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Review

The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder

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Abstract

There is evidence that abnormalities within the dopamine system in the brain play a major role in the pathophysiology of attention deficit hyperactivity disorder (ADHD). For instance, dopaminergic psychostimulants, the drugs of first choice in ADHD, interact directly with the dopamine transporter (DAT). Molecular genetic studies suggest involvement of a polymorphism of the DAT gene in ADHD. More recent imaging studies show abnormalities in various brain structures, but particularly in striatal regions. In the current paper we review recent studies in this area. First in vivo measurements of DAT with single photon emission computed tomography (SPECT) in ADHD patients revealed an elevation of striatal DAT density. No differences in DAT density between the left and right side and between putamen and caudate nucleus have been found in [^{99m}Tc]TRODAT-1 SPECT of ADHD patients. Patients with ADHD and with a history of nicotine abuse both displayed lower values of DAT density in [^{99m}Tc]TRODAT-1 SPECT than non-smokers with ADHD. DAT seem to be elevated in non-smoking ADHD patients suffering from the purely inattentive subtype of ADHD as well as in those with the combined or purely hyperactive/impulsive subtype.

Keywords: Dopamine transporter; Attention deficit hyperactivity disorder; Single photon emission computed tomography; Nicotine; TRODAT-1

Contents

1. Introduction

In this review, we discuss the relationships between the dopamine system, especially the dopamine transporter

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(DAT) in the striatum, and attention deficit hyperactivity disorder (ADHD). The results of neuroimaging with magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) will be described. Results using these technologies are consistent with the hypothesis of a cerebellar–prefrontal–striatal dysfunction in ADHD. SPECT imaging studies of DAT activity demonstrating an elevation of DAT associated with ADHD will be reported. A possible methylphenidate (MPH)-like influence of nicotine on DAT will be described. Finally, the relationship between ADHD subtypes and DAT activity will be discussed in the context of our own results. Future investigations will be proposed, in the light of the new dual pathway model of ADHD [1].

2. Function of dopamine and the dopamine transporter

Dopaminergic projections from the A9 and A10 region of the midbrain ventral tegmental area (VTA) to striatal and prefrontal cortical areas play a major role in motor control and attention [2]. Abnormal dopamine function within these branches is implicated in many psychiatric disorders including depression, schizophrenia, and Tourette syndrome [3,4].

Within these branches nerve impulses lead to a release of dopamine in the synaptic cleft, which are received by a set of different dopamine receptors (DRD1–5) differentially distributed within the brain, inducing a cascade of postsynaptic events. The signal transduction via the Adenylate Cyclase system eventually leads to an alteration in gene expression. The amount of released dopamine depends on the availability of intra-vesicle dopamine and the sensitivity of the presynaptic autoreceptors that regulate dopamine release. The major deactivation mechanism is the reuptake of dopamine through the DAT in the presynaptic nerve membrane (Fig. 1).

Dopamine transport was first described 30 years ago [5]. DAT was itself identified and its molecular structure described a considerable number of years later [6]. The human DAT gene is localized on chromosome 5p15.3 [6–8]. A genetic polymorphism of a 40 bp variable tandem nucleotide repeat (VNTR) polymorphic sequence in the 3′ untranslated region of exon 15 of the gene is described [8–10]. This VNTR of exon 15 is repeated 3–11 times, most typically 10 times. The 10-repeat shows an ethnic heterogeneity with a frequency of 0.7 among Caucasians and Hispanics in USA, 0.54 in African Americans and 0.9 in Asians [11–14]. DATs are expressed in a small number of neurons in the brain, mainly in striatum and nucleus accumbens, but also in the globus pallidus, cingulate cortex, olfactory tubercle, amygdala and the midbrain [15].

The DAT, like the transporters for norepinephrine and serotonin, is a Na^+/Cl^- dependent transmembrane transport protein [16], which regulates the concentration of dopamine in the synaptic cleft. Knock-out mice lacking DAT show higher dopamine in the synaptic cleft. In addition, the amount of released dopamine modulates DAT activity [17–19]. A decline of striatal DAT is observed at a rate of approximately 6–7% per decade in the human striatum [20–25]. For more than 20 years specific radioactive labelling techniques have been used to image DAT activity.

3. DAT and ADHD

The strongest evidence for an involvement of the DAT in the pathophysiology of a psychological disorder comes from investigations of ADHD, the most common childhood-onset psychiatric disorder. The condition is heritable and the patients behaviour symptoms can be

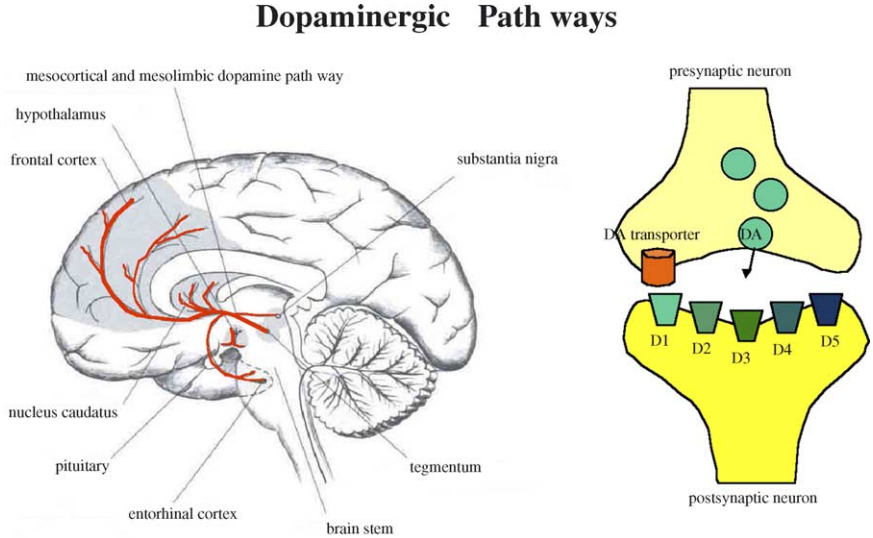

Fig. 1. Dopamine (DA) neurons in the human brain and location of DA transporter (D1–D5 = DA receptors).

controlled by psychostimulants such as MPH and dexamphetamine, which are known to act directly on DAT function [26]. Cocaine and related drugs prevent dopamine transport by blocking the DAT. Dopamine function is modulated by amphetamines in two ways: first, by release of dopamine from vesicular stores and second, by an increase of dopamine within the synaptic cleft via blockade of the DAT [3,27,28]. It is widely accepted that in this way psychostimulants increase the extracellular concentrations of dopamine. In a PET study, it was shown that cocaine, in a dose equivalent to that used by human abusers, resulted in a 60–80% blockade of DAT sites, with the degree of blocking correlating with subjective effects of a 'high' [29]. After intake of 5 mg MPH a 12% reduction of DAT has been found in normal adults using PET with ^{11}C-cocaine [30]. Interestingly Moll and colleagues [31] found no persistent reduction of rat DAT, when MPH was given after puberty; however, a reduction of DAT was found when MPH was given in high doses to prepubertal rats.

Other studies describe a significant association of the 10 copy VNTR polymorphism with ADHD [32–34]. It is of interest that in the study of Waldman and colleagues [34] this relation has been documented for both hyperactive–impulsive and combined subtypes of ADHD. Generally it should be mentioned that there are numerous difficulties in establishing association and/or linkage in disorders like ADHD. The diagnostic categories and criteria are complex and heterogeneous, especially in adult ADHD; the biological basis is assumed to be polygenetic, and the contribution of single genes may vary across various populations. It is estimated that for individuals, who carry the putative susceptibility alleles of the DAT1 gene, the risk of manifesting ADHD may be increased by 20–40% [35]. On the other hand, the DAT1 gene has not been found as a major gene for ADHD susceptibility in a first genome-wide scan in 126 sibling pairs affected with ADHD [36].

4. Neuroimaging in ADHD

4.1. Magnetic resonance imaging

Previous magnetic resonance imaging (MRI) studies have reported smaller volumes of the basal ganglia [37–42], corpus callosum [43–47], prefrontal cortex [38,41,48,49] and cerebellum [40,50,51] in patients with ADHD, which would be consistent with the hypothesis of a cerebellar–prefrontal–striatal dysfunction in ADHD. In one MRI study, Castellanos and colleagues [52] described smaller brain volumes in a number of cortical and subcortical structures in unmedicated patients. With the exception of the caudate nucleus, longitudinal growth curves of ADHD patients and controls were roughly parallel. Furthermore, the caudate nucleus was smaller compared to the controls only in medicated, but not in unmedicated ADHD patients.

Reduced striatal activation in children and adolescents with ADHD has been found in fMRI studies during performance of response inhibition tasks: Vaidya and colleagues [53] found differences between the frontal–striatal function of 10 boys with ADHD and six controls while subjects were performing two go/no-go tasks. Without medication, ADHD children had greater frontal activation while performing one task and reduced striatal activation while performing the other task. MPH improved response inhibition in both groups on one task and only in ADHD children on the other task. MPH appeared to modulate brain activation during response inhibition on only one task with increased frontal activation to an equal degree in both groups. However, there were different influences on striatal activation: in ADHD children striatal activation was increased under MPH, in healthy children it was reduced. It can be concluded that MPH may affect striatal activation differently in ADHD and healthy controls. Comparing seven adolescent boys with ADHD to nine control subjects Rubia and colleagues [49] found a subnormal activation of the prefrontal systems, responsible for higher-order motor control, in ADHD, using functional MRI during performance of a stop task and a motor timing task. Using a new fMRI procedure (T2 relaxometry), developed by Teicher and colleagues [54], 11 boys with ADHD were shown to have higher T2 relaxation time measures in the putamen bilaterally than six normal controls. Furthermore activation level strongly correlated with a child's capacity to sit still and his accuracy when performing a computerized attention task. Treatment with MPH significantly changed the T2 relaxation times in the putamen [54].

4.2. Positron emission tomography

In a positron emission tomography (PET) study in children with ADHD, increased [F-18]F-DOPA uptake in the right midbrain was found [55]. On the other hand, in medication naive adults with ADHD F-DOPA uptake has been observed in left and medial prefrontal cortex with no differences in striatum or midbrain regions [56]. It is not clear whether these contradictory findings are due to weakness of the signal from [F-18] F-DOPA uptake outside the striatum or differences between adolescents and adults. To our knowledge at this time no PET study has been published with ADHD children using a specific marker for DAT, such as C-11-cocaine. Only effects of MPH on the DAT in normals have been shown with C-11-cocaine PET by Volkow and colleagues [30].

4.3. Single photon emission computed tomography

Preliminary studies with Xenon-133 inhalation single photon emission computed tomography (SPECT) demonstrated hypo-perfusion in the frontal lobes and the caudate nuclei (of some ADHD patients), especially the right caudate; 30 min after oral administration of MPH

the perfusion increased [57]. This finding was replicated using the same technique in studies with greater power—again a decrease in activity in the right striatum was observed, along with increased activity in the occipital lobe [58,59]. Studies using hexamethyl-propylene-amineoxime (HMPAO) brain SPECT have demonstrated decreased prefrontal activity in ADHD children and adolescents in response to mental stress [60]. Using iodine-123 *N*-isopropyl-4-iodoamphetamine (IMP)-SPECT an asymmetry of striatal perfusion with decreases of the right side compared to the left has been found, in another study decreases in left-sided frontal, parietal and total hemispheric regions [61]. Rohde and colleagues [62] described significantly higher regional cerebral blood flow in ^{99m}Tc-ethylcysteinate dimer (ECD)-SPECT in the medial frontal and left basal ganglia areas in ADHD boys with homozygosity for the 10-repeat allele of DAT1 gene, compared to boys without this homozygosity during MPH therapy.

4.3.1. Measuring DAT in vivo with SPECT

The studies reported above suggest involvement of striatal structures in ADHD. In view of the evidence from molecular genetic studies of the involvement of DAT in ADHD, it does seem appropriate to investigate DAT in patients with ADHD. Furthermore it is known that the therapeutic effects of MPH, the drug of first choice in ADHD, results from its ability to increase the synaptic concentration of dopamine by blocking the DAT [29].

A variety of radiolabelled ligands are available for imaging DAT. For SPECT imaging these radiopharmaceuticals are mostly labelled with ^{123}I. In a first study in patients with ADHD the radiopharmaceutical [^{123}I] altropane has been used [63]. This ligand binds to the human striatal DAT with high affinity, enters the brain rapidly and accumulates in the striatum within 30 min [64,65]. In six non-medicated adult patients with ADHD DAT levels were approximately 70% higher than in controls [63]. At the same time another SPECT investigation was conducted with one of the first technetium-labelled ligands for imaging the DAT, TRODAT-1 [66–69]. Compared to iodine-bound ligands, this radiopharmaceutical has numerous advantages: ^{99m}Tc is the radionuclid of choice for nuclear medicine, because it is readily available, relatively inexpensive and gives lower radiation exposure as compared with ^{123}I, so that [^{99m}Tc]TRODAT-1 may be easily used in most nuclear medicine facilities. [^{99m}Tc]TRODAT-1 yields high-contrast SPECT images at 2–3 h after injection with reliable assessment of the human DAT status [66,70–75]. In our investigations, subjects were injected with 740 MBq [Tc-99m]TRODAT-1 3 h before scanning. In each patient, data were evaluated in the two consecutive transverse slices that showed the highest tracer accumulation in the basal ganglia [76,77]. Templates were used for defining the striatal regions of interest (ROI). The size and shape of the templates was established and optimized using the data of a control group. The templates were adjusted to fit individuals and corrected for anatomical differences in angle, size and distance between the structures of interest. The observer was blind with respect to the clinical data. For semi-quantitative evaluation of the DAT, specific binding was calculated in the striatum (STR) with respect to background levels in the cerebellum (BKG) ([STR–BKG]/BKG).

In the first investigation, 10 medication naive adults with ADHD displayed a 16% increase in striatal specific binding of [^{99m}Tc]TRODAT-1 compared to controls matched for age and sex [77]. This was a much smaller increase than that found in a multi-center study of Altropane in which a DAT increase of about 30% was reported (ADHD Report 9, 2001, p. 10, see also Ref. [78]). In contrast, in a study with [^{123}I]beta-CIT no elevation of DAT was found [79]. In a separate study, a group of nine ADHD adults using ^{123}I-fluoropropyl (FP)-CIT showed an elevation of DAT binding of over 20% with correlations between the DAT density and memory task performance (Sitte et al., personal communication, unpublished results). In a study with three children, aged between 6 and 9 years, high levels of DAT have been found with FP-CIT, however, normal values for children are yet to be established [80]. Recently, DAT density has been compared in a first study in children with and without ADHD, using ^{123}I-IPT-SPECT [81] in nine drug-naive children, aged 6–12 years with the combined type of ADHD, and in six normal children. Mean DAT binding ratio in the basal ganglia was increased significantly with 40% on the left and 51% on the right side, compared to the controls of the same age without ADHD or other psychiatric disorders. No significant correlation was found between DAT binding ratio and severity scores of ADHD, either for inattention or for hyperactivity/impulsivity [81]. In conclusion, this study confirms that elevation of DAT already occurs in childhood ADHD. It remains unclear why, in the investigation of adults with ADHD using beta-CIT [79], no elevation of DAT binding was found. Perhaps this may be related to clinical differences between childhood and adult ADHD such as the severity and duration of the disorder. Alternatively these differences may be caused by the very slow kinetics of beta-CIT, or to less specificity of this substance, which also labels the serotonin transporter. Beta-CIT may bind to other substructures of the DAT than FP-CIT, altropane, TRODAT and IPT.

5. DAT and nicotine

As part of an investigation into the potential reasons for the lower elevation in the TRODAT-1 study compared to the altropane study, we identified a subgroup of patients with relatively small increases in DAT despite very high clinical scores; further questioning of these patients revealed that all were cigarette smokers. Comparing 11 smoking non-medicated patients with ADHD to sex and age matched non-smoking drug-naive adults with ADHD showed significantly higher DAT density in

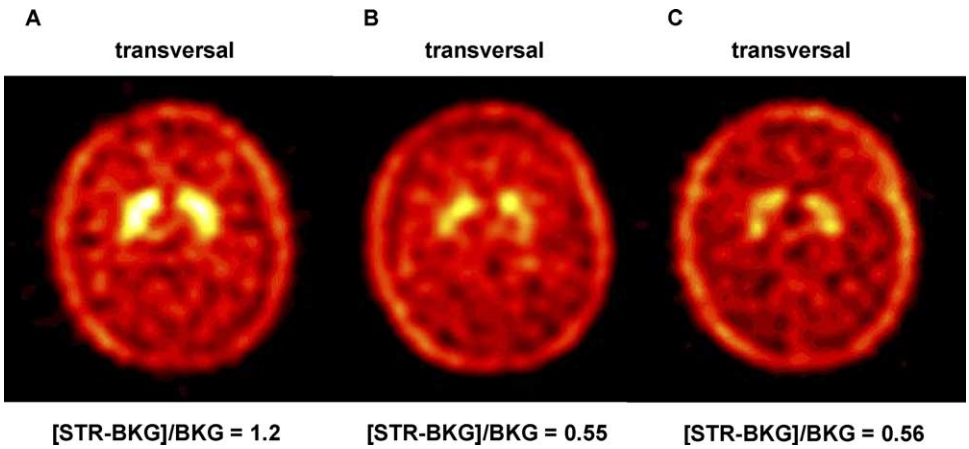

Fig. 2. Dopamine transporter binding in the striatum of a 53 years old non-smoker before (A), after 5 h of intake of 20 mg methylphenidate (Ritalin SR®) (B), and 3 months later after 5 h of wearing a 17.5 mg/24 h nicotine skin patch (C), shown by specific accumulation of [Tc-99m]TRODAT-1 in SPECT scans.

the non-smoking patients, despite higher ADHD scores for the smokers [82]. It is not clear, in which way nicotine alters the measurement of DAT, but this finding suggests that nicotine may act directly on DAT in a similar way to stimulants. For MPH a marked lowering of DAT has been found in rats with TRODAT-1 [71]. In normal adults, Volkow and colleagues [30] described a reduction of DAT density of 12% after receiving 5 mg of MPH, with ^{11}C-cocaine PET. In patients with ADHD in the TRODAT-1 study a considerable reduction of DAT of approximately 30% after intake of 5 mg MPH three times a day has been found [77]. In a self-administration trial with one of the authors as a subject (KHK) DAT density was reduced over 50% 5 h after intake of 20 mg MPH in a slow releasing formulation (unpublished data). Wearing a nicotine skin patch (equivalent to 10–20 cigarettes per day) for 5 h an effect similar to MPH was seen 3 months later (Fig. 2). This supported the view that the lowering of DAT after use of nicotine was not a sign of a neurochemical adaptation associated with chronic exposure to nicotine [82]. Further evidence for the impact of nicotine on DAT comes from the re-evaluation of a female ADHD smoker (unpublished data). At the time of the first investigation with TRODAT-1, she was smoking 15 cigarettes per day. She demonstrated no elevation of DAT; 4 weeks after the intake, 3 × 5 mg MPH led to a marked reduction in DAT similar to that found with other patients in this group. One year later, the patient stopped the nicotine and MPH intake; 2 years after the first investigation she returned with increased complaints of ADHD. At this time she underwent another TRODAT-1 SPECT scan, presenting with a 19% elevation compared to the first scan with nicotine and a 61% elevation compared to the second scan with nicotine and MPH (Fig. 3). This finding is in accordance with the opinion that the effect of nicotine on DAT does not result in a persistent loss of DAT [83]. In this context, it is of interest that an investigation with [^{123}I]beta-CIT SPECT showed no altered striatal uptake in smokers versus controls [84]. This parallels the above-mentioned findings of no DAT elevation in ADHD with this method. In the study of Staley and colleagues [84] a higher DAT availability has been observed in females compared to

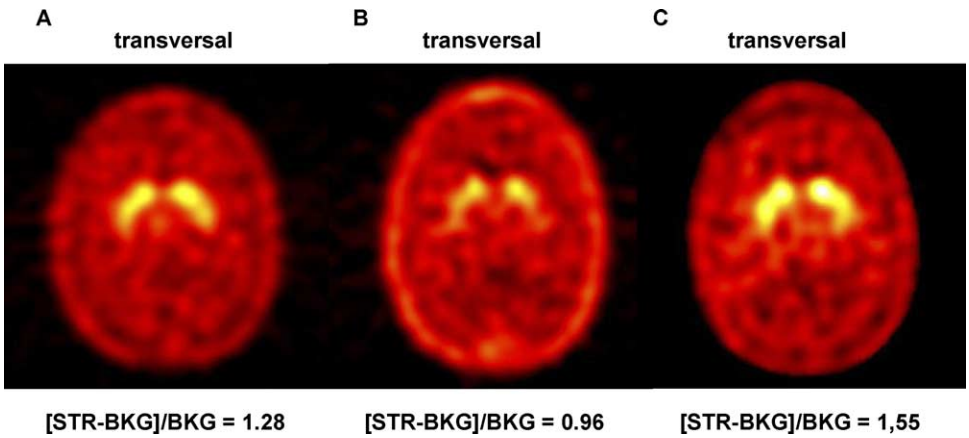

Fig. 3. Dopamine transporter binding in the striatum of a 29 years old female smoker with ADHD before (A), after 4 weeks of intake of 3 × 5 mg methylphenidate (Ritalin®) per day (B), and 2 years later after 1 year of cessation of nicotine abuse and intake of methylphenidate, shown by specific accumulation of [Tc-99m]TRODAT-1 in SPECT scans.

males; this aspect should be considered in further imaging studies of DAT and ADHD.

6. DAT density and DAT gene

Concerning the influence of the 3′ VNTR polymorphism on the DAT density in humans, three SPECT studies have been performed, all of which use [^{123}I]beta-CIT. In a group of 14 abstinent alcoholics and 11 controls 9-repeat individuals (e.g. 9–10 heterozygotes) had a mean 22% decrease of DAT binding compared to 10-repeat subjects (10–10 homozygotes) [85]. In 44 subjects (14 recently detoxified cocaine abusers and 30 healthy controls) 9-repeat carriers (9–9 homozygotes and 9–10 heterozygotes) showed a mean 13.4% increase in striatal [^{123}I]beta-CIT binding compared to 10–10 homozygotes [86]. In a sample with 29 patients with schizophrenia and 31 healthy controls no significant association was found between VNTR polymorphism and DAT density [87]. Thus, the impact of the abnormalities of VNTR polymorphism of the DAT1 gene seen in ADHD on the striatal DAT is far from clear. It will be important to compare the DAT density measured with other specific methods than [^{123}I]beta-CIT in ADHD patients with 9- and 10-repeat alleles. In this context sequence analysis of the tandem repeat region in the 3′-UTR of the DAT gene in patients with ADHD would be of interest. In rhesus monkeys, one particular single nucleotide polymorphism in the fixed number tandem repeat region has been found to occur with greater frequency in the most active monkeys [88]. Concerning relationships between polymorphisms of the DAT1 gene and response to medication, in two studies a smaller response to MPH has been found in ADHD patients with homozygosity for the 10-repeat allele [89,90]. In cocaine abusers, without transcription factor NURR1, a marked reduction of DAT gene expression has been recently found. This suggests that NURR1 may play a critical role in vivo in controlling human DAT gene expression in these people [91].

7. DAT in subtypes of ADHD

It will be important to investigate DAT differences in the subtypes of ADHD as defined in DSM IV. First, our own results in non-smoking adults with persistent symptoms of ADHD revealed that the type of ADHD patient with attention deficit (in childhood) alone had a similar elevation of DAT as patients with symptoms of hyperactivity and impulsivity [92] (Fig. 4). There was a slight tendency towards higher levels when symptoms of hyperactivity and impulsivity were present (mean of DAT density in non-smoking 20–40 years old patients with hyperactivity 1.52, with pure attention deficit 1.49, in patients with age over 40 years 1.34 (hyperactivity) and 1.30 (attention deficit), see Fig. 4). From these preliminary results it can be postulated that DAT increases in ADHD are not restricted to the hyperactive type and that it does play an important role for the inattentive type.

It was striking how many of the 20–40 years old patients in our group, who had shown symptoms of hyperactivity and impulsivity in childhood, were smokers: nine smoked and only three were non-smokers (Fig. 4). The opposite was shown in the patients with only inattentive symptoms

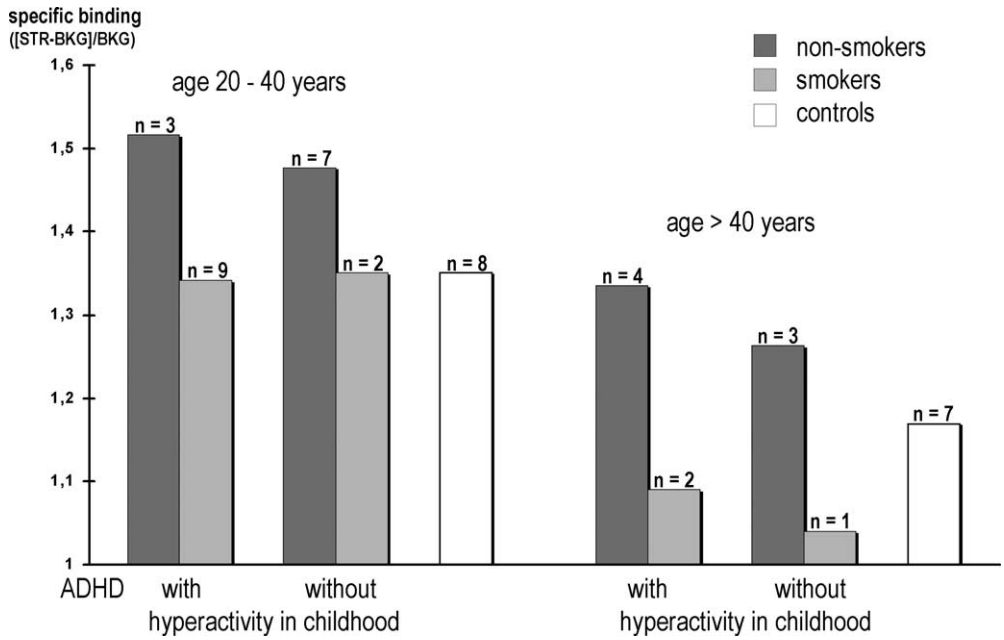

Fig. 4. Dopamine transporter binding in the striatum of smoking and non-smoking adults with ADHD with only inattentive symptoms since childhood and with hyperactivity/impulsivity in the childhood, mostly in combination with attention deficit and in non-smoking controls, shown by specific accumulation of [Tc-99m]TRODAT-1 in SPECT scans, in the age groups of 20–40 years and over 40 years.

throughout their whole life: only two smoked, seven were non-smokers. These findings are in contrast to the results of Tercyak and colleagues [93]. They found that adolescents with inattention smoked more heavily than those with hyperactivity and impulsivity [93]. Because the symptoms of ADHD in this study were assessed only by self-report rating of behaviour over the previous 6 months, one explanation for the different findings could be that symptoms of hyperactivity and impulsivity have been successfully treated by self-medication with nicotine.

8. Conclusions

From the existing data it can be postulated that DAT density is increased in ADHD, and that this increase is not specific to particular symptoms of hyperactivity and impulsivity. It is not clear, however, how the form of DAT1 alleles, found in ADHD patients, influences DAT density. It seems that nicotine, frequently abused by patients with ADHD, may have an influence on DAT similar to that of stimulants. Further investigations will show, whether non-smoking and non-treated patients with relatively low levels of DAT density generally may not respond to stimulants as good as the other patients presenting with elevated DAT.

Recently, a dual pathway model of ADHD has been presented by Sonuga-Barke [1]. He showed that delay aversion and poor inhibitory control are independent co-existing characteristics of the combined type of ADHD. In the model ADHD has two neuropsychological subtypes. In one it is a disorder of thought and action resulting from poor inhibitory control, which is associated with the meso-cortical branch of the dopamine system projecting in the prefrontal cortex. In the other it is a motivational problem with delay aversion and high impulsiveness and linked to the ventral–striatal network, including the nucleus accumbens, associated with the meso-limbic branch of the dopamine system. At this time, the role of DAT concerning these differential ADHD pathways is not clear. In further investigations with neuroimaging of the DAT, possible differences in DAT density could be sought in brain regions differentially involved in patients with these two different physiopathological subtypes of ADHD.

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