

Editorial

Attention deficit/hyperactivity disorder—from brain dysfunctions to behaviour

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Abstract

This special issue represents an attempt to answer fundamental brain and behaviour issues in attention-deficit hyperactivity disorder (ADHD). The European network on hyperkinetic disorders (Eunethydis) is trying to develop a novel, testable theory of ADHD, giving an account of its causes, its development from brain dysfunctions to behavioural symptoms and co-morbidity and explaining why no current therapy produces long-lasting improvements. The combined insights of the articles presented here suggest that there is no brain damage in ADHD, but hypo-efficient dopamine systems which give rise to neurochemical imbalances. These cause behavioural problems: deficits in sustained attention, overactivity and impulsiveness. Impulsiveness is increasingly being seen as a key characteristic of the disorder. None of these symptoms are necessarily primary, but may be secondary to an underlying deficit in reinforcement processes seen particularly in a greater than normal sensitivity to variations in the timing of stimulus presentation. Other symptoms can also be seen: altered effects of reinforcers, increased behavioural variance and motor co-ordination problems. Medication produces temporary, plastic changes in cellular components like receptors and transduction mechanisms normalising dopamine functions and behaviour. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

The primary aim of the present collection of publications is to develop a novel, testable theory of attention-deficit/hyperactivity disorder (ADHD) [1], accounting for its causes, its development from brain dysfunctions to behavioural symptoms and co-morbidity, to show how effective medication works and explain why the presently-available therapies do not produce long-lasting improvements.

ADHD is a disorder that defies conceptualisation at any one level of explanation. For this reason, ADHD is the perfect candidate for a topic on which to develop an

interdisciplinary research network. Therefore, a substantial portion of the research in this issue presents the proceedings of the European network on hyperkinetic disorders (Eunethydis), the first multi-disciplinary study of ADHD employing both a clinical and an animal model in order to study neurobiological and behavioural bases of ADHD.

ADHD is a seemingly heterogeneous group of behaviour disorders affecting between 1.3 and 5% of grade-school children [80,82]. For simplicity, ADHD is used as a common term for these diagnoses. The disorder is not well understood. It is argued that there is no focal brain damage involved but genetic factors mainly giving rise to dopamine hypofunctioning that causes the behavioural symptoms. Other neurochemical imbalances may also be involved. The disorder usually mani-

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fest itself before the child is 7 years old. In childhood, the disorder is more common in boys than in girls and at least 75% will continue to suffer from the disorder after they have grown up. Then more females are still suffering from the disorder in adulthood [5].

ADHD is a major risk factor for later delinquency, substance abuse and personality disorders. For instance, about half of the children diagnosed as having ADHD grow up to have psychiatric disorders later on in life [82]. ADHD, therefore, constitutes one of the strongest risk factors known for mental illness in early adult life. ADHD is associated with proneness to repeated accidents [82]. Given this, it is not surprising that the social and economic, as well as the personal costs of ADHD, are great. An increased understanding of the disorder will lead to improved and more focused approaches to interventions.

2. The three main symptoms of ADHD

Impulsiveness, inattentiveness and overactivity are presently regarded as the main symptoms of ADHD [82]. Although, there is considerable overlap between these symptoms, impulsiveness is increasingly seen as the symptom of greatest significance [82]. Impulsiveness is reflected in an inability to withhold inappropriate responses [19], such as premature responding, over rapid responsiveness, excessive attraction to immediate reward, acting without reflecting, recklessness and impetuous behaviour. Attention problems are typically described as distractibility and trouble with sustaining attention [18]. An excessive level of activity is typically seen in restlessness, fidgeting and generally unnecessary gross bodily movements [46]. ADHD correlates with aggression, conduct disorder, oppositional defiant disorder, learning disabilities, depression, anxiety and low self-esteem [82]. The diagnosis is by no means simple, the symptoms are not that well defined and requirements vary between the ICD and DSM taxonomies [80,82]. According to DSM-IV criteria, it is possible to have ADHD without being inattentive. Inattentiveness is, however, a necessary requirement for a hyperkinetic disorder (HKD) according to ICD-10 criteria [82].

It is argued (below) that the combined insights of the articles presented here point out that neither of these symptoms are primary but may be secondary to an underlying deficit in reinforcement processes. This is expressed as an increased sensitivity to the timing of stimulus presentation and in part due to a hypo-efficient central-nervous dopaminergic system. The symptoms seem to be genetically based and may, therefore, last for life although they may be temporarily alleviated by medication (below). Long-lasting effects of medication are not to be expected because the treatment does not alter the genetic component(s), only their expres-

sion. Methylphenidate hydrochloride (Ritalin®) produces temporary, plastic changes in neuronal components like receptors and transduction mechanisms (below) and should, therefore, normalise the symptoms only as long as the ADHD sufferer is chronically medicated.

2.1. Impulsiveness

The behavioural characteristics of ADHD have been explained as a lack of behavioural inhibition. Based on Jeffrey Gray's model [24] with three main interacting systems, the behavioural inhibition system (BIS), the behavioural activation system (BAS) and the flight/fear system, Quay [48,49] argued that ADHD was a failure of the BIS. This model has been systematically tested by using various stop-signal tasks [7,41,52,85]. Inhibitory behavioural control refers to the ability to withhold a planned response, to interrupt a response that has been started, to protect an ongoing activity from interfering activities and to delay a response. Inhibition overlaps with a variety of terms: perseveration, withholding a goal-directed or motivated response, impulsiveness, delay of gratification, sensation seeking, risk taking and over-reactivity to frustration [52]. This disinhibition model has been supported by several researchers [41,52]. There is evidence, however, that both ADHD as well as disruptive children show poor response inhibition [41]. Other results [7,63,79,85,85] contradict this hypothesis. In a series of studies Sonuga-Barke and colleagues [75,77,78] have shown that inhibitory problems only occur in certain situations and that these are more likely to reflect a sensitivity to delay rather than an underlying inhibitory deficit. Furthermore, in some situations ADHD children have problems because they respond too slowly rather than too quickly. It seems that ADHD children are also deficient in response re-engagement [41]. At another level, poor behavioural response inhibition would have been hard to explain as an underlying deficient neurophysiological inhibition simply because any behavioural response is the result of an enormously complicated interaction between excitatory and inhibitory synaptic activity.

Taylor [82] argued that impulsiveness can be reduced to the peculiar ADHD style of brief, short sequences of activity on tasks and rapid change associated with the sort of sensitivity to delay described above and below. By analysing experimentally the various behavioural components in ADHD behaviour, it can be shown that impulsiveness, defined as bursts of responses with short inter-response times, could be explained by altered reinforcement processes [63]. It is suggested that impulsiveness is due to altered reactivity to reinforcers and not vice-versa. These results were replicated by using an animal model [4]. Impulsiveness could be modified by

drug treatment [6] and may be induced by environmental toxins probably affecting dopamine [26].

2.2. Overactivity

Overactivity is commonly seen in ADHD but there is little correlation between various activities and even the movements of the various body parts of ADHD children [46]. Although overactivity is seen in some situations like the classroom, it might not be present in others like in play [82]. Overactivity may be absent in novel situations [73]. This phenomenon was experimentally analysed [63]. The activity level of ADHD was normal at the start of the experimental session but increased as the session progressed. Impulsiveness, defined as bursts of responses with short inter-response times, was shown to be a major component of the ADHD overactivity and was ascribed to altered reinforcement processes [63](see also [57,58]).

2.3. Deficient sustained attention

Children with ADHD tend to behave in inattentive ways but the role of attention in ADHD is still quite unclear [70]. It is hard to differentiate between the frequently used clinical terms distractibility, short attention span and sensation seeking. Perceptual processes may be altered in ADHD [39]. There is evidence for changed initial orienting responses to stimuli, even in children with subclinical ADHD, when various aspects of neuroelectric activity are recorded [7,85]. However, other results show that perceptual (input) processes are not altered [69] but output processes are deficient [84]. Interestingly, van der Meere [83] has argued that problems of sustained attention only occur in situations where stimuli are widely spaced in time. Once again the behavioural disturbance typical of ADHD seem specifically linked to disturbed inter-temporal sensitivities.

This suggests that the apparent deficient sustained attention may actually be an effect of a shorter than normal delay-of-reinforcement gradient (below). Thus, one explanation may be that all three symptoms, impulsiveness, overactivity and deficient sustained attention, may all be due to one single factor: a shorter delay-of-reinforcement gradient. This may explain why these three symptoms sometimes emerge as one factor in factor analyses [82]

3. Altered effects of reinforcers

It is increasingly clear that children with ADHD are abnormally sensitive to variations in temporal features of attentional tasks and reinforcement schedules. They prefer an immediate reinforcement and cannot wait for a delayed one [76,82]. Their problems seem to occur in

situations with low stimulus or low reinforcer density. Although not always present [79], several of the present [4,63] and previous [18,20,21,57,58,60,61,63,76,86] authors have argued that altered reinforcement processes are important in ADHD symptomatology.

Reinforcers change the probability of future responding by acting retroactively on responses that already occurred [11]. 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 of 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 [11] (see Fig. 1 in [63]). Furthermore, a reinforcer acts not only on the response that produces it, but also, to a lesser degree, on responses emitted earlier [10].

We will argue that children with ADHD have a steeper and shorter delay gradient [57,58,63] based on a genetically-based hypofunctional dopamine system. A reinforcer in close proximity to a response may, therefore, be more effective in ADHD children than in normals. This will in itself generate overactivity as gradually more reinforcers act on the behaviour taking place in a particular situation.

Not only single responses, but also relations between responses (e.g. interresponse times, IRTs) are conditioned and maintained by reinforcers [10,11]. In contrast to the normal delay gradient, only short IRTs may be reinforced and maintained by a short delay gradient (see Fig. 1 in [63]). This explains why hyperactivity and responses emitted with short interresponse times, impulsiveness, are not present in a novel situation, but develop gradually as more reinforcers modify the behaviour of ADHD [63,73]. Analyses of activity level as functions of reinforcement densities [61] showed no difference between hyperactives and controls when the reinforcers were frequent, only when they were infrequent. The density of reinforcement may be critical whenever ADHD behaviour deviates from normal.

3.1. Impaired sustained attention explained as altered reinforcement processes

Since a reinforcer acts not only on the response occurring immediately prior to its delivery but also on responses emitted earlier (above), all responses occurring between the delivery of two consecutive reinforcers will be reinforced in normal children. Since the delay gradient seems steeper and shorter for ADHD children than for normal children, relatively fewer of the correct responses are reinforced in ADHD than in normal children simply because the delay gradient is too short to affect all responses occurring in the time interval between two reinforcers. This results in poor stimulus

control and possibly impaired sustained attention [12,63].

3.2. Increased variability

There are systematic differences in the behavioural problems of ADHD depending on the type of situation [82]. Variability is adaptive in some situations and acts as an operant response that may be modified by reinforcers [64]. ADHD behaviour is generally more variable than what is normal [41,52]. Saldana and Neuringer [64] using a Markov-prediction procedure where reinforcers were given contingent upon whether or not a computer program was able to predict the subject's next response from the history of this subject's previous responding, failed to find increased variability in ADHD. The lack of effect may be due to the high density of reinforcement used [61].

4. An animal model

In all areas of research, one is trying to find, or build, models that can be used to summarise and simplify the disorder, research problem or phenomenon under examination. In clinical research there are several advantages associated with animal models of disorders [57,74,82]. The researcher deals with a simpler system yielding data that may be easier to interpret than the full-blown clinical case, the groups may genetically be more homogeneous, environmental control is simpler and interventions of various sorts are possible.

Several animal models of ADHD have been proposed: rats selected from a general population [47], rats reared in social isolation [50], rats exposed to environmental pollutants (lead [72], PCBs [25,26]), rats that have undergone neurotoxic brain lesions [3,71]), genetic models (SHR: see below, Naples high/low excitability rats [55,56], knock out mice [23]). The various models may complement each other by shedding light on different aspects of the disorder.

The spontaneously hypertensive rat (SHR), is the most frequently used ADHD model. This is a strain that has been bred from progenitor Wistar-Kyoto rats (WKY) [40]. SHR develops response bursts similar to ADHD children [4,6,59]. It becomes hyperactive in a variety of behavioural paradigms [28,34,37,38,59,62, 88,87] and it has sustained attention problems [4,6,59, 60,62]. SHR also shows increased behavioural variability [36]. The validation of the animal model facilitates ADHD research that previously was not possible.

Estimation of the magnitude of the altered reactivity to reinforcers in SHR has shown that SHR did not show higher maximal response rates than the controls and is hyperactive only when reinforcers are relatively sparse. The group differences in behaviour were solely

due to a changed reactivity to reinforcers in the SHR strain [60,61].

In the model studies, an operant analysis of behaviour has been used, a type of analysis originated by Skinner [22]. This method is used because the results are generally easy to replicate, it is possible to study only one or a few aspects of the behaviour, there is a common nomenclature of behaviour and, finally, comparative research is possible (e.g. [4,32,59,63]).

Presently, behavioural and central-nervous substrates of ADHD are examined in more detail than is possible with humans by using analogous behavioural tasks in humans with ADHD [63] and animal models [4,6,26,44]. The findings opened a new way of conceptualising ADHD.

5. The neurobiology of ADHD

It is generally agreed that the pattern of symptoms of ADHD is likely to be mediated by some abnormalities in brain functioning [7,9,31,39,57,74,82,85]. Currently, neuroimaging results are inconsistent and implicate a variety of loci in ADHD. This may in part be due to procedural differences between research groups and to sampling effects. ADHD seems mainly, but not exclusively, to be associated with reduced metabolism and volume of right frontal cortex and right subcortical structures, smaller total cerebral volume and smaller cerebellum as well as reduced corpus callosum [39,74].

There are many competing hypotheses about the specific cognitive processes implicated in ADHD. One is the frontal lobe hypothesis suggesting that ADHD is the result of a general disorganisation in behaviour linked to problems of inhibition that are mediated by a genetically-based abnormality in the functioning of the frontal structures responsible for so-called executive functions [17].

Several tests or tasks have been used for investigating frontal functions: continuous performance task (CPT), Go/No-go task, incompatibility tests and Stroop test. The present investigations did not find unequivocal support for the frontal hypothesis. Event-related brain potentials (ERPs) were recorded during Go/No-go task. The ERPs showed identifiable components with stable activity maps (microstates) within a few hundred milliseconds following the stimulation [7,85]. Low-resolution electromagnetic tomography (LORETA) for estimation of realistic 3-D source distributions underlying the microstates showed that the neuroelectric changes associated with ADHD were not located frontally but more caudally [7,85]. The sources were more bilateral and less concentrated to the right occipital region in the subclinical ADHD group than in the control group [85]. The more caudal location of the changed functions

associated with ADHD [7,85] may be in accordance with the neostriatal changes seen both in ADHD individuals (above) and in the animal model (below). Furthermore, the changes were not associated with disinhibition but with initial orienting of attention to stimuli.

ADHD seems to be associated with dopamine hypo-functioning (below). 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 [8]. The dopaminergic system consists of two major branches: the nigro-striatal branch originating in the substantia nigra and projecting mainly to the neostriatum (the caudate-putamen complex); and the meso-cortico-limbic branch originating in the ventral tegmental area and projecting to the prefrontal cortex, the nucleus accumbens septi and the olfactory tubercle.

ADHD seems to have genetic components associated with genes coding for receptors in the dopamine D-2 family and membrane dopamine transporter (DAT) proteins [15,29]. Russell [54] presents evidence in favour of an impaired vesicular storage in the animal model. It is, however, unlikely that any one gene will account for the whole of the ADHD syndrome [82].

There might be an impaired cross-talk between the various brain structures of an ADHD child [39]. Such an impaired dialogue is seen as uniformly high correlations between the cytochrome oxidase activities of the various brain areas in the SHR but not in the WKY [44]. This lack of modulation in the SHR could be due to reduced dopaminergic functions [6,8,16,42,44,45,53].

By using an in vitro superfusion technique, reduced dopamine release was shown in the prefrontal cortex and in the neostriatum of the male SHR as well as a hypofunctional nucleus accumbens [53,54]. The subdivision of accumbens [8,45] is probably the reason why Russell [53,54] did not find any reduced dopamine release in accumbens. The functional imaging studies [8,45] simply had a finer spatial resolution than the superfusion studies. Reduced SHR extracellular concentrations of neostriatal dopamine are also shown with microdialysis [30].

The male SHR may have an impaired vesicular storage of dopamine causing leakage of dopamine into the cytoplasm [54] where it might be metabolised by monoamine oxidase (MAO). MAO metabolises catecholamine molecules that are not stored in vesicles, but are free in the cell's cytoplasm and, therefore, susceptible to the actions of MAO. It is presently not known if reduced dopamine is restricted to the male SHR or whether it is the case with the female SHR as well.

Boix [6] showed that treatment with the MAO inhibitor L-deprenyl increased dopamine levels in all areas of the male SHR brain. Without treatment, the male SHR showed a lower dopamine turnover (homovanillic acid, HVA:DA) ratio in the neostriatum as

well as an asymmetric HVA:DA ratio in the accumbens with a lower ratio in the right accumbens.

The central-nervous system of the juvenile, prehypertensive, male SHR may compensate for the reduced release of dopamine by increasing the numbers of dopamine D-1/D-5 receptor binding sites in the rostral portions of the neostriatum, the core and the shell of the accumbens and the olfactory tubercle in SHR as shown by quantitative receptor autoradiography [8]. Such increased levels are associated with lower receptor affinities.

The impaired dopamine storage in the male SHR might not only have caused reduced release and lower D-1 receptor affinities of DA, but also reduced Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), the major protein of the postsynaptic density and in signal transduction, in the anterior portions of the accumbens shell and a lower expression of peptide products of the immediate early genes of the *fos* family (*c-fos*, in particular) and *ZIF-268* [45]. The lower expressions of both CaMKII and the immediate early genes are most likely due to reduced neuronal activity in these areas [45].

A major developmental strategy in the mammalian brain is the initial overproduction of synapses and receptors in infancy and the later pruning in the transition from adolescence into adulthood. Too fast or too slow pruning has been hypothesised to be associated with psychopathology [65,66]. Andersen and co-workers [2] investigated sex differences in dopamine receptor overproduction and elimination. Density of dopamine receptors of the D-1- and D-2-families are differently expressed in rats from infancy through adolescence. The male striatum had almost 5-fold overproduction and elimination of D-1 and D-2 receptors by comparison with females, settling on the same densities as adults. Males overproduced D-1, but not D-2, receptors in the accumbens and retained the elevated densities in adulthood. It was suggested [2] that such gender differences are involved in a variety of clinical disorders: ADHD, schizophrenia, Tourette's syndrome and drug addiction which are all more common in males. Thus, the hypofunctioning dopamine system seen in the male SHR combined with the sex differences in D-1 receptor overproduction and elimination from infancy through adolescence into adulthood may explain why the impulsiveness is seen in the male SHR and not in the female [4]. Similar factors may explain the sex differences in ADHD.

5.1. The role of other amines in ADHD

If the impaired vesicular storage of dopamine [54] is due to a deficient vesicular amine transporter in SHR as well as ADHD, not only dopaminergic systems, but also the other aminergic systems, noradrenaline, adrenaline, serotonin and histamine, should be hypo-

functioning (see Refs. in [8]). However, if the genetic alteration in ADHD is coding for the dopamine receptors and/or membrane transporters only [15,29], the primary changes may well be quite restricted to dopamine. Solanto [74] reviews roles of the aminergic systems and suggests the possibility of relative overactivity both in the dopaminergic as well as the noradrenergic systems. Boix [6] found that both SHR and WKY had higher noradrenergic concentrations in the left neostriatum and that this asymmetry was less pronounced in the SHR. There is also a higher serotonergic activity in the neostriatum and the frontal cortex of the SHR [6] and altered metabolite:serotonin ratios in several brain areas of the SHR [16].

Neurotransmitter input to a cell carrying a specific message will usually be mediated by neurotransmitters like glutamate and GABA. These inputs will then interact with G-protein-coupled receptors for neuromodulators like dopamine, serotonin and noradrenaline in order to produce long-term effects [33]. Thus, in order to affect cellular functions normally, neuromodulatory functions will have to be normal. Contrary to Solanto's [74] suggestion, we propose [6,8,16,42,44,45,53] that ADHD symptoms are caused by reduced dopaminergic functions impairing the cell's processing of stimuli, especially, if they arrive after some time interval.

6. Three different neuroanatomical systems with reduced dopamine functions

6.1. *Accumbens*

Accumbens is usually implicated in reinforcement (above). We suggest that the altered delay-of-reinforcement gradient seen in ADHD is associated with the dopamine deficiency seen in the male accumbens possibly associated with a putative abnormal control of the overproduction and pruning of D-1 receptor complexes [2,65,66]. Accumbal dopamine D-1 stimulation has been suggested to be involved in addictive behaviour [2]. Since some self-medication may be expected in the population and since dopamine hypofunctioning may be genetically determined in ADHD, an increased substance abuse is predicted not only among inadequately medicated ADHD persons but also among their relatives. As predicted, there is an increased incidence of substance abuse among ADHD persons [27] as well as an increased incidence of ADHD problems in sons of substance abusers [51].

6.2. *Frontal cortex*

Frontal cortex receives a major dopamine input from the ventral tegmental area. However, although there are well-documented changes in the structure and function

of the right frontal cortex in ADHD [39,74] and in the frontal cortex of the animal model [16,53,54] and impaired executive functions associated with frontal dysfunctions [17], the present research did not unequivocally support such dysfunctions, neither behaviourally nor electrophysiologically (above).

6.3. *Neostriatum*

The caudate and putamen receives the most dense dopamine input of all central-nervous structures. There are both anatomical as well as functional changes in the ADHD neostriatum (above). Parkinsonism is the best known disorder following deficient dopamine input to the neostriatum. 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 [82]. This might implicate neostriatal hypofunctioning also in ADHD. It might well be that results previously ascribed to response disinhibition due to frontal-lobe dysfunction, may be due to impaired motor functions associated with dopamine hypofunctioning of the neostriatum. This might explain the longer and more variable reaction times in STOP tasks [7,41,52], the increased variability in speed and the less accurate response re-engagement in stop tasks [41], impaired orienting responses and an increased number of responses with very long reaction times [52,64,79]. Language delays [9,82] etc. may also easily be explained as (minor) motor problems. We suggest that future research should investigate more closely to what extent minor motor problems are associated with ADHD.

7. Other factors producing dopamine hypofunctioning

Our position is that dopamine hypofunction plays a pivotal role in the neurobiology of ADHD. Therefore, ADHD-like symptoms may be produced not only by genetic factors but also by other agents altering the neonatal dopamine systems. There are geographic variations in the percentage of children receiving an ADHD diagnosis [82]. Some of this variation could be due to different referral practices and different criteria [80] but this might not be the whole story. Chronic intake of dopamine agonists like cocaine, crack and amphetamines [74] 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 [81]. Other agents like some environmental pollutants may cause dopamine hypofunctioning [13,14,68]. The concentrations and types of these pollutants varies a lot between countries and regions within countries [35]. Polychlorinated biphenyls (PCBs) is a group of halogenated aro-

matic hydrocarbons consisting of 209 possible congeners with a variety of industrial uses like in paint for ships, in lubricants and in dielectric and heat-exchange fluids in transformers and heat exchangers. PCBs are lipophilic and, consequently, bioaccumulating environmental pollutants [25,26]. 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 [67] for references).

A series of studies of effects of PCB exposure on behaviour and brain chemistry [25,26] 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 when they grow up. Their behaviour was closely similar to that shown by SHR [4,6,59] and ADHD children [63]. Although the various PCBs work via different routes, the most likely mode of action of di-ortho-substituted PCB congeners like PCB 153 is via monoaminergic pathways. Dopamine and serotonin levels are reduced [13,14] probably by a combination of an inhibition of dopamine synthesis and deficient vesicular storage or release [13].

8. Medication

ADHD is usually treated with psychostimulants (methylphenidate, d-amphetamine or pemoline). Methylphenidate is the drug of choice [74]. Since dopamine release is reduced in the SHR [16,53,54] and these drugs enhance catecholamine neurotransmission, the exact mechanisms of action were studied in more detail [54]. It was shown that methylphenidate releases dopamine from vesicle stores only and is 7–17 times less potent than d-amphetamine, thus making it possible to adjust the dose and thereby normalise reduced dopamine functions more precisely than is possible with d-amphetamine.

The reduced release of dopamine may have caused the apparent supersensitivity of dopamine D-1/D-5 receptor subtypes in SHR [8]. A 15-day sub-chronic treatment with methylphenidate normalised the dopamine D-1/D-5 receptors by decreasing the number of binding sites and increasing the affinity to control levels [8] and normalised CaMKII levels [43] in the male SHR without affecting the WKY. The impaired cross-talk between various brain structures of the animal model was also improved by methylphenidate treatment [43].

The reduced dopamine receptor functions in unmedicated SHR [8,44,45] explain why the animal model shows a reduced behavioural reactivity to both methylphenidate as well as to d-amphetamine [60]. The behavioural modes of action of psychomotor stimulants seem to be associated with decreased relative effective-

ness of immediate reinforcement and increased relative effectiveness of delayed reinforcers [60]. This result parallels others [6] finding normalisation of impulsiveness in L-deprenyl-treated SHR. These effects support the conclusion of Virginia Douglas [18] (p. 322) suggesting that one important effect of these drugs on ADHD behaviour is to decrease 'the impact of immediate reward on their behaviour'.

9. Future challenges and predictions

The first central conclusion developed directly out of the present articles is that at a behavioural level, the clinical phenomenon of ADHD is underpinned by a hypersensitivity to time interval between stimuli that leads to problems in the integration of cognition and behaviour over time. The abnormal IRT pattern, impulsiveness, is predicted from the altered delay gradient and should be tested systematically in many situations in order to determine the generality and prevalence of this behaviour. Its contribution to hyperactivity should be measured and evaluated.

The second central conclusion is that, at the neurobiological level, ADHD symptoms may be caused by hypofunctioning dopamine systems associated with reduced efficacy either of the vesicular monoamine transporter, the proton pump of monoaminergic vesicles, the membrane dopamine transporter and/or postsynaptic dopamine receptors. This in turn impairs the conduction of other non-dopaminergic inputs in the frontal cortex, the nucleus accumbens and the neostriatum. Thus, the shorter delay-of-reinforcement gradient gives rise to impulsiveness, hyperactivity and deficient sustained attention associated with a hypofunctioning meso-cortico-limbic system. In addition, a hypofunctioning nigro-striatal system may cause several extrapyramidal symptoms associated with ADHD: 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.

It might be that in some cases ADHD is genetically determined while in other cases ADHD is induced by environmental factors like drugs of abuse or pollutants. If dopamine hypofunction were the mode of action in these cases, one would predict similar symptoms. These two classes of putative causes of ADHD may to some extent explain why the prevalence of ADHD differs between the various areas of the world: the prevalence of genetically-caused ADHD might well be quite similar everywhere but not all areas are polluted with organic environmental pollutants, e.g. with PCBs, and the various areas that are polluted may not be exposed to the same levels and patterns of, e.g. PCB congeners. Hypothetically, this will cause considerable regional

differences in ADHD-like symptoms induced by contaminants like PCB 153. One would predict that methylphenidate will work as medication also in the case when dopamine hypofunctioning is environmentally induced. Obviously, there is now a strong need for studies examining relations between regional levels of central-nervous DA function-reducing pollutants like di-ortho-substituted PCB congeners and prevalence of ADHD in that region.

The life-long nature of ADHD is a logical consequence of hypofunctioning dopamine systems produced genetically or by irreversible consequences of drugs and pollutants. It is predicted that symptoms should be alleviated only as long as medication is given. Soon after the medication is terminated the reduced dopamine release will again produce hypofunctioning dopamine synapses.

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