ELSEVIER

Behavioural Brain Research 130 (2002) 37–45

BEHAVIOURAL BRAIN RESEARCH

www.elsevier.com/locate/bbr

Attention-deficit/hyperactivity disorder (ADHD) behaviour explained by dysfunctioning reinforcement and extinction processes

Espen Borgå Johansen [a], Heidi Aase [a], Anneke Meyer [b], Terje Sagvolden [a,*]

[a] *Department of Physiology, University of Oslo, PO Box 1103 Blindern, N-0317 Oslo, Norway*
[b] *Department of Psychology, University of the North, Private Bag X1106, Sovenga 0727, South Africa*

Received 5 July 2000; accepted 13 August 2001

Abstract

Inattentiveness, overactivity and impulsiveness are presently regarded as the main clinical symptoms of attention-deficit/hyperactivity disorder (ADHD). Inattention is, however, a characteristic of most psychiatric disorders. It is argued that the ADHD Inattentive subtype may have heterogeneous origins and be qualitatively different from the ADHD Hyperactive/Impulsive subtype. At the neurobiological level, ADHD symptoms may to a large extent be caused by a dysfunctioning dopamine system: A dysfunctioning meso-limbo-cortical dopamine branch will produce altered reinforcement and extinction processes, on a behavioural level giving rise to deficient sustained attention, hyperactivity, motor and cognitive impulsiveness. A dysfunctioning nigro-striatal dopamine branch will cause 'extrapyramidal' symptoms. Our model disentangles the behaviours usually explained by 'executive functions' into cognitive impulsiveness, motor impulsiveness and deficient motor control. The various dopaminergic branches may not be equally dysfunctional in all individuals with ADHD. Etiologically, dopamine dysfunctioning will probably mainly be genetically determined while sometimes be induced by environmental factors like drugs of abuse or pollutants, which may explain geographical differences in prevalence rates.

Keywords: Hyperkinesis; Overactivity; Variability; Clumsiness; Soft signs; Reward; Monoamine; Catecholamine; PCB; Dioxin; Pollutants

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) [1] is a seemingly heterogeneous group of behaviour disorders affecting between 2 and 5% of grade-school children [65,69]. The disorder usually manifests itself before the child is 7 years old. In childhood, the disorder is more common in boys than in girls, but during adolescence and young adulthood relatively more females are affected [4]. 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 [6,76] while the full ADHD syndrome is found in only 4% of the adult population [30].

Inattentiveness, overactivity, and impulsiveness are presently regarded as the main clinical symptoms of ADHD [1]. Although there is considerable overlap between these symptoms, impulsiveness is increasingly seen as the symptom of greatest significance [69]. Admittedly, the symptoms are not that well defined and requirements vary somewhat between the ICD and DSM taxonomies [65,69]. 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 [69].

ADHD is associated with altered dopamine function [15,21,28]. We will argue that the ADHD symptoms, to a large extent, are caused by dysfunctioning dopamine branches impairing non-dopaminergic signal transmission (Fig. 1):

1. A dysfunctioning meso-limbo-cortical dopamine branch will produce altered reinforcement and extinction processes, on a behavioural level giving rise to deficient sustained attention, hyperactivity, behavioural variability, motor and cognitive impulsiveness.

* Corresponding author. Tel.: +47-22851286; fax: +47-22851249.
E-mail address: terje.sagvolden@basalmed.uio.no (T. Sagvolden).

0166-4328/02/$ - see front matter
PII: S0166-4328(01)00434-X

2. A dysfunctioning nigro-striatal dopamine branch will cause poor motor control.

2. Symptoms

2.1. Deficient sustained attention

It seems that perceptual processes are not altered in ADHD [58]. The attention problems of children with ADHD are typically described as 'distractibility' and trouble with 'sustaining attention' [18]. It is not convincingly established, however, that children with ADHD have attention problems in the same sense as seen in non-hyperactive, rather dreamy, inert children with attention problems [69].

The problems related to *sustained* attention occur in situations where stimuli are widely spaced in time [75]. 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 [69], p. 15).

The attention deficit in ADHD is *in the manner* in which these children attend, not whether they attend or not. Psychometric tests like Continuous Performance Task (CPT), Children's Checking Task, Letter Cancelling Task, Stroop Task, Test of Variables of Attention (TOVA), to mention some, are designed to measure different aspects of attention, while the final scores are resulting from a variety of different contingencies and processes that differ between these tests.

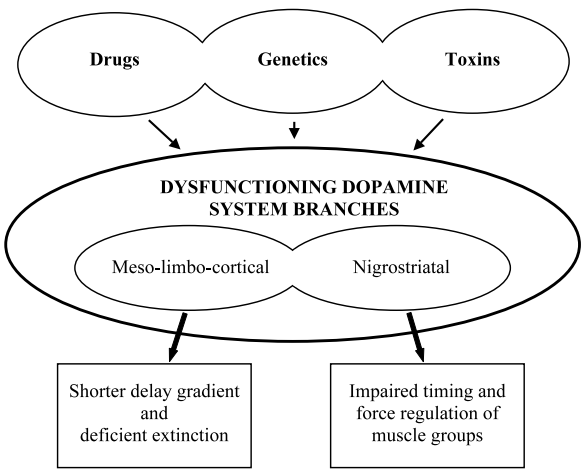

Fig. 1. ADHD symptoms may to a large extent be caused by dopamine dysfunction. A dysfunctioning meso-limbo-cortical dopamine branch contributes to a shorter delay-of-reinforcement gradient and deficient extinction, and a dysfunctioning nigro-striatal dopamine branch causes impaired timing and force regulation of muscle groups ('extrapyramidal' symptoms or neurological 'soft signs'). Dysfunctioning dopamine systems may result from genetic transmission, environmental pollutants, or drug abuse.

The tests do distinguish between groups of children with ADHD and normal children, but they also distinguish between normal children and groups with other disorders like learning disabilities, depression, anxiety, schizophrenia, and diabetes (e.g. [17]). Inattention is a characteristic of most psychiatric disorders, except mania [68]. Therefore, ADHD cannot be defined by symptoms of inattention unless it is specifically described how the ADHD inattention can be distinguished from that in the other disorders.

The concept of inattention is very vague and implies that nothing is going on. The opposite, attention, is no less problematic. Attention is modified by emotional state, by season [3], by motivation, by sensory problems, by physiological state (hypoglycaemia, anaemia, migraine, hunger, fatigue, medication etc.) [73], and by situational characteristics or by culture [29,30,71]. Further, it may be possible that some non-ADHD disorders masquerade as ADHD [64]. Usually, ADHD inattention has been synonymous with distractibility. However, the item 'is often easily distracted by extraneous stimuli' in the DSM IV and the Disruptive Behavior Disorders rating scale [38,39] is actually loading higher on the 'Hyperactive/Impulsive' factor than on the 'Inattention' factor in factor analysis [32]. Experimental findings on inattentive behaviour include 'a reduced length of time spent on a task or toy presented by the examiner; an increase in the number of orientations away from a centrally presented task and more rapid changes between activities' (Taylor [69] p. 14). We will argue that 'cognitive impulsiveness' is a better concept for this kind of behaviour (below).

The preceding reasoning inevitably leads to questioning the fruitfulness of the present ADHD Inattentive type as a subgroup of ADHD (see also Barkley [2]). This subtype is more common than the ADHD Hyperactive/Impulsive or the ADHD Combined subtypes [22,32]. The attention problems of these subtypes may be very different [2,69] and the subtypes may have very different developmental courses both in terms of outcome and co-morbidity. While individuals with ADHD Inattentive subtype may be more socially withdrawn, experience greater academic problems, and develop comorbid anxiety or other mood disorders, early hyperactive-impulsive behaviour is associated with externalising problems like aggression, oppositional behaviour, adolescent delinquency, and substance abuse [2]. The attention problems of children with the ADHD Inattentive subtype are general and non-specific, related to poor focused or selective attention and less accurate information processing, and may be associated with reduced IQ. The more specific attention problems, i.e. distractibility and reduced persistence, of children with ADHD Hyperactive/Impulsive subtype are still present after correcting for IQ [70]. Thus, the ADHD Inattentive subtype may have a different aetiology than the ADHD

Hyperactive/Impulsive subtype. Further, the aetiology of inattention in general may be quite heterogeneous and therefore difficult to disentangle. There is little or no data on medical treatment of ADHD Inattentive subtype [35] although there seems to be a common clinical notion that methylphenidate also helps these children. Response to medication is not a diagnostic criterion, as practically all children will function better when given central stimulants [8]. Also, most explanatory models of ADHD are assumed to apply exclusively to the ADHD Combined subtype or the Hyperactive/Impulsive subtype [67].

2.2. Hyperactivity

An excessive level of activity is typically seen in ADHD as restlessness, fidgeting, and a general increase in gross body movements [41,69,72]. Movement analyses have shown that there is neither good correlation between the frequencies of various activities nor between the rates of movement of the various body parts of children with ADHD [41]. Although they move twice as frequently and cover a fourfold wider area, their movement pattern is less complex and more linear (side to side) compared with normal controls [72]. Overactivity is seen in some situations like in the classroom, but might not be present in others like in play [41]. Finally, it seems that the ADHD overactivity is absent in novel situations [46,61].

Mechanical counts of activity are not related to CPT measures of attention and impulsiveness, while clinical evaluation of hyperactivity statistically often overlaps with impulsiveness [69]. Ratings of hyperactivity (and of impulsiveness) involve an element of overstepping implicit or explicit social rules and are judged according to situational appropriateness [69].

2.3. Impulsiveness

In our model, we will try to disentangle aspects of 'executive functions' into motor and cognitive impulsiveness, and deficient motor control. Motor and cognitive impulsiveness will be explained by the same basic mechanisms: deficient reinforcement processes.

Executive functions denote an assembly or a summary of psychological processes involved in organisation and planning of behaviour (among others), and do not refer to any basic cognitive or neuropsychological mechanisms underlying these capacities [67]. Response inhibition has been proposed as one such basic mechanism that underlies executive functions and the development of self-control, while at the same time response inhibition is defined as one of the executive functions [2,67]. Besides being an ambiguous term, response inhibition may not be as basic a mechanism as often suggested (e.g. by Barkley [2]). Response inhibition is the result of a complex sequence of neural excitations and inhibitions, and as long as the unit of behaviour (i.e. the inhibited response) is not defined, it is difficult to agree on the level of analysis [48]. Also, empirical findings on 'disinhibition' as a characteristic of ADHD are inconclusive [19,57].

In general terms, impulsiveness means acting without reflecting and failure to plan ahead. Thus, 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. This behaviour has been shown to emerge in children with ADHD [46]. 'Cognitive impulsiveness' implies that private events like thoughts and plans are dealt with for short sequences of time with rapid shifts, resulting in problems generating and following plans, problems organising own behaviour, and forgetfulness and inefficient use of time. Further, in our terminology, problems like increased reaction times and speed variability [5,37,42] that have been described as evidence of impaired executive functions, belong to 'extrapyramidal' symptoms.

3. Reinforcement, extinction, and the role of dopamine

The behaviour of children with ADHD and normal children is differently affected by reinforcement contingencies [20,27,63,74]. It has been argued that the key features of ADHD, deficient sustained attention, overactivity, and impulsiveness, may all be due to altered reinforcement mechanisms and a shorter delay-of-reinforcement gradient [46,48].

A stimulus is a positive reinforcer if its presentation increases the probability of future occurrence of the responses that produced it. The reinforcement contingencies are the conditions under which a response produces a reinforcer [10]. Thus, reinforcers act on responses that already took place by increasing the probability of future responding [12]. Reinforcers may vary along several dimensions like density (frequency), the temporal response-reinforcer relationship (contiguity), 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 the delivery of the reinforcer. 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' [12,46] (Fig. 2). Further, a reinforcer acts not only on the response that produced it, but also, to a lesser degree, on responses emitted earlier [9]. Finally, reinforcers are required both in acquisition and in maintenance of behaviour.

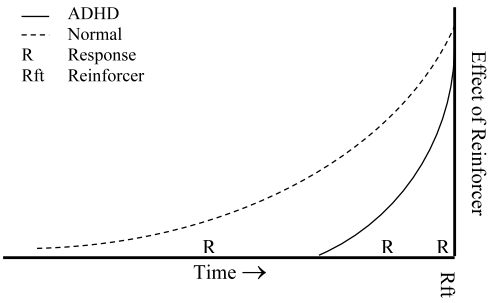

Fig. 2. Theoretical delay-of-reinforcement ('reward') gradients. The effect of a reinforcer is more potent when the delay between the response and the reinforcer is short than when the delay is long. The delay gradient may be steeper and shorter in children with ADHD than in normal children.

Discontinuation of reinforcer deliveries (i.e. an extinction 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 previous to reinforcement, when this contingency is discontinued [10].

Extracellular dopamine levels are characterised by low, tonic background activity and short-lasting phasic activity [54]. Reinforcement is associated with dopamine release in the nucleus accumbens shell. Dopamine release is seen when reinforcers start controlling behaviour (acquisition) and is associated with reinforcer unpredictability. Dopamine is released by unpredicted reinforcers and reinforcers with higher values or earlier occurrence than predicted [54]. When stable-state behaviour is reached and the animal correctly predicts reinforcer deliveries, the phasic release of dopamine is transferred to the earliest stimulus predicting future reinforcers (discriminative stimuli or conditioned reinforcers). Dopamine release may thus be seen as a teaching signal working according to a prediction rule [54].

Omissions of predicted reinforcers (extinction) and reinforcers with a lower than predicted reinforcer value are signalled by a short-lasting phasic decrease in tonic dopamine activity. The phasic decrease in tonic dopamine activity has also been observed in animals failing to obtain a reinforcer due to erroneous behaviour [54]. Thus, the extinction signal depends on the tonic dopamine activation constituting the background for a phasic depression of dopamine activity.

4. Behaviour explained by dysfunctioning dopamine systems

Dopamine, like the other monoamines, is a neuromodulator that modulates the actions of neurotransmitters like glutamate. The dopaminergic system has two main branches: the meso-limbo-cortical originating in the ventral tegmental area and projecting to the prefrontal cortex, the nucleus accumbens septi, and the olfactory tubercle; and the nigro-striatal branch originating in the substantia nigra and projecting mainly to the neostriatum (the caudate–putamen complex). There are five distinct dopaminergic receptors coded by five different genes (D-1–D-5). These are grouped into two families: D-1/D-5 and D-2/D-3/D-4 (for details see e.g. [7]). ADHD seems to have genetic components associated with genes coding for receptors in the dopamine D-2 family and membrane dopamine transporter (DAT) proteins [15,28]. In an animal model [43] there might be an impaired vesicular storage. It is, however, unlikely that any one gene will account for the whole of the ADHD syndrome [69].

4.1. The meso-limbo-cortical dopamine branch

Both phasic and tonic dopamine activities seem to play significant roles in reinforcement and extinction (above) [54]. A dysfunctioning meso-limbo-cortical dopamine branch in ADHD may alter reinforcement and extinction signals and thereby be the neurobiological foundation of the altered reinforcement processes repeatedly suggested as one factor in ADHD symptomatology [18,20,44,46,47,63,77].

4.2. Altered reinforcement processes

We have argued that the delay-of-reinforcement gradient is shorter in ADHD than in normals (Fig. 2), implying that only responses in close proximity to the delivery of the reinforcer will be effective in ADHD [44,46,47,49].

Assuming that the same phasic extracellular dopamine level is needed in children with ADHD as in normals for reinforcement to take place, several interesting implications will follow. Compared with normals, a reduced tonic dopamine level in children with ADHD will require an increased release of dopamine during phasic activation to affect a sufficient number of dopamine-receptor associated ion channels for reinforcement to take place. Also, the phasic dopamine activation as a prediction error signal will require a relatively greater 'error' (e.g. reinforcer value contrast) to release sufficient dopamine for a correction to take place. 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 behaviour. They are also less sensitive to changes in reinforcement contingencies [27].

4.2.1. Motor impulsiveness explained as due to altered reinforcement processes

Not only *single* responses, but also *relations between* responses (e.g. interresponse times, IRTs) are conditioned and maintained by reinforcers [9,12,46,48]. In contrast to the normal delay gradient, only short IRTs may be reinforced and maintained by a short delay gradient (Fig. 2). This explains why motor impulsiveness, responses emitted with short interresponse times, is not present in a novel situation, but develops gradually as more reinforcers modify the behaviour [46,48].

4.2.2. Cognitive impulsiveness as due to altered reinforcement processes

Impaired 'executive functions' are usually associated with frontal dysfunctions [16]. There are well-documented changes in the structure and function of the right frontal cortex in ADHD [36,62]. Not only dopamine, but also other neuromodulators affect frontal-lobe activity. Although an imbalance in one or more of these systems will have an impact on problems with organising and controlling own behaviour, we will emphasise the role of the dopamine system through its close connection to reinforcement and extinction processes. The importance of reinforcement is supported by the fact that children with ADHD are not always cognitively impulsive as they temporarily do manage to plan ahead, organise themselves and remember important things, *if this behaviour is maintained by potent and frequent reinforcers* [19].

Impulsiveness is not unique to ADHD. All children are impulsive as infants and young toddlers. This impulsiveness is gradually reduced during child development as a consequence of reinforcement processes producing increasingly longer sequences of behaviour. In addition, behaviour is brought under discriminative control including the establishment of rule-governed (verbally-governed) behaviour. The development of longer sequences of behaviour and establishment of rule-governed behaviour will be hampered by a short delay gradient. Therefore, both in normal and in ADHD children impulsiveness will be reduced, but this process is stunted in children with ADHD. ADHD impulsiveness will consequently be manifested differently at different ages. Motor impulsiveness is predominant in infants and young toddlers, while cognitive impulsiveness is more prevalent in older children and adolescents. Clinically, this will mean that diagnosing ADHD at very early ages will be difficult since impulsiveness is typical of all small children. Thus, ADHD impulsiveness may be understood as a maturational lag [52,53].

4.2.3. Impaired sustained attention explained as due to altered reinforcement processes

Normally, effects of reinforcers will bridge the time interval between two reinforcers [11]. This will elicit associations between discriminative stimuli present throughout this interval, responses emitted, and the reinforcer (i.e. the three-term contingency [60]). An abnormally steep and short delay gradient will result in an apparently less consistent relation between the factors in the three-term contingency, causing poor stimulus control and an impaired 'sustained attention' in ADHD [11,46].

4.3. Altered extinction processes

Procedurally and behaviourally, extinction is defined in relation to reinforcement. Neurobiologically, however, reinforcement and extinction may be separate processes associated with different aspects of dopamine activity. Dopamine dysfunction may lead to a reduced tonic dopamine activity in ADHD. Omission of a predicted reinforcer (i.e. extinction) is normally signalled by a depression in tonic dopamine activity [54]. An abnormally low tonic dopamine activity may thus cause a failing extinction signal due to a 'floor' effect. In this perspective, acquired responses are not subject to extinction, but accumulate as a function of exposure to different reinforcement contingencies. This view is consistent with studies finding excessive responding during extinction in children with ADHD [46] as well as in an animal model of ADHD [45]. It is also consistent with studies showing that children with ADHD are not hyperactive in novel situations [46,61].

Reduced tonic dopamine activity in ADHD may be normalised by low doses of psychostimulants. Following low doses of psychostimulants, the phasic dopamine release is at the most doubled in the living rat brain while the tonic dopamine level is increased 6-fold [56]. The therapeutic effect of clinical doses of psychostimulants may, therefore, be mediated by an increase in tonic dopamine activity on a neurobiological level and increasing effects of extinction on a behavioural level. However, the exact working mechanisms of stimulant drugs are not known and may differ across brain regions [40].

4.3.1. Overactivity explained as due to failing extinction

Altered reinforcement processes characterised by a shorter delay gradient in ADHD will not by itself generate the gradually developing overactivity. It is hypothesised that the ADHD overactivity is acquired and maintained by a combination of scheduled and unscheduled ('intended' and 'unintended') reinforcers and failing extinction increasing the frequency of acquired responses. 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. [41,46,72]).

4.3.2. Increased behavioural variability explained as due to the combined effects of a shorter delay gradient and failing extinction

Clinically, ADHD behaviour varies according to situational and task characteristics [1]. Experimentally, it has been shown to be more variable than what is normal [26,33,42,59,72]. Variability acts as an operant that may be modified by reinforcers [34,50]. Just as variability in the form of spontaneous mutations is necessary for evolution to take place, so is variability of spontaneously emitted behaviour necessary for the emergence and shaping of new behaviour. Introducing a reinforcer may lead to induction (response generalisation) 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 [10].

At a neurobiological level, both the reinforcement signal (phasic increase in the tonic dopamine activity) and the extinction signal (phasic decrease in the tonic dopamine activity) may be necessary for an efficient differentiation of responses. In ADHD, the establishment of functional response classes and differentiation may be quite inefficient due to the less effective extinction of behaviour resulting from a failing extinction signal. On a behavioural 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. This will cause both a general overactivity level and an increased behavioural variability in ADHD.

4.4. The nigro-striatal dopamine branch

4.4.1. Impaired timing and force regulation of muscle groups

Children with ADHD may show several motor problems: longer and more variable reaction times [5,37,42], increased variability in speed and less accurate response re-engagement [37], and impaired orienting responses and an increased number of responses with very long reaction times [19]. ADHD children with a pervasive problem are more likely to show language and motor delays and to have an onset in the first 2 years of life [69]. A dysfunctioning nigrostriatal dopamine branch will cause several 'extrapyramidal' symptoms (neurological 'soft signs') associated with ADHD in the form of impaired timing and force regulation of muscle groups: poor motor control (clumsiness), longer reaction times, poor response timing, abnormal control of eye saccades, poor handwriting, poor correlation of the activity of different body parts, etc. [25]. Thus, findings previously attributed to response disinhibition due to frontal-lobe dysfunction may rather be due to impaired motor control associated with dopamine dysfunctioning of the neostriatum [19,44,47,48].

5. Aetiology

Family and twin studies provide convincing evidence for a genetic component in ADHD (for a review see [51]). There are, however, geographic variations in the percentage of children receiving an ADHD diagnosis [69]. Some of this variation could be due to different referral practises and different diagnostic criteria [65], but this might not be the whole story.

As argued above, it is likely that dopamine dysfunction plays a pivotal role in the neurobiology of ADHD (Fig. 1). Therefore, ADHD-like symptoms may be produced not only by genetic factors, but also by other agents altering dopaminergic functioning. Chronic intake of dopamine agonists like cocaine, crack, and amphetamines will produce a down-regulation of dopamine synthesis. The down-regulation will persist for some weeks after the drug intake is terminated and ADHD-like symptoms should be observed in the period until dopamine functions normalise [66].

Also some environmental pollutants may cause dopamine dysfunction (see [23] for references). The concentrations and types of these pollutants may vary between countries and regions within a country [31]. Polychlorinated biphenyls (PCBs) constitute a group of halogenated aromatic hydrocarbons that is lipophilic and, consequently, is bioaccumulating [24]. The lipophilic nature of PCBs makes organs like the brain particularly vulnerable. Intake of these pollutants cause developmental abnormalities in humans including low birth weight, disruptive behaviour and overactivity (see [55] for references).

A series of studies of effects of PCB exposure on behaviour and brain chemistry [23,24] 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 grew up. Their behaviour was closely similar to that shown by the animal model of ADHD [45]. 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 [14] probably by a combination of an inhibition of dopamine synthesis and deficient vesicular storage or release [13].

6. Conclusions

At the neurobiological level, ADHD symptoms may to a large extent be caused by a dysfunctioning dopamine system [48]. A dysfunctioning meso-limbo-cortical dopamine branch will produce altered reinforcement and extinction processes that, on a behavioural level, give rise to deficient sustained attention, hyperactivity, increased behavioural variability, and impulsiveness. A dysfunctioning nigro-striatal dopamine branch will cause poor motor control. Etiologically, dopamine dysfunctioning will probably mainly be genetically determined. Non-genetic factors like drugs of abuse and environmental toxins may also contribute to the regional differences found in the prevalence of ADHD.

Acknowledgements

This work was supported by grants from Dr Letten F. Saugstad's Fund (Espen Borgå Johansen), The National Council for Mental Health-Norway (Heidi Aase), and The Norwegian Council of Development Research and Education (Anneke Meyer).

References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., Washington, DC: American Psychiatric Association, 1994.
[2] Barkley RA. ADHD and the Nature of Self-Control. New York: Guilford, 1997.
[3] Batejat D, Lagarde D, Navelet Y, Binder M. Evaluation of the attention span of 10 000 school children 8–11 years of age. Arch Pediatr 1999;6:406–15.
[4] Biederman J, Faraone SV, Spencer T, Wilens T, Mick E, Lapey KA. Gender differences in a sample of adults with attention deficit hyperactivity disorder. Psychiatry Res 1994;53:13–29.
[5] Brandeis D, van Leeuwen TH, Rubia K, Vitacco D, Steger J, Pascual-Marqui RD, Steinhausen H-C. Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. Behav Brain Res 1998;94:111–25.
[6] Cantwell DP. Attention deficit disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1996;35:978–87.
[7] Carey MP, Diewald LM, Esposito F, Pellicano MP, Gironi Carnevale UA, Sergeant JA, Papa M, Sadile AG. Differential distribution, affinity and plasticity of dopamine D-1 and D-2 receptors in the target sites of the mesolimbic system in an animal model of ADHD. Behav Brain Res 1998;94:173–85.
[8] Carey WB. What the multimodal treatment study of children with attention deficit/hyperactivity disorder did and did not say about the use of methylphenidate for attention deficits. Pediatrics 2000;105:863–4.
[9] Catania AC. Reinforcement schedules: the role of responses preceding the one that produces the reinforcer. J Exp Anal Behav 1971;15:271–87.
[10] Catania AC. Learning, fourth ed. Englewoods Cliffs, Upper Saddle River, NJ: Prentice Hall, 1998.
[11] Catania AC, Sagvolden T, Aase H. Delay of reinforcement and the hyperactivity syndrome, Society for the Quantitative Analysis of Behavior, 1997: Meeting Abstract.
[12] Catania AC, Sagvolden T, Keller KJ. Reinforcement schedules: retroactive and proactive effects of reinforcers inserted into fixed-interval performance. J Exp Anal Behav 1988;49:49–73.
[13] Chishti MA, Fisher JP, Seegal RF. Aroclors 1254 and 1260 reduce dopamine concentrations in rat striatal slices. Neurotoxicology 1996;17:653–60.
[14] Chu I, Villeneuve DC, Yagminas A, Lecavalier P, Poon R, Feeley M, Kennedy SW, Seegal RF, Hakansson H, Ahlborg UG, Valli VE, Bergman A. Toxicity of 2,2′,4,4′,5,5′-hexachlorobiphenyl in rats: effects following 90-day oral exposure. J Appl Toxicol 1996;16:121–8.
[15] Cook EH Jr, Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, Leventhal BL. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet 1995;56:993–8.
[16] Denckla MB. A theory and model of executive function. A neuropsychological perspective. In: Lyon GR, Krasnegor NA, editors. Attention, Memory, and Executive Function. Baltimore: Brookes, 1996:263–78.
[17] Dienske H, de Jonge G, Sanders-Woudstra JA. Quantitative criteria for attention and activity in child psychiatric patients. J Child Psychol Psychiatry 1985;26:895–915.
[18] Douglas VI. Attentional and cognitive problems. In: Rutter M, editor. Developmental Neuropsychiatry. New York: Guilford, 1983:280–329.
[19] Douglas VI. Cognitive control processes in Attention-Deficit/Hyperractivity Disorder. In: Quay HC, Hogan AE, editors. Handbook of Disruptive Behavior Disorders. New York: Plenum, 1999:105–38.
[20] Douglas VI, Parry PA. Effects of reward and nonreward on frustration and attention in attention deficit disorder. J Abnorm Child Psychol 1994;22:281–301.
[21] Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A/fluorine-18/fluorodopa positron emission tomographic study. J Neurosci 1998;18:5901–7.
[22] Faraone SV, Biederman J, Weber W, Russell RL. Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: results from a clinically referred sample. J Am Acad Child Adolesc Psychiatry 1998;37:185–93.
[23] Holene E, Nafstad I, Skaare JU, Bernhoft A, Engen P, Sagvolden T. Behavioral effects of pre- and postnatal exposure to individual polychlorinated biphenyl congeners in rats. Environ Toxicol Chem 1995;14:967–76.
[24] Holene E, Nafstad I, Skaare JU, Sagvolden T. Behavioural hyperactivity in rats following postnatal exposure to sub-toxic doses of polychlorinated biphenyl congeners 153 and 126. Behav Brain Res 1998;94:213–24.
[25] Kadesjo B, Gillberg C. Developmental coordination disorder in Swedish 7-year-old children. J Am Acad Child Adolesc Psychiatry 1999;38:820–8.
[26] Kinsbourne M. Testing models for attention deficit hyperactivity disorder in the behavioral laboratory. In: Conners K, Kinsbourne M, editors. ADHD: Attention Deficit Hyperactivity Disorder. Munich: MMV Medizin Verlag Muenchen, 1990:51–70.
[27] Kollins SH, Lane SD, Shapiro SK. Experimental analysis of childhood psychopathology: A laboratory matching analysis of the behavior of children diagnosed with attention deficit hyperactivity disorder (ADHD). Psychol Record 1997;47:25–44.
[28] LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1996;1:121–4.
[29] Livingston R. Cultural issues in diagnosis and treatment of ADHD. J Am Acad Child Adolesc Psychiatry 1999;38:1591–4.

[30] Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry 1998;155:493–8.
[31] McFarland VA, Clarke JU. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ Health Perspect 1989;81:225–39.
[32] Meyer A, Eilertsen D-E, Sundet JM, Tshifularo JG, Sagvolden T. Screening for DSM-IV Attention-Deficit/Hyperactivity Disorder symptoms based on teacher's ratings of South-African primary school children shows striking similarities among six different cultural groups, J Am Acad Child Adolesc Psychiatry. In press.
[33] Mitchell WG, Chavez JM, Baker SA, Guzman BL, Azen SP. Reaction time, impulsivity, and attention in hyperactive children and controls: a video game technique. J Child Neurol 1990;5:195–204.
[34] Mook DM, Jeffrey J, Neuringer A. Spontaneously hypertensive rats (SHR) readily learn to vary but not repeat instrumental responses. Behav Neural Biol 1993;59:126–35.
[35] NIH Consens Statement. Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. National Institutes of Health Consensus Development Conference. Nov 16–18, 1998. Statement No. 110. NIH Online 1998;16:1–37.
[36] Oades RD. Frontal, temporal and lateralised brain function in children with attention-deficit hyperactivity disorder (ADHD): a psychophysiological and neuropsychological viewpoint on development. Behav Brain Res 1998;94:83–95.
[37] Oosterlaan J, Sergeant JA. Response inhibition and response re-engagement in ADHD, disruptive, anxious and normal children. Behav Brain Res 1998;94:33–43.
[38] Pelham WE, Murphy DA, Vannatta K, Milich R, Licht BG, Gnagy EM, Greenslade KE, Greiner AR, Vodde-Hamilton M. Methylphenidate and attributions in boys with attention-deficit hyperactivity disorder. J Consult Clin Psychol 1992;60:282–92.
[39] Pillow DR, Pelham WE Jr, Hoza B, Molina BS, Stultz CH. Confirmatory factor analyses examining attention deficit hyperactivity disorder symptoms and other childhood disruptive behaviors. J Abnorm Child Psychol 1998;26:293–309.
[40] Porrino LJ, Lucignani G. Different patterns of local brain energy metabolism associated with high and low doses of methylphenidate. Relevance to its action in hyperactive children. Biol Psychiatry 1987;22:126–38.
[41] Porrino LJ, Rapoport JL, Behar D, Sceery W, Ismond DR, Bunney WE. A naturalistic assessment of the motor activity of hyperactive boys. I. Comparison with normal controls. Arch Gen Psychiatry 1983;40:681–7.
[42] Rubia K, Oosterlaan J, Sergeant JA, Brandeis D, van Leeuwen T. Inhibitory dysfunction in hyperactive boys. Behav Brain Res 1998;94:25–32.
[43] Russell V, de Villiers A, Sagvolden T, Lamm M, Taljaard J. Differences between electrically-, ritalin- and D-amphetamine-stimulated release of [3H]dopamine from brain slices suggest impaired vesicular storage of dopamine in an animal model of attention deficit hyperactivity disorder. Behav Brain Res 1998;94:163–71.
[44] Sagvolden T. The attention deficit disorder might be a reinforcement deficit disorder. In: Georgas J, Manthouli M, Besevegis E, Kokkevi A, editors. Contemporary Psychology in Europe: Theory, Research, and Application. Göttingen: Hogrefe and Huber, 1996:131–43.
[45] Sagvolden T. The spontaneously hypertensive rat as a model of attention-deficit/hyperactivity disorder. In: Solanto-Gardner MV, Arnsten AFT, Castellanos FX, editors. The Neuropharmacology of Psychostimulant Drugs: Implications for AD/HD. NewYork: Oxford University Press, 2000.
[46] Sagvolden T, Aase H, Zeiner P, Berger DF. Altered reinforcement mechanisms in attention deficit/hyperactivity disorder. Behav Brain Res 1998;94:61–71.
[47] Sagvolden T, Archer T. Future perspectives on ADD research—an irresistible challenge. In: Sagvolden T, Archer T, editors. Attention Deficit Disorder: Clinical and Basic Research. Hillsdale, NJ: Lawrence Erlbaum Associates, 1989:369–89.
[48] Sagvolden T, Sergeant JA. Attention deficit/hyperactivity disorder—from brain dysfunctions to behaviour. Behav Brain Res 1998;94:1–10.
[49] Sagvolden T, Wultz B, Moser EI, Moser M-B, Mørkrid L. Results from a comparative neuropsychological research program indicate altered reinforcement mechanisms in children with ADD. In: Sagvolden T, Archer T, editors. Attention Deficit Disorder: Clinical and Basic Research. Hillsdale, NJ: Lawrence Erlbaum Associates, 1989:261–86.
[50] Saldana RL, Neuringer A. Is instrumental variability abnormally high in children exhibiting ADHD and aggressive behavior. Behav Brain Res 1998;94:51–9.
[51] Samudra K, Cantwell DP. Risk factors for attention-deficit/hyperactivity disorder. In: Quay HC, Hogan AE, editors. Handbook of Disruptive Behavior Disorders. New York: Plenum, 1999:199–220.
[52] Saugstad LF. Deviation in cerebral excitability: possible clinical implications. Int J Psychophysiol 1994;18:205–12.
[53] Saugstad LF. The maturational theory of brain development and cerebral excitability in the multifactorially inherited manic-depressive psychosis and schizophrenia. Int J Psychophysiol 1994;18:189–203.
[54] Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.
[55] Seegal RF. Epidemiological and laboratory evidence of PCB-induced neurotoxicity. Crit Rev Toxicol 1996;26:709–37.
[56] Seeman P, Madras B. Methylphenidate elevates resting dopamine which lowers impulse-triggered release of dopamine: a hyphothesis. Behav. Brain Research 2001;130:79–83.
[57] Sergeant JA, Oosterlaan J, van der Meere J. Information processing and energetic factors in attention deficit/hyperactivity disorder. In: Quay HC, Hogan AE, editors. Handbook of Disruptive Behavior Disorders. New York: Plenum, 1999:75–104.
[58] Sergeant JA, Scholten CA. On resource strategy limitations in hyperactivity: cognitive impulsitivity reconsidered. J Child Psychol Psychiatry 1985;26:97–109.
[59] Shaywitz BA, Fletcher JM, Shaywitz SE. Attention-deficit/hyperactivity disorder. Adv Pediatr 1997;44:331–67.
[60] Skinner BF. The Behavior of Organisms. New York: Appleton-Century-Crofts, 1938.
[61] Sleator EK, Ullman RK. Can a physician diagnose hyperactivity in the office. Pediatrics 1981;67:13–7.
[62] Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res 1998;94:127–52.
[63] Sonuga-Barke EJS, Taylor E, Sembi S, Smith J. Hyperactivity and delay aversion I: the effect of delay on choice. J Child Psychol Psychiatry 1992;33:387–98.
[64] Swanson J, Posner MI, Cantwell D, Wigal S, Crinella F, Filipek P, Emerson J, Tucker D, Nalcioglu O. Attention deficit/hyperactivity disorder: symptom domains, cognitive processes, and neural networks. In: Parasuraman R, editor. The Attentive Brain. Cambridge, MA: MIT, 1998:445–60.
[65] Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJS, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet 1998;351:429–33.
[66] Swartz CM, Breen KJ. Elevated serum CK in long abstinent cocaine abusers. Am J Drug Alcohol Abuse 1993;19:327–35.
[67] Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry 1998;39:65–99.

[68] Taylor E. Syndromes of attention deficit and overactivity. In: Rutter M, Taylor E, Hersov L, editors. Child and Adolescent Psychiatry. Modern Approaches. Osney Mead. Oxford: Blackwell, 1994:285–307.
[69] Taylor E. Clinical foundations of hyperactivity research. Behav Brain Res 1998;94:11–24.
[70] Taylor E, Sandberg S, Thorley G, Giles S. The Epidemiology of Childhood Hyperactivity, first ed. Oxford: Oxford University Press, 1991.
[71] Taylor E, Sergeant J, Doepfner M, Gunning B, Overmeyer S, Möbius H-J, Eisert H-G. Clinical guidelines for hyperkinetic disorder. Eur Child Adolesc Psychiatry 1998;7:184–200.
[72] Teicher MH, Ito Y, Glod CA, Barber NI. Objective measurement of hyperactivity and attentional problems in ADHD. J Am Acad Child Adolesc Psychiatry 1996;35:334–42.
[73] Topitsch D, Schober E, Wurst E, Kryspin-Exner I. Changes in attention with hypo- and hyperglycaemia in children with insulin dependent diabetes mellitus. Eur J Pediatr 1998;157:802–5.
[74] Tripp G, Alsop B. Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. J Clin Child Psychol 1999;28:366–75.
[75] van der Meere JJ. The role of attention. In: Sandberg ST, editor. Monographs in Child and Adolescent Psychiatry. Hyperactivity Disorders of Childhood. Cambridge: Cambridge University Press, 1996:109–46.
[76] Weiss G, Hechtman L. Hyperactive Children Grown Up, second ed. New York: Guilford, 1993.
[77] Wender PH. Minimal Brain Dysfunction in Children. New York: Wiley, 1971.