as well as poorer attention towards target (Kojima & Goldman-Rakic, 1982). These problems will, in a developmental perspective, result in difficulties with controlling behavior and directing actions towards longer-term accomplishments.

The limbic loop is mainly involved in reinforcement and extinction processes, the main components in the establishment of stimulus control and verbally-governed ("rule-governed") behavior (verbal instructions that regulate the behavior of the listener) (Catania, 1998). Stimulus control is considered to be a prerequisite for the establishment verbally-governed behavior. A dysfunctioning mesolimbic dopamine branch will contribute to problems establishing these functions. A lack of stimulus control will be manifested in deficient sustained attention. Problems in establishing verbally-governed behavior will result in difficulties with making and following plans. Thus, in our theory, the multifaceted attention problems of children with ADHD may be due to at least two different neurobiological systems related to dopamine dysfunction.

3.2. Clumsiness

ADHD children with a pervasive problem are more likely to show developmental delays in language (mainly expressive) and in motor functions, and to have an onset of symptoms in the first two years of life (Blondis, 1999; Gillberg & Rasmussen, 1982; Polatajko, Fox, & Missiuna, 1995; Willoughby & Polatajko, 1995; Kadesjo & Gillberg, 1999; Teicher et al., 1996; Taylor, 1998). A dysfunctioning nigrostriatal dopamine branch (Fig. 1) will probably cause several "extrapyramidal" symptoms (neurological "soft signs") associated with ADHD in the form of clumsiness, i.e., poor motor control, longer and more variable reaction times (Oosterlaan et al., 1998), poor response timing, poor handwriting, poor correlation of the activity of different body parts, etc. Also deficient nondeclarative habit learning and memory (Knowlton et al., 1996) might result from a dysfunction of the nigrostriatal dopamine branch. Thus, findings previously attributed to response disinhibition may rather be due to impaired motor control and to deficient nondeclarative habit learning and memory associated with dopamine dysfunction in the neostriatum (Sagvolden et al., 1989; Sagvolden et al., 1998b).

3.3. Reinforcement and extinction

It is likely that a two-factor explanation of ADHD (delay aversion and response disinhibition) is better than a one factor explanation (Solanto et al., 2001a; Sonuga-Barke, 2002). The present dynamic developmental theory suggests that the delay aversion is associated with a dysfunctioning mesolimbic dopamine branch, producing a shorter delay-of-reinforcement gradient (see below). The response disinhibition may partly be rooted in an extinction deficit and partly be caused by a dysfunctioning nigrostriatal dopamine branch causing impaired modulation of motor functions in terms of poor timing of starting and stopping of responses, deficient acquisition, retrieval, and relearning of programs for sequential motor tasks.

As reviewed above, release in association with reinforcement is one of several dopamine functions. We will argue that this is a particularly important function for understanding ADHD. Further, reinforcement is associated with a phasic increase of dopamine activity (Schultz, 1998; Schultz, 2002; Waelti et al., 2001). Dopamine depletion of nucleus accumbens biases animals from instrumental responding for a normally highly-preferred food to consumption of freely available, but normally less preferred food (Salamone, Cousins, & Bucher, 1994). This behavior appears similar to

ADHD children's aversion to delayed reinforcers and preference for immediate reinforcers even when those have a lower value than reinforcers that are available after a delay (Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Sonuga-Barke, 2002) and may indicate reduced accumbal dopamine functioning associated with reinforcers also in ADHD.

The postulation of a hypofunctioning dopamine system leads to several interesting predictions about reinforcement and extinction processes in ADHD if one assumes that the same phasic extracellular concentration of dopamine is required in the brains of children with ADHD as in normals for reinforcement and extinction to occur. Compared to normals, a reduced tonic dopamine level in children with ADHD will require an increased phasic release of dopamine to produce the post-synaptic changes required for normal reinforcement to take place. Similarly, normal tonic, but reduced phasic dopamine release associated with a reinforcer, will also result in less efficient reinforcement in ADHD. In both cases, an elevation of the reinforcer value is required to normalize the reinforcement process. These arguments are in accordance with the clinical observation that children with ADHD have a "motivation" problem: Stronger and more salient reinforcers are needed to control their behavior. They are also less sensitive to changes in reinforcement contingencies (Kollins, Lane, & Shapiro, 1997). Assuming these underlying principles, it is unnecessary to predict general facilitating or inhibitory deficits associated with ADHD. Synapses that are active at the same time repeatedly, whether excitatory or inhibitory, are probably active because they participate in the same function.

As discussed above, extinction is associated with a phasic depression of tonic dopamine neuronal activity. We predict that abnormally low tonic dopamine activity associated with ADHD may cause failure of extinction, in particular of previously reinforced behavior, due to a "floor" effect (Fig. 6). Similar arguments have been forwarded by Wolfram Schultz "Hypodopaminergic function will lead to a deficient prediction error and result in slower and less efficient learning" (Schultz, 2002) p. 256). Hence, a hypofunctioning mesolimbic dopamine branch in ADHD may alter both reinforcement and extinction processes, and thereby be the neurobiological basis of the altered reinforcement processes repeatedly suggested as one factor in ADHD symptomatology (Douglas, 1983; Douglas & Parry, 1994; Johansen et al., 2002; Sagvolden et al., 1989; Sagvolden et al., 1998a; Sonuga-Barke, 2002; Sonuga-Barke et al., 1992; Wender, 1971). This suggestion is supported by several studies showing that the behavior of children with ADHD is differently affected by

reinforcement contingencies (Douglas et al., 1994; Sagvolden et al., 1998a; Sonuga-Barke et al., 1992).

The theory predicts that symptoms like deficient attention processes and impaired motor functions may be caused by hypofunctioning dopaminergic loops. These symptoms will be modified by the altered reinforcement processes and deficient extinction, and develop dynamically as the child grows older interacting with within-family factors and societal demands (below).

Reinforcers act on responses that have already taken place by increasing the probability of future responding (Catania, 1971; Catania, Sagvolden, & Keller, 1988). Thus, reinforcement is the selection mechanism in the evolution of behavior in ontogenesis. Reinforcers may vary along several dimensions like density (frequency), the temporal response-reinforcer relationship (contiguity, delay of reinforcement), predictability, and value (attractiveness). The reinforcing effect is largest when the reinforcer is delivered immediately after the occurrence of the response and wanes as a function of the delay in reinforcer delivery. This relation between the effect of the reinforcer and the time interval between response and reinforcer is commonly known as the "delay-of-reinforcement gradient", or simply as the "delay gradient" (Catania et al., 1988; Sagvolden et al., 1998a) and may be expressed as a hyperbolic decay function of time (Johnson & Bickel, 2002).

We have argued that a main component of the altered reinforcement process is a shorter and steeper delay-of-reinforcement gradient in ADHD (Fig. 7, left), implying that mainly responses in close proximity to the delivery of the reinforcer will be effective (Johansen et al., 2002; Sagvolden et al., 1989; Sagvolden, Wultz, Moser, Moser, & Mørkrid, 1989; Sagvolden et al., 1998a). In a novel situation, there will be a stream of spontaneously emitted, random responses of various kinds. If one of these, e.g. R_C, is reinforced, the reinforcer will be less effective in ADHD than in normal children. This means that it is less likely that the ADHD child will repeat the response than a normal child (though – as the stimulus is functioning as a reinforcer – the ADHD child is more likely to repeat the response than it was before the reinforcer was delivered). Further, a reinforcer acts not only on the response that produced it, but to a lesser extent, also on responses emitted earlier (Catania, 1971). Thus, the response R_A will be reinforced, but to a lesser extent in an ADHD child than in a normal child. The R_D response will normally be reinforced, but is outside the reach of the reinforcer when the delay gradient is short and steep.

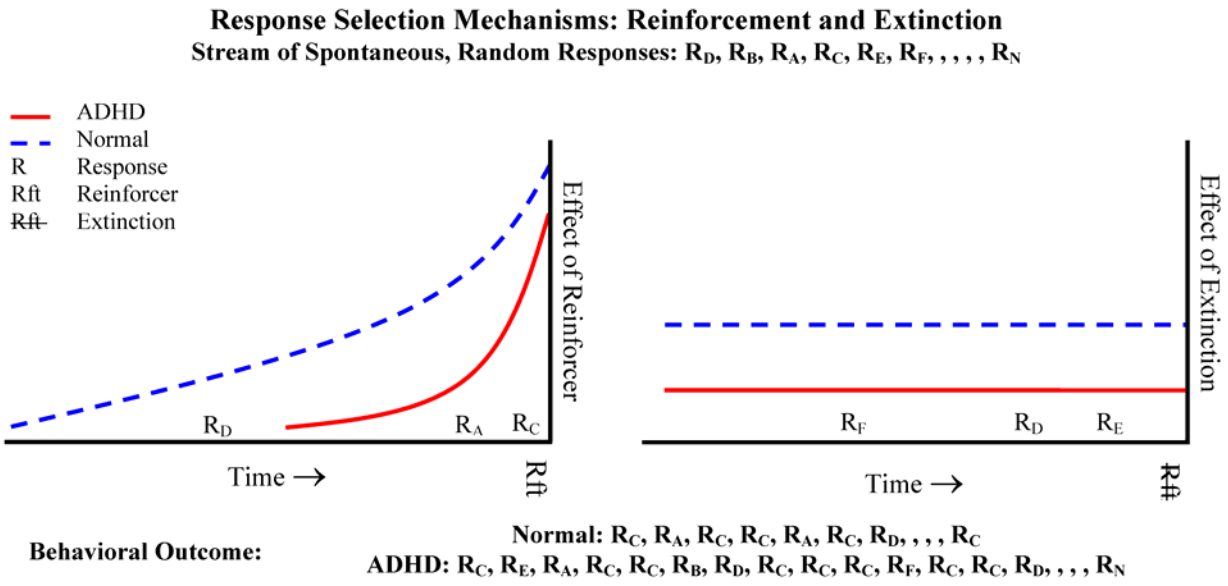

Figure 7. Response selection is a function of reinforcement and extinction. Left: Theoretical delay-of-reinforcement ("reward") gradient. The effect of a reinforcer is more potent when the delay between the response and the reinforcer is short than when the delay is long. The delay gradient may be steeper and shorter in children with ADHD than in normal children. Right: The theoretical extinction process is faulty in ADHD. This means that the normal elimination, in particular of previously established but no longer reinforced responses, will take place to a lesser extent in ADHD than normally. Altered reinforcement processes characterized by a shorter delay gradient in ADHD will not by itself generate the gradually developing overactivity. It is hypothesized that the ADHD overactivity and increased behavioral variability are acquired and maintained by a combination of scheduled and unscheduled reinforcers and failing extinction, increasing the frequency of acquired responses without pruning ineffective and inadequate responses.

The establishment of novel behavioral relations by reinforcement is essentially a matter of neuronal detection of coincident response-reinforcement or stimulus-response-reinforcement relations. Consequently, despite apparent differences in time scales, we suggest that the delay-of-reinforcement gradient neurobiologically is associated with the time window available for coincidence detection and thereby for mobilization of “silent” AMPA receptors necessary for LTP to take place (Malenka et al., 1999). Dopamine stimulation, as well as stimulation by other monoamines and estrogen, may increase the opening time of NMDA receptors and therefore the time window available for coincidence detection (Pedarzani et al., 1995; Stein et al., 1993). Consequently, reduced dopamine function associated with ADHD produces shorter than normal time windows for coincidence detection resulting in a shorter delay gradient.

A multitude of processes contribute to reduction of responding: neurobiological factors associated with the extinction procedure, lack of maintenance of acquired responses, and acquisition of incompatible responses (Fig. 7, right). The dynamic developmental theory proposes that extinction is less efficient in ADHD than in normal children. This means that the normal elimination, in particular of previously established but no longer reinforced responses, will take place to a lesser extent in ADHD than in normal children. This view is consistent with studies finding excessive responding during extinction of previously reinforced responses in children with ADHD (Sagvolden et al., 1998a) as well as in an animal model of ADHD (Sagvolden, 2000). It is also consistent with studies showing that children with ADHD are not hyperactive in novel situations (Sagvolden et al., 1998a; Sleator et al., 1981). We suggest that a ‘failure to inhibit responding' (Barkley, 1997) in most cases is the result of a faulty extinction process.

3.4. Overactivity

Introducing a reinforcer may lead to induction (response generalization), which is a general increase in responding. Responses may be defined either as belonging to a *descriptive* or *nominal class* (the responses that are reinforced), or a *functional class* (all the responses generated by reinforcement). During *differentiation*, responding gradually becomes more restricted to the nominal class producing the reinforcer (Catania, 1998), i.e., R_C will be more frequent than other responses (Fig. 7). At a neurobiological level, both the phasic increase in dopamine release associated with reinforcement and the phasic decrease in dopamine neuronal activity associated with extinction, may be necessary for efficient differentiation of responses. In ADHD, the establishment of functional response classes and differentiation may be inefficient due to the less effective extinction of behavior. On a behavioral level, responses in general will be induced resulting in an increased frequency of all responses in the functional class without the normal differentiation into the nominal response class.

The dynamic developmental theory predicts that the failing extinction process in ADHD will result in an increased number of responses, as well as an increased behavioral variability (below), despite a reduced effect of each reinforcer. Altered reinforcement processes characterized by a shorter delay gradient in ADHD will not by itself generate the gradually developing overactivity. It is hypothesized that the ADHD overactivity is acquired and maintained by a combination of scheduled

and unscheduled reinforcers and failing extinction, increasing the frequency of acquired responses without the pruning of ineffective and inadequate responses (Fig. 7). The deficient extinction process will lead to an accumulation of responses which may be seen as excess motor activity where no reinforcer can be identified (cf. (Porrino et al., 1983; Sagvolden et al., 1998a; Teicher et al., 1996). An increased number of responses with short interresponse times (motor impulsiveness) in ADHD is also contributing to the overactivity (below).

3.5. Increased behavioral variability

Clinically, ADHD behavior varies according to situational and task characteristics (American Psychiatric Association, 1994). Experimentally, it has been shown to be more variable than normal (Kinsbourne, 1990; Rubia et al., 1998; Teicher et al., 1996; Scheres et al., 2001). Variability acts as an operant that may be modified by reinforcers (Mook, Jeffrey, & Neuringer, 1993; Saldana & Neuringer, 1998). Just as variability in the form of spontaneous mutations is necessary for evolution to take place, so is variability of spontaneously emitted behavior necessary for the emergence and shaping of new behavior (Catania, 2000). According to the dynamic developmental theory, a combination of a general induction of responding and inefficient response differentiation due to a deficient extinction process in ADHD will result in an increased number of slightly different responses in the functional class and hence increased behavioral variability (Fig. 7). This means that normal children's responding increasingly will be within the nominal response class (i.e. the class of responses that generates reinforcement, (Catania, 1998) and inefficient responses (responses that do not generate reinforcement) will be extinguished. However, the behavior of children with ADHD will continue to include responses outside the nominal class. In addition, a response accidentally occurring just before the delivery of a reinforcer may quickly be part of the behavioral repertoire of a child with ADHD (cf. superstitious behavior, (Skinner, 1948) and not be extinguished in spite of lack of subsequent reinforcement.

An efficient reinforcer may select short sequences of behavior that function well under one set of circumstances, like during learning of new material when the situation is motivating. But, as situations change, the behavior of a child with ADHD will not change accordingly and the learned behavior will not adapt to changes in the reinforcement contingencies (e.g., (Kollins et al., 1997). Thus, as the child may seem to function well under one set of conditions, the lack of adaptability of

behavior to slight changes in the environment will be characterized as dysfunctional by the surroundings. The dynamic developmental theory of ADHD may thus explain the common observation that ADHD behavior is quite variable.

3.6. Impulsiveness

Impulsiveness is often exemplified by the choice of a small or less attractive reinforcer that is available immediately, in preference to a larger but delayed reinforcer. Selective lesions of the nucleus accumbens core induce persistent impulsive choice in rats. In contrast, damage to two of nucleus accumbens' afferents, the anterior cingulate cortex and the medial prefrontal cortex, do not increase impulsiveness (Carli, Evenden, & Robbins, 1985). Thus, dysfunction of the nucleus accumbens core, and therefore reinforcement functions, may be a key element in the neuropathology of impulsiveness.

Not only *single* responses, e.g. R_C (Fig. 8, top), but also the *relationships between* responses (e.g. interresponse times, IRTs, Fig. 8 bottom) are conditioned and maintained by reinforcers (Catania, 1971; Catania et al., 1988; Sagvolden et al., 1998a). In contrast to the normal delay gradient, only short IRTs are reinforced and maintained by a short delay gradient because only the normal gradient is long enough to reinforce the long IRT involved in the sequence R_D - R_C, (Fig. 8, bottom). This reinforcement process explains why motor impulsiveness, responses emitted with short IRTs, is not present in a novel situation, but develops gradually as more reinforcers modify the behavior (Sagvolden et al., 1998a). In addition, since the normally occurring medium and long IRTs necessarily will reduce the overall behavioral output, the selective reinforcement of short IRTs following a short delay gradient probably explains a substantial part of the ADHD overactivity.

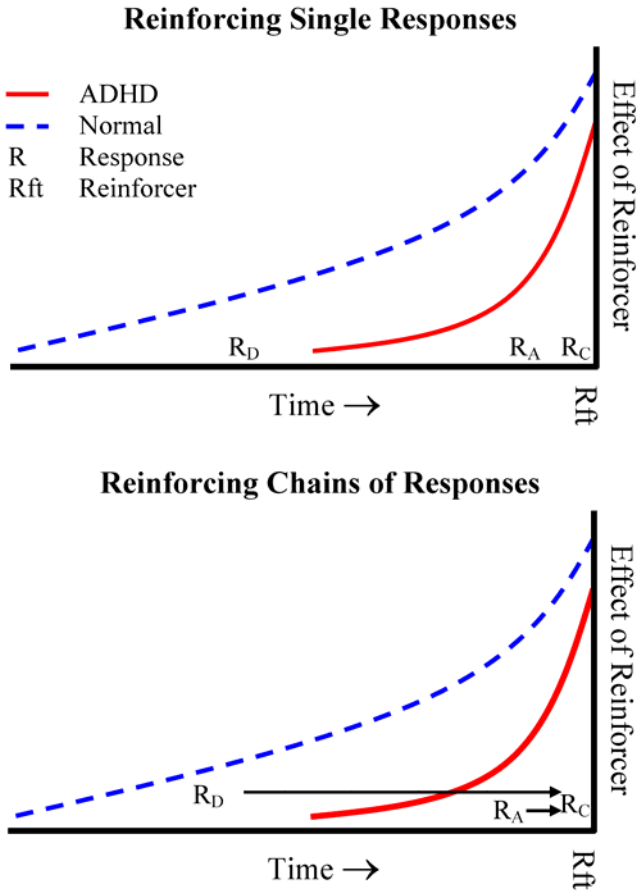

Figure 8. Different types of operants are reinforced and maintained by reinforcers: Single responses (top) and chains of responses (bottom). A shorter delay-of-reinforcement gradient will reinforce somewhat fewer R_C, but no R_D responses (top), and only chains of responses with short interresponse times (IRTs, bottom).

The importance of reinforcement in impulsive behavior is supported by the fact that children with ADHD are not always impulsive as they temporarily do manage to plan ahead, organize themselves, and remember important things, *if this behavior is maintained by potent and frequent reinforcers* (Douglas, 1999). Further, impulsiveness is not unique to ADHD. All children are impulsive as infants and young toddlers (Fig. 9).

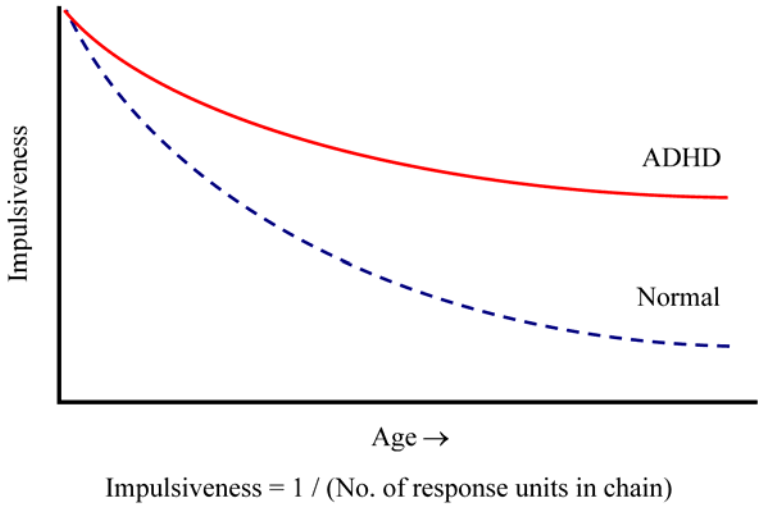

Figure 9. Impulsiveness, operationalized as short response sequences, is gradually reduced during the development of the child as a consequence of reinforcement processes establishing increasingly longer sequences of behavior that are brought under discriminative control including verbally-governed ("rule-governed") behavior. Thus, a child with ADHD behaves like a younger normal child.

Behavior is gradually brought under discriminative control, including the establishment of verbally-governed behavior, as a function of training (Barkley, 1997; Catania, 1998). Verbally governed behavior, or the control over behavior by verbal stimuli, will be gradually established as the child enters the verbal community (i.e., learns to understand speech and to speak). Verbal stimuli controlling future non-verbal behavior includes instructions, directions, demands, requests, urges, and written or spoken rules or norms for conduct in specified situations (see (Skinner, 1957)). Verbal stimuli may also be defined as contingency-specifying stimuli, as they often describe the situation in which a specific behavior is warranted (e.g. "at the second intersection, turn left") (Catania, 1998). Very briefly, the establishment of verbally-governed behavior goes on continuously from (but probably even before) the child learns to name objects and to use object names to get what they want. Simultaneously, the parents introduce instructions and immediately reinforce consequences for following instructions (e.g., "look at me – Good!"). A further step is through play and interaction with other children and parents where overt verbal directions for actions play a central part ("I go to your house and you open the door"). Gradually, more sophisticated, covert verbal self-talk direct more behavior over longer time periods. This account is in line with Vygotsky's theory of the development of private speech (Vygotsky, 1978) and internalization of speech (Winsler & Naglieri, 2003).

The development of longer sequences of behavior and establishment of verbally-governed behavior will be hampered by a short delay-of-reinforcement gradient. Therefore, both in normal and in children with ADHD, impulsiveness will be reduced as they grow older, but this process is stunted in children with ADHD. ADHD impulsiveness will consequently be manifested differently at different ages. Motor impulsiveness (bursts of responses) is predominant in infants and young toddlers, while cognitive impulsiveness (poor verbal control of behavior) is more prevalent in older children and adolescents. Clinically, this will mean that diagnosing ADHD at very early ages will be difficult partly because impulsiveness is typical of all young children's behavior. Thus, ADHD impulsiveness may be understood as a maturational lag with later achievement of language milestones, simpler expressive language, impaired sensory-motor coordination, poor handwriting, and reading ability that are all behind that which is expected for this child's chronological age (Saugstad, 1994b; Saugstad, 1994a; Taylor et al., 1998).

3.7. Impaired sustained attention

'Attention' denotes the control over behavior by some stimulus features and not by others (Catania, 1998). Sustained attention means that this stimulus controls behavior over time.

The establishment of the relation between a discriminative stimulus, behavior, and the reinforcement contingency (i.e. the three-term contingency) is a prerequisite for stimulus control. There are two essential factors: stimulus properties and reinforcer timing. Firstly, important stimulus properties include the contribution of new and significant information about reinforcement. If behavior is already controlled by one stimulus, the behavioral effects of adding a new stimulus is "blocked", i.e. behavior will not be controlled by this new stimulus (Catania, 1998). Neurophysiologically, blocking is seen in the lack of a phasic dopamine response if the added stimulus is later presented alone (Waelti et al., 2001). Secondly, the introduction of a reinforcer must be contingent on the behavioral changes following stimulus changes in order for the behavior to be related both to the stimulus and the reinforcer. The three-term contingency will not be established if the onset of the discriminative stimulus is outside the reach of the reinforcer. The potency of a stimulus as a conditional reinforcer depends on the time between its onset and the subsequent delivery of a reinforcer in its presence, according to the same delay gradients as operate for the relation between

responses and subsequent reinforcers (Figs. 7 and 8). Ordinarily, the delay gradient decreases slowly enough that stimuli become effective even when many seconds pass between their onset and the reinforcer (Fig. 10, top). But if the gradient is short, the reinforcer must follow quickly after stimulus onset. If not, the stimulus does not become a potent reinforcer and the individual will not attend to it when it appears (Fig. 10, middle). Thus, the sustained attention deficit is derived from the same source as hyperactivity. The dynamic developmental theory predicts that the delay gradient will bridge longer time intervals in normal children (Fig. 10, top) than in children with ADHD (Fig. 10, middle).

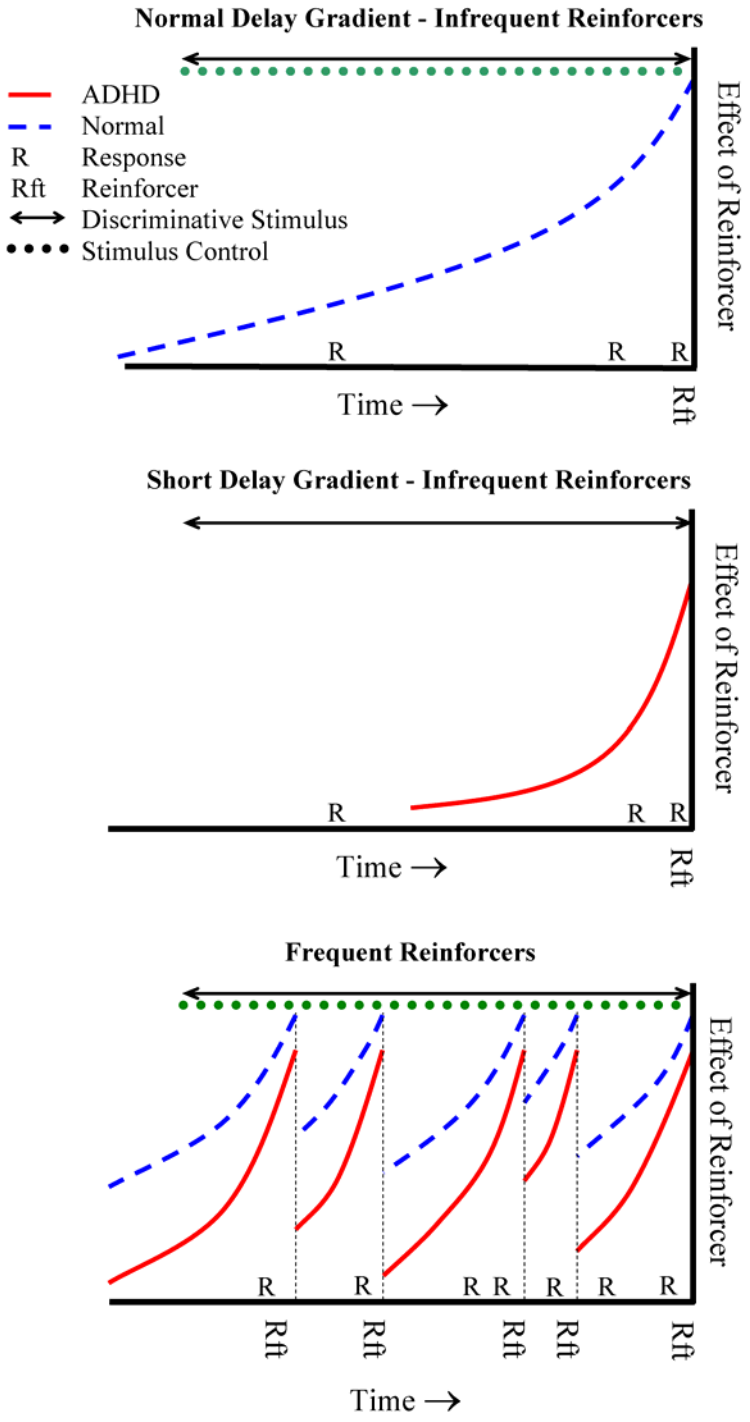

Figure 10. To be effective, onset of the discriminative stimulus will have to be within reach of the delay-of-reinforcement gradient (top). Consequently, an abnormally steep and short delay gradient will result in an "impaired sustained attention", i.e., a less consistent relation between the discriminative stimulus, response, and the reinforcement contingency (middle). It is possible to establish stimulus control in ADHD by presenting the reinforcers frequently (bottom).

The deficit in sustaining attention may be remedied by increasing the reinforcer frequency and thereby increasing the probability of bringing the stimulus onset within reach of the delay-of-reinforcement gradient (Fig. 10, bottom). A short delay gradient implies that poorly sustained attention in ADHD is seen whenever the frequency of reinforcers is too low for stimulus control to be properly established in children with ADHD, but high enough for such control of normal children's behavior. Further, it is predicted that normal children will also show lack of sustained attention if the frequency of reinforcers is very low. In addition, there will be individual differences both between children with ADHD and between normal children, as stimulus control by distanced stimuli will be a result both of individual dopamine levels and individual learning histories.

As Catania describes in more detail in the precommentary that follows this article, according to our theory, individual differences between delay gradients in children with ADHD will give rise to differences in symptoms. Consider a child whose gradient quickly drops to zero. Then, responses must be very close to the reinforcer to be captured by it and only single responses will be strengthened (Fig. 8, top). If chains of responses are not strengthened, there will be little motor inpulsiveness (Fig. 8, bottom). In this instance, there should be a profound sustained attention deficit because only brief stimuli quickly followed by reinforcers will acquire any conditional reinforcing effectiveness.

Now consider an ADHD child with a somewhat longer delay gradient. This child is likely to show a lot of responses with short IRTs (impulsiveness). Poor stimulus control (attention deficit) is still likely to be a problem. Thus, in this instance we can expect to see both impulsiveness and sustained attention deficit.

If we were able to lengthen the delay gradient, e.g., by medication (below), the longer time period means that sustained attention deficit will be less of a problem (discriminative stimuli in the presence of which reinforcers come available soon enough will acquire conditional reinforcing properties of their own, and therefore they will be attended to when they appear), but the IRTs that can be captured by the reinforcer will still be shorter than some of those captured by a normal gradient. In this case, the individual will probably show mild impulsiveness and mild attention deficit, with the former dominant.

3.8. Effects of stimulants

A review of effects of stimulant drugs is outside scope of the present article. In brief, psychostimulants such as methylphenidate and amphetamines have for several decades provided the primary pharmacological treatment for ADHD (Bradley, 1937; Solanto et al., 2001a; Vitiello et al., 2001). Methylphenidate probably acts by blocking the dopamine transporter (DAT1) and thus increases the temporal and spatial presence of dopamine at the synapse where it is released (Volkow et al., 1998).

It has been argued that psychostimulants lengthen the delay-of-reinforcement gradient (Sagvolden, Slåtta, & Arntzen, 1988). Similar arguments have been forwarded by Wolfram Schultz: "Psychostimulant drugs increase synaptic availability of dopamine and produce an exaggerated reinforcement prediction error message that will constitute a very powerful focusing and teaching signal and produce modifications in synaptic transmission leading to substantial behavioral changes" (Schultz, 2002) p. 256).

Stimulants have previously been shown to be equally effective in reducing motor activity and reaction time, and improving performance on cognitive tests in ADHD/MBD and normal children (Rapoport et al., 1978; Rapoport et al., 2002). Stimulants affect the functioning of the various loops that have a substantial dopamine innervation (Fig. 4). Correct medication not only reduces core symptoms, but also reduces the risk of maladaptive behavior such as subsequent drug and alcohol use disorders (Biederman, Wilens, Mick, Spencer, & Faraone, 1999; Wilens, Faraone, Biederman, & Gunawardene, 2003). Reduced phasic, but also tonic, dopamine neuron activity in ADHD may be normalized by low doses of psychostimulants. Low doses of psychostimulants primarily affect the tonic dopamine level that is increased several-fold (Seeman & Madras, 2002). Consequently, the therapeutic effect of psychostimulants may be mediated by an increase mainly in the tonic level of dopamine activity thereby improving reinforcement and extinction on a behavioral level. However, the exact mechanisms of action of stimulant drugs are not known (Solanto et al., 2001a) and may differ across brain regions (Porrino & Lucignani, 1987; Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1998).

The mechanism by which psychostimulants alleviate ADHD symptoms may be by increasing tonic extracellular dopamine concentrations, the increased dopamine activates DRD2 autoreceptors that inhibit dopamine release and reduce the amplitude of action-potential-triggered dopamine release, resulting in less activation of postsynaptic dopamine receptors (Seeman et al., 2002). However, electrically stimulated release of dopamine *in vivo* is not in fact reduced, it is increased by low, clinically relevant, doses of d-amphetamine (Seeman et al., 2002; Suaud Chagny, Buda, & Gonon, 1989; Parker & Cubeddu, 1986) which would support the dopamine hypofunction hypothesis of ADHD. In addition, extrasynaptic dopamine may be required to act at more distant DRD4 heteroreceptors to inhibit glutamate release from cortico-striatal afferents (Berger, Defagot, Villar, & Antonelli, 2001; Tarazi, Campbell, Yeghiayan, & Baldessarini, 1998). We suggest that inappropriate overactivity of mesolimbic ventral-tegmental-area (VTA) dopamine neurons at an early stage of development of ADHD could activate DRD5 receptors on dendrites of VTA dopamine neurons and increase expression of functional NMDA receptors in VTA dopamine neurons. Increased NMDA function could give rise to compensatory changes that result in depolarization block of VTA dopamine neurons and hypoactivity of the mesolimbic dopaminergic system.

4. ADHD in a developmental perspective

In a developmental perspective, one has to consider the child's behavioral characteristics, the neurobiological development during the child's life, and the interplay between these two factors and the environment (Karmiloff-Smith, 1998). This interplay is not unidirectional and will have many different outcomes as the capacity for learning and change is life-long. Herein lays also the possibility that a caregiver may adjust the environment to the child's needs for optimal development of adaptive skills. These skills may, of course, develop into a behavioral style with which the world is met, determining the long-term consequences of the initial interplay between the child and the environment.

At a neurobiological level, all neurotransmitter and neuromodulator systems undergo growth spurts and pruning several times during ontogenesis (Andersen, Rutstein, Benzo, Hostetter, & Teicher, 1997; Saugstad, 1994b; Saugstad, 1994a). The growth spurts and pruning will be associated with synaptic supersensitivity and therefore associated with enhanced vulnerability to negative as well as

positive environmental (parental, family, and societal) influences. Considering the neurobiological bases of acquisition and maintenance of behavior at such critical stages in the individual's neurodevelopmental history, the environment may influence symptom development in either negative or positive directions.

ADHD in a neurodevelopmental perspective is a vast topic. So far we have considered the dynamic interplay between neurobiological processes, environmental events, and behavior. The following section will discuss some aspects of the dynamic development of the behavior of the child with ADHD on a macro level, taking into account behavioral and environmental properties and principles. We will limit the discussion to the most important predictions for within-child factors; proceed to consider these factors in a family and a societal perspective pointing out important relations, and how they can lead to different short- and long-term consequences. The discussion is summarized in Figure 2.

4.1. Within-child factors

There is substantial evidence for a neurobiological predisposition in ADHD. Increasing amounts of genetic, neurobiological, and neuropsychological data support the biological underpinning of the disorder (Wilens, Biederman, & Spencer, 2002a; Wilens, Spencer, & Biederman, 2002b). In addition, ADHD is often chronic with prominent symptoms and impairment spanning into adulthood. ADHD is often associated with co-occurring anxiety, mood, and disruptive disorders, as well as substance abuse (Wilens et al., 2002a; Wilens et al., 2002b). The neurobiological predisposition can be viewed as a risk factor or vulnerability for maladjustment. In the dynamic neurodevelopmental theory of ADHD, the vulnerability consists, in particular, of inefficient reinforcement and extinction processes.

A short and steep delay-of-reinforcement gradient implies that reinforcement should be immediate to be effective. As discussed above, the short delay gradient and impaired extinction may cause impulsiveness and hyperactivity, and hamper the establishment of stimulus control and verbally-governed behavior. Disrupted discriminative control of behavior will result in developmental delays in several areas of daily life. A young child with ADHD will have problems with learning the relationships between situational or instructional demands and its own behavior, and will thus

receive little reinforcement for compliant behavior. As the child grows older, he or she will have problems with anticipating the proper behavior for a given situation, and will not have developed self-directed speech for guiding or controlling own behavior (although the child will not have problems learning verbal responses to verbal questions – for instance describing verbally what would be the proper behavior in a certain situation).

ADHD children's aversion to delayed reinforcers and preference for immediate reinforcers even when those have a lower value than reinforcers that are available after a delay (Solanto et al., 2001a; Sonuga-Barke, 2002; Sonuga-Barke et al., 1992; Sonuga-Barke, 2002) may be a behavioral product of the shorter delay gradient. When the delay gradient is short and steep, even short reinforcer delays may be too long for establishment of stimulus control (Fig. 10). We suggest that it is aversive not to "master" or "understand" a situation because choices may be perceived to be forced, not free (cf., (Catania & Sagvolden, 1980). An alternative interpretation of this aversion has been forwarded as a secondary effect of a combination of altered reinforcement mechanisms and characteristics of the child's early environment (Sonuga-Barke, 2002). As long as behavior is not compliant or adjusted in structural situations or in situations mandating certain behaviors, the child with ADHD will be met with negative consequences or ignorance, and develop an aversion. The resulting behavioral style will only strengthen the negative interaction.

A positive developmental trajectory predicted from the theory involves the frequent and immediate delivery of reinforcers. Most behavioral treatment programs for children with ADHD have included increased frequency of reinforcement as this is found to be effective (e.g. (Barkley, 1998). In addition, caregivers of ADHD children should prevent development of unwanted behavior because the extinction deficit makes it difficult to reverse such behavior once established. But, the underlying dopamine hypofunction, probably lasting for life, explains why intensive behavioral therapy will not be able to remove behavioral symptoms, except under special circumstances where reinforcers are delivered frequently without delay. Since such conditions are rare, people with ADHD run the risk of developing maladaptive behavior if the core deficits are not remedied with proper medication.

Efficacy of medication is well established for the most problematic behavior of ADHD (Bradley, 1937; Solanto et al., 2001a; Vitiello et al., 2001). Correct medication also reduces the risk of

maladaptive behavior like later substance abuse (Biederman et al., 1999; Wilens et al., 2003). The dynamic developmental theory suggests that the long-term effects of medication on a behavioral level is mediated by normalized reinforcement and extinction processes, improved attention responses, and enhanced motor control. Thus, medication will influence both the interaction between the child and its parents (e.g. (Barkley, 1989) and between the child and society, in addition to ameliorating maladaptive and negative outcomes.

It is now evident that disruptive behavior (ODD and CD) co-occur with ADHD (Biederman et al., 1996; Jensen et al., 2001). Early-onset CD almost invariably occurs in combination with ADHD (Pliszka, 1999). It is not yet clear whether the combined ADHD-CD case is a separate disorder, or a more severe case of ADHD. What seems to be the case is that late-onset CD (with ADHD or not) probably is a product of psycho-social influence, while early-onset CD (which never occurs without ADHD) is genetically based. The interactions are not simple. The probability of developing CD from early oppositional behavior seems to be mediated by high levels of socio-economic disadvantage and negative family climate, while this probability is almost absent given low levels of these risk factors (McGee & Williams, 1999). Parent-child conflict appears to act as a common vulnerability that increases risk for multiple childhood disorders. Furthermore, the association between parent-child conflict and childhood disorders is mediated via common genetic and environmental factors. These findings support the idea that the comorbidity among these disorders partially reflects core psychopathological processes in the family environment that link putatively separate psychiatric disorders (Burt, Krueger, McGue, & Iacono, 2003)**.**

Most ADHD children with comorbid CD also often meet criteria for ODD, which usually precedes CD onset by several years. Although there seems to be two subtypes of ODD associated with ADHD: one that is prodromal to CD and another that is subsyndromal to CD but not likely to progress into CD in later years (Biederman et al., 1996; Jensen et al., 2001). The possibility of a combination of disruptive behavior being reinforced by its short-term consequences *and* deficient extinction in ADHD is severe. In ADHD with co-occurring disruptive behavior, the short-term consequences of lying, stealing, threatening etc. can reinforce and maintain the disruptive behavior. In the dynamic developmental theory we predict that a subgroup of the disruptive behavior disorders is caused by the core deficits involved in ADHD and hence is secondary to ADHD (same etiology). Thus, this behavior may also be controlled by a short delay-of-reinforcement gradient. Law-

breaking behavior is often associated with lack of proper verbally-governed behavior, sensation seeking, and substance use (Rasmussen, Almvik, & Levander, 2001). The extinction problem in ADHD will add to the negative effect, as the deviant behavior is not easily reduced by punishment or lack of reinforcement. The societal actions like punishment and prison will be ineffective and in the long term possibly lead to an elevated prevalence of criminal offense in persons with ADHD symptoms (Crowley, Mikulich, MacDonald, Young, & Zerbe, 1998).

High heritability or a neurobiological basis does not imply determinism. The "positive" or successful adult with ADHD might have had insightful teachers and parents understanding the importance of immediacy of reinforcers and computer-assisted instruction. As adults, children with ADHD may very well end up with a Type A-like personality (Whalen et al., 1986), directing activity towards work, being creative and relatively well adapted although they might be easily stressed and develop hypertension.

The dynamic developmental theory explains why the severity of the behavioral problems of individuals with ADHD varies tremendously, not just between persons, but also within individual persons, as they encounter changing situations with differing contingencies operating. The variability is enhanced by the nature of the long-term neuromodulatory changes caused by dopamine influences where the time scale is not milliseconds, but rather seconds and minutes (Byrne, 1998). This fact explains why people with ADHD can stay focused when high densities of reinforcement or potent reinforcers are operating, e.g. when playing video games or performing hazardous acts. Then the reinforcers may release enough dopamine and related neuromodulators to bring the performance of the central nervous system within normal functional range without medication. Increased release of dopamine might be a part of a sensation-seeking behavior associated with ADHD (Blum et al., 1995; Petry, 2001). Substances of abuse also increase dopamine levels (Di Chiara et al., 1988), which might be an important aspect of self-medication too often leading to substance abuse associated with ADHD (Biederman et al., 1999).

4.2. Family interactions and parenting style

The dynamics of family interaction is influenced both by behavioral characteristics of the child and the parenting style of the child's primary caretakers. A child with ADHD affects the family

interaction in ways other than normally developing children. Research indicates that the presence of ADHD in a child is associated with disturbances in family and marital functioning, disrupted parent-child relationships, reduced parenting self-efficacy, and increased levels of parental stress (Johnston & Mash, 2001; DuPaul, McGoey, Eckert, & VanBrakle, 2001).

Genetics, not family environments, produce ADHD (Rey, Walter, Plapp, & Denshire, 2000). However, negative emotional family environments predispose unfavorable behavioral development in an ADHD child (Hinshaw et al., 2000) and increase the risk of later ODD and CD (Taylor, 1999; Biederman, Mick, Faraone, & Burback, 2001), particularly in boys (Biederman, Faraone, & Monuteaux, 2002a). Biederman and colleagues showed that a number of risk factors like low social class, maternal psychopathology, and family conflict were associated with a greater risk for ADHD and other comorbidity in a "dose-dependent" fashion, irrespective of gender, parental ADHD, and maternal smoking during pregnancy (Biederman et al., 2002a). A possible developmental trajectory is outlined and evidenced in coercion theory for the development of antisocial behavior in children (e.g. (Patterson, 2002). This theory explains how coercive behavior develops through reinforcement processes: the child's nagging is reinforced when the parent gives in, and the parent's behavior of giving in is reinforced by the removal of nagging, i.e., negative control. According to the dynamic developmental theory, this behavior, once established, is harder to extinguish in the ADHD child than in other children.

A child with ADHD requires exceptional parenting skills. Preschool children with ADHD are at an early age (typically 3 to 5 yr) rated by their parents as showing more noncompliant and inappropriate behavior, they are significantly more aggressive, more demanding of parental time, less socially skilled, and less adaptable to change in routine, compared to parent ratings of normally developing children (DeWolfe, Byrne, & Bawden, 2000; DuPaul et al., 2001). In order to secure an optimal upbringing, caregivers have to adapt to the ADHD child's needs by taking into account the implications of the underlying deficits and adjust expectations and demands to the child's functional age (Barkley, 1998). Thus, in addition to coping with ongoing challenging behavior, the altered reinforcement and extinction processes require parents to behave in a consistent and organized way toward their child. This includes reinforcing adaptive behavior by frequent and immediate reinforcers and at the same time not allowing maladaptive behavior to develop. However, 15-20% of the mothers and 20-30% of the fathers may also have ADHD themselves. Furthermore, parents of

children with ADHD often show conduct problems and antisocial behavior (~25%), alcoholism (14-25%), histrionic or affective disorder (10-27%), or learning disabilities (Barkley, 1998). Thus, parents with any of these problems will have even greater difficulty in coping with their ADHD child's special needs than other parents.

Parental ADHD is associated with a disruptive family environment which increases the risk of a negative outcome in the child with ADHD (Biederman, Faraone, & Monuteaux, 2002b). Weiss and coworkers (Weiss, Hechtman, & Weiss, 2000) have suggested several ways that adult ADHD may influence parenting skills: reduced patience with and responsiveness to the child, difficulty maintaining attention during supervision, difficulty remembering or keeping appointments with day care or school, difficulty with instrumental and organizational tasks like remembering birthday parties, activities or play dates, problems with disengaging emotionally in their child's temper tantrum and instead contribute to escalation, and difficulties with organizing both domestic duties and care for the child. Fathers with ADHD use less effective discipline towards their ADHD child than fathers without ADHD (Arnold, O'Leary, & Edwards, 1997). In these circumstances the parent will not be able to create a predictable environment for the child, where certain behaviors consistently are followed by certain consequences.

Supporting this, maternal ADHD has been shown to be the sole factor accounting for lack of change in child ADHD after intensive parent training, while the presence of ADHD symptoms in the child was significantly and long-lastingly (15 weeks) reduced when mothers scored low on ADHD symptoms (Sonuga-Barke, Daley, & Thompson, 2002). The long-term consequences of an upbringing characterized by inconsistency, impulsiveness, and disorganization are grave compared to a well-structured environment. A corollary of this reasoning is that the situation may improve if the ADHD parent was allowed adequate medication (Fig. 2) in addition to attending parent-training programs.

In the framework of our theory, a normal parent will have a long delay-of-reinforcement gradient and good stimulus control in the sense that she or he can verbalize the rules applicable in a certain situation and behave accordingly (Fig. 11, upper left). Combined with an understanding of the need for frequent and immediate reinforcers, the dynamic developmental theory predicts that establishment of stimulus control is possible (Fig. 11, lower left). When the parent also has ADHD,

it is likely that there is deficient stimulus control and she or he may have poor verbally-governed behavior (Barkley, 1997) (Fig. 11, upper right). In this case, establishment of adequate stimulus control in the child with ADHD will be unlikely (Fig. 11, lower right).

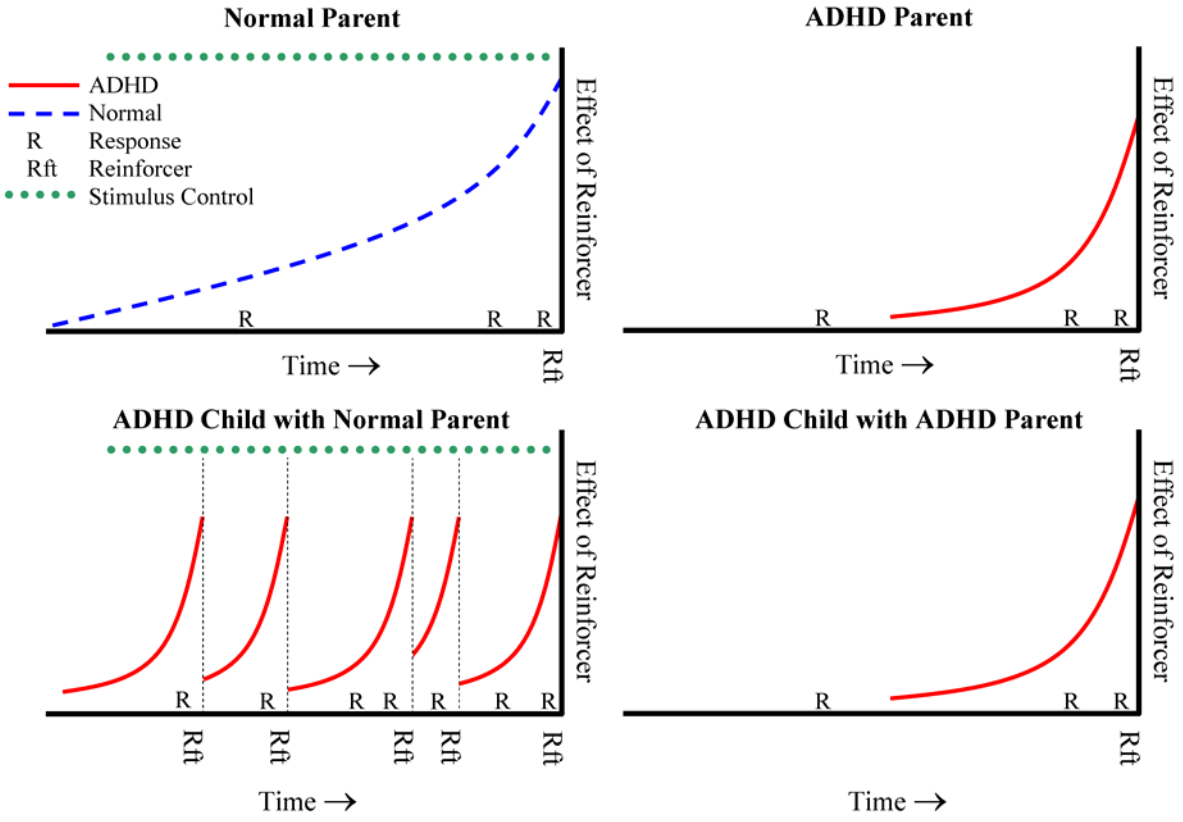

Figure 11. An abnormally steep and short delay gradient will result in poor stimulus control when reinforcers are infrequent both in children and adults with ADHD, but not when the density of reinforcement is high enough for the three-term contingency to work. Accordingly, the dynamic developmental theory predicts that it is possible to establish stimulus control in ADHD by presenting the reinforcers frequently. A normal parent will have a long delay-of-reinforcement gradient and good stimulus control in the sense that she or he can verbalize the rules applicable in a certain situation (upper left). Combined with frequent and immediate reinforcers, establishment of stimulus control and verbally-governed behavior in an ADHD child may be possible (lower left). In the case when the parent also has ADHD, there is poor stimulus control and she or he may have poor verbally-governed behavior (upper right). Under such circumstances, there will be poor stimulus control and an ADHD child will probably not establish verbally-governed behavior (lower right).

4.3. Societal style

From time to time, professionals and lay people suggest that ADHD is a product of the Western way of life where events happen quickly, contingencies change incessantly, and reinforcers never have to be postponed. Such allegations are contradicted by research showing that ADHD is found in all kinds of cultures around the world (e.g. (Meyer, Eilertsen, Sundet, Tshifularo, & Sagvolden, 2003)). This is not to say that societies do not create influential contingencies for its inhabitants. In the dynamic developmental theory, societal style is predicted to influence the behavior of people by the prevailing "culture" of for instance child upbringing and in the way disorders and disabilities are defined. In Western cultures, children are allowed to behave in certain ways when they are young ("Let him keep on, he is just a child!"), but when the child gets older, unwanted behaviors are supposed to extinguish (by parenting practices like rule learning, lack of reinforcers, punishment, and ignoring). A child with ADHD in a Western culture will have acquired quite a lot of the behavior described as unwanted when young, but combined with the ADHD extinction deficit, getting rid of it will be difficult. Other cultures with a stricter child upbringing than is common in Western countries may see less maladaptive behavior and lower prevalence of ADHD because disruptive behavior is not accepted even in very young children (Meyer et al., 2003).

The severity of the behavioral problems of ADHD children varies. Approximately 50% have significant problems in social relationships with other children (Bagwell, Molina, Pelham, Jr., & Hoza, 2001). Not only the parents, but also the society in general interact with the child and shape its behavior. The society requires that its inhabitants develop adequate self-control, learn to use time efficiently, learn to foresee consequences of their behavior in order to socialize, obtain an education, and get a job. All these requirements are very difficult for people with ADHD. Behavioral training programs may generate optimal environments with frequent and immediate reinforcers as well as short and clear instructions. For instance, in the multimodal treatment study of ADHD (MTA) the children receiving either only intensive behavioral treatment or the combination of medication and behavioral treatment started the treatment period with an eight-week summer school program (Pelham et al., 2000). Here, all children continuously received reinforcers for proper, prosocial behavior, rules of conduct were explicit and frequently repeated, and violations to the rules resulted in predictable consequences. Behavior was evaluated by parents, and there were no differences between the children that received medication in addition to the intensive behavioral treatment and

the children that only had the behavioral treatment package, and they all showed significant improvement over a range of behaviors (Pelham et al., 2000). The problem is that optimal contingencies only exist during the training session or under certain circumstances. Outside these, inconsistent and unpredictable contingencies are the rule. The school may, however, help an ADHD child to adjust to the school requirements by creating an optimal learning environment (Hoffman & DuPaul, 2000). Such an environment should include structure, clear instructions, and frequent reinforcers in order to establish stimulus control and verbally-governed behavior. Programs like "Positive Behavior Intervention and Support" (e.g. (Wolf, 1998) specifically seek to optimize these contingencies by increasing reinforcer density and clarify rules for preventing and treating conduct disorders on a school wide basis. The effect of such programs on the behavior of children with ADHD has yet to be established empirically, but according to our theory programs built on the above listed principles should improve their level of functioning.

5. Conclusions

The dynamic developmental theory for the ADHD predominantly hyperactive/impulsive and combined subtypes is based on the hypothesis that altered dopaminergic function plays a pivotal role by failing to modulate non-dopaminergic (primarily glutamate and GABA) signal transmission appropriately. Genetic links to ADHD do not represent mutations, but polymorphisms.

1) The theory offers an explanation of why ADHD is not a pathology that represents a separate entity with behavior qualitatively distinct from normal behavior, but is a case where the function of the central nervous system occasionally exceeds the limits of normal variation and adaptation.
2) A dysfunctioning mesolimbic dopamine branch will produce altered reinforcement of behavior and deficient extinction of previously reinforced behavior. This will, on a behavioral level, give rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioral variability, and failure to "inhibit" responses ("disinhibition"). It might be that the disorder in the future should be named RED (Reinforcement/Extinction Disorder).
3) A dysfunctioning mesocortical dopamine branch will cause attention response deficiencies (deficient orienting responses, impaired saccadic eye movements, and poorer attention

responses towards a target) and poor behavioral planning (poor executive functions).

4) A dysfunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions (poor timing of starting and stopping of responses, deficient acquisition, retrieval, and relearning of programs for sequential motor tasks), and deficient nondeclarative habit learning and memory. These impairments will give rise to apparent developmental delay, clumsiness, neurological "soft signs", and a "failure to inhibit" responses when quick reactions are required.
5) The theory predicts that symptoms will in part be produced by deficient regulation of attention and impaired motor functions. These symptoms will develop as a result of the altered reinforcement processes and deficient extinction, and be dynamically modified as the child grows older interacting with within-family and societal styles.

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