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The dopaminergic hypothesis of attention-deficit/hyperactivity disorder needs re-examining

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Although psychostimulants alleviate the core symptoms of attention-deficit/hyperactivity disorder (ADHD), recent studies confirm that their impact on the long-term outcomes of ADHD children is null. Psychostimulants enhance extracellular dopamine. Numerous review articles assert that they correct an underlying dopaminergic deficit of genetic origin. This dopamine-deficit theory of ADHD is often based upon an overly simplistic dopaminergic theory of reward. Here, I question the relevance of this theory regarding ADHD. I underline the weaknesses of the neurochemical, genetic, neuropharmacological and imaging data put forward to support the dopamine-deficit hypothesis of ADHD. Therefore, this hypothesis should not be put forward to bias ADHD management towards psychostimulants.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is considered to be the most common neuropsychiatric disorder of childhood with a prevalence rate of ~7–9% [1,2]. Many recent review articles about ADHD assert that it is caused by a deficit of the dopaminergic system, the origin of which is mainly genetic. For example, Swanson *et al.* [3] said 'Multiple theories of ADHD have been proposed but one that has stood the test of time is the dopamine deficit theory'. Moreover, the dopaminergic hypothesis of ADHD is often based upon the dopaminergic theory of reward. Here, I do not question the fact that psychostimulants used to treat ADHD increase the extracellular dopamine level and that they exert short-term therapeutic effects. However, in my opinion, the dopamine-deficit theory of ADHD is too weak to be considered to be established fact. Here, I first show that neurochemical, genetic, pharmacological and imaging studies do not strongly support the view that a dopaminergic deficit underlies ADHD. Second, I question the relevance of recent theories of dopamine function regarding the understanding of ADHD. Third, children with ADHD are clearly at risk of later development of antisocial behavior, substance abuse and significant academic underachievement. I review recent articles confirming that psychostimulants do not significantly affect these adverse outcomes. Finally, I point out the negative consequences of the dopamine dogma. Indeed, when it is asserted that 'clinical methylphenidate doses produce their therapeutic effects by increasing dopamine and correcting an underlying dopamine deficit' [3], the dopaminergic hypothesis of ADHD is considered as an established fact and this gives an excessive scientific credence to the questionable opinion that, regarding long-term outcomes, psychostimulant medication represents the most effective option in the treatment of ADHD.

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Is ADHD caused by a deficit of the dopaminergic systems?

Neurochemical data

There is no doubt that psychostimulants inhibit the dopamine transporter (DAT) and, thus, enhance the extracellular dopamine [4]. Therefore, abnormal DAT functioning has long been suspected to be involved in ADHD. However, results have been inconsistent [5]. Recent studies, rather, conclude that DAT is not altered in ADHD patients [3,6].

The fact that psychostimulants enhance the extracellular dopamine level has repeatedly been put forward to indicate that this level might be abnormally low in ADHD patients [3,7]. This crucial but difficult question has been addressed by two imaging studies that monitored the binding of [^{11}C]raclopride to dopaminergic receptors of the D_2 type. Because the extracellular dopamine level influences the availability of D_2 receptors, an increase in this level should result in a decrease in [^{11}C]raclopride binding. For example, in healthy adults, methylphenidate increases the extracellular dopamine level and decreases the [^{11}C]raclopride binding [8]. One study in adolescents with ADHD reported that the magnitude of the methylphenidate-induced decrease in the [^{11}C]raclopride binding in the right striatum was positively correlated with the severity of the symptoms [9]. By contrast, another study compared healthy to ADHD adults who had never received medication and reported that the effect of methylphenidate on the [^{11}C]raclopride binding in left and right caudate was smaller in subjects with ADHD [10]. Starting from the assumption that the effect of methylphenidate on extracellular dopamine reflects the spontaneous dopamine release, the authors conclude 'the blunted response to methylphenidate suggests that subjects with ADHD have lower dopamine release than controls' [10]. However, the same study also reports that, in basal condition (i.e. before methylphenidate), the [^{11}C]raclopride binding is significantly lower in the caudate of ADHD patients. This lower availability of the D_2 receptor might indicate instead that the basal extracellular dopamine level is higher in subjects

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with ADHD. Indeed, the authors say later in the text 'we cannot rule out the possibility that the blunted dopamine responses to methylphenidate in subjects with ADHD could reflect higher baseline dopamine tone' [10].

Several studies, which directly measured the extracellular dopamine level by microdialysis, compared two groups of rats differing by their strain or by their spontaneous behavior and showed that a higher basal extracellular dopamine level is always associated with a larger effect of DAT inhibitors [11–13]. In particular, 6-week-old spontaneously hypertensive rats (SHRs), which are considered as an animal model of ADHD, exhibit a higher basal extracellular dopamine level and a larger methylphenidate-induced increase in extracellular dopamine compared with control rats [13]. Compared with microdialysis studies in rats, the interpretation of the data obtained by [^{11}C]raclopride binding in terms of changes in extracellular dopamine seems far from being clear regarding ADHD. Indeed, the magnitude of the methylphenidate-induced DAT blockade does not significantly correlate, between healthy adults, with the resulting decrease in [^{11}C]raclopride binding [8]. Moreover, the two studies on [^{11}C]raclopride binding in subjects with ADHD are not consistent and opposite interpretations can be made [9,10]. Therefore, in my opinion, these studies do not prove that a dopamine deficit underlies ADHD.

Genes involved in the dopaminergic system

Review articles often put forward genetic studies in support of the dopaminergic hypothesis of ADHD. For example, Casey *et al.* [14] say 'Two meta-analyses confirmed an association of ADHD with alleles of the D4 dopaminergic receptor'. Indeed, 'the most robust finding in ADHD is the association of a variable number tandem repeat polymorphism in exon 3 of the D4 receptor gene' [15]. However, the corresponding odds ratio is low: the 7-repeat allele of this gene is more frequent in ADHD patients (23%) than in healthy subjects (17%) [16]. Moreover, patients 'with ADHD carrying the D4 7-repeat allele had a better clinical outcome' than those carrying the more common 4-repeat allele [16]. In addition, most recent articles and meta-analyses also consider that there is a statistically significant association between ADHD and the gene coding for the DAT [3,14,15,17] (but also see Ref. [18]). However, these genetic effects are small and not sufficient to establish a strong link between ADHD and the dopaminergic systems. Nevertheless, these genetic associations might play a part in the susceptibility to environmental risk factors [3] such as prenatal smoking exposure [19].

Pharmacological data

According to numerous articles, 'the effectiveness of the dopamine-based stimulant drugs in ADHD treatment suggests an underlying dopamine hypofunctional state' [7]. However, psychostimulant medication induces the same behavioral effects, including improved attention, in ADHD and normal children [20,21]. Indeed, healthy teenagers and young adults often use misappropriated ADHD medication to increase their productivity [22]. Therefore, the fact that psychostimulant drugs increase the extracellular dopamine level and improve attention and cognitive performance of ADHD patients cannot be used to argue that ADHD is caused by a dopamine deficit.

Psychostimulants used to treat ADHD equally inhibit the DAT and the noradrenaline transporter. Drugs that selectively inhibit the noradrenaline transporter (e.g. desipramine and atomoxetine) and that do not affect the DAT are as efficient as psychostimulants to alleviate ADHD symptoms [23]. Moreover, most studies that put forward the role of cortical dopamine in ADHD do not consider the fact that the noradrenergic innervation of the cortex is denser than the dopaminergic innervation. Indeed, in all human cortical areas, the tissue content of dopamine is always lower than that of noradrenaline [24]. The noradrenaline transporter represents the main mechanism that clears dopamine in the mouse prefrontal cortex [25]. Therefore, it is likely that pharmacological treatments of ADHD, including psychostimulants, increase the extracellular dopamine level in cortical areas via the inhibition of the noradrenaline transporter [26,27]. Furthermore, agonists of the α_2 adrenoceptor, such as clonidine, are effective at treating ADHD whereas dopaminergic agonists are not [23]. In particular, L-DOPA, which enhances dopamine release and effectively alleviates parkinsonian symptoms by correcting an overt dopamine deficit, is not effective in ADHD [28]. 'Thus, treatment studies are not consistent with the hypothesis that ADHD is caused by a simple dopamine deficiency' [23].

Although it is outside the scope of this article, it must be noted here that, according to the available genetic data, the link between noradrenaline dysfunction and ADHD is even weaker than that regarding dopamine [15,17,29].

Animal models of ADHD

A recent review article described and compared 14 animal models of ADHD [30]. They concluded that 'the neonatal 6-hydroxydopamine lesioned rat and DAT knockout mice have the highest degree of validity for ADHD'. In the former model, most dopaminergic neurons are permanently destroyed and the basal extracellular dopamine level is decreased to ~40% of the normal level in the striatum [31]. In the latter model, the DAT deletion results in a fivefold increase in the extracellular dopamine level [32]. In both models, the animals are hyperactive and are calmed by psychostimulants. Therefore, huge differences in the extracellular dopamine level are associated with the same hyperactive phenotype. Moreover, in *DAT*$^{-/-}$ mice the calming effect of psychostimulants has been attributed to their inhibitory effect on the serotonin transporter [33]. Likewise, the hyperactivity at 25 days postnatal of 6-hydroxydopamine-lesioned rats is calmed by methylphenidate via the inhibition of either the noradrenaline or the serotonin transporter but not via DAT inhibition. Indeed, desipramine and citalopram are as effective as methylphenidate, whereas the specific DAT inhibitor GBR 12909 does not inhibit this hyperactivity [34]. Taking into account the fact that specific inhibitors of the serotonin transporter do not alleviate ADHD symptoms [23], both animal models do not closely fit the neuropharmacology of ADHD and do not support the dopamine-deficit theory.

Another review article concluded that the best animal model of ADHD is the SHR [35]. According to these

authors, these rats 'compare well with clinical cases of ADHD' because they are more hyperactive, impulsive and inattentive than their controls, the wistar Kyoto (WKY) rats [35]. Moreover, these ADHD-like behaviors are corrected either by amphetamine [36] or by guanfacine, an α_{2A} adrenoceptor agonist [37]. However, the validity of this animal model has been questioned by others for two reasons [30]. First, the WKY rats might not represent a valid control to SHR because WKY rats are obviously less active than wistar rats. Actually, SHR are either more or less active than WKY and than Sprague-Dawley rats depending on the tests [38] and are less impulsive than wistar rats [39]. Second, methylphenidate does not decrease the locomotor activity and impulsivity of SHR, whereas it depresses the excessive impulsivity of wistar rats [39]. Likewise, in tasks requiring time estimation and motivation, methylphenidate and amphetamine disrupted performances to a similar extent in SHR, WKY and Sprague-Dawley rats [40].

The promoters of the SHR model said that the dopaminergic system is hypofunctional in SHR compared with WKY rats [35]. Indeed, they cited a report showing that the dopamine release either evoked by methylphenidate or by electrical stimulation is depressed in slices of nucleus accumbens of SHR compared with WKY rats [41]. However, they did not mention two *in vivo* microdialysis studies that measured basal and psychostimulant-evoked dopamine extracellular levels in the striatum of SHR and WKY rats. The first study reported that both dopamine levels were higher in SHR than in WKY rats [13] and the second one reported no strain differences [42]. Taken all together, animal models bearing experimentally induced abnormalities in their dopaminergic system, in addition to rodents strains selected for their behavioral traits mimicking ADHD, do not strongly support the dopamine-deficit theory of ADHD.

Brain imaging studies

Brain imaging studies have revealed structural and functional anomalies in ADHD patients. These anomalies are moderate and only statistically significant in terms of populations, but 'neuroimaging is not helpful in making the ADHD diagnosis' [1]. The most prominent structural differences between healthy and ADHD patients are observed in some small areas of the cerebellum [43], and these regions are not innervated by dopaminergic neurons. The only brain region that is abnormally smaller in ADHD children and that is strongly innervated by dopaminergic terminals is the right caudate. This structural anomaly spontaneously normalizes at adolescence whether children were treated with psychostimulants or not [44].

Several functional imaging studies investigated the effect of executive tasks, including response inhibition, on cerebral activation in ADHD patients and healthy controls. A meta-analysis taking into account 16 functional imaging studies reported 'significant patterns of frontal hypo-activity were detected in patients with ADHD' [45]. However, this hypo-activity is widely distributed, affecting numerous prefrontal, cingulate and parietal cortical regions and related subcortical areas in the basal ganglia and thalamus. Moreover, some other regions show locally greater activations in ADHD patients compared with control, 'suggesting that ADHD is not purely accounted for by hypofunction' [45]. According to some authors, these complex and widely distributed abnormalities in the cortical–striatal–thalamic brain circuits give support to the dopamine-deficit theory [3]. However, Diskstein *et al.* [45] concluded 'the results of this meta-analysis do not support simpler models which posit that ADHD is strictly a disorder resulting from deficits of activity in a few isolated brain regions'. Therefore, imaging studies do not establish a close link between ADHD and a hypothetical dopaminergic deficit.

Taken all together, the main arguments, which have been put forward to support the dopamine-deficit theory of ADHD, are strongly questioned by the available data (see a summary in Table 1).

Are theories of dopamine function relevant to the neurobiology of ADHD?

ADHD and the dopaminergic theory of reward

When examining the dopamine-deficit theory of ADHD it is useful to also consider the dopaminergic theory of reward and of positively reinforced learning for two reasons. First, this dopaminergic theory is often put forward to explain ADHD. For example, Casey *et al.* [14] said 'since dopamine is involved in forming predictions about future outcomes and optimizing behavior, by detecting discrepancies between actual and expected outcomes, this neurotransmitter plays an important role in learning in the current model of ADHD'. As a matter of fact, recordings of the discharge activity of dopaminergic neurons in behaving monkeys show that these neurons respond to unexpected reward, to the prediction of reward and to discrepancies between the reward expectation and the actual reward [46]. However, these observations do not prove that dopaminergic neurons have an important causal role in learning. Second, the dopaminergic theory of reward is often put forward to explain the high co-morbidity between ADHD and drug abuse [47].

Hypotheses regarding dopamine function

In the eyes of the general public and in the media 'the dopaminergic hypothesis of reward has achieved the kind of intellectual ubiquity that often characterizes a dominant paradigm' [48]. However, some studies in the 70 s and 80 s already questioned this hypothesis (for review, see Ref. [49]). More recently, this hypothesis has been strongly questioned in several review articles written by leading experts in the field [50–53]. I summarize below the main arguments.

First, recordings in behaving animals also show that several types of non-dopaminergic neurons, located in various cortical and subcortical regions, respond to reward and to its prediction [46,54,55]. Second, when monkeys are trained to select between two levers to maximize their reward, dopaminergic neurons are activated, but the delay of this response shows that they are not directly involved in the process of decision making [56]. The prefrontal and cingulate cortex seem more directly involved in learning and decision making [55]. Third, we must consider with caution time correlations between phasic changes in the

Table 1. Summary of the most often cited arguments put forward to support the dopamine-deficit theory and of the facts that question their strength

	Most often cited arguments in favor of the dopamine-deficit theory	Refs[a]	Facts questioning the strength of these arguments	Refs
Pharmacology	The effectiveness of the dopamine-based stimulant drugs in ADHD treatment suggests an underlying dopamine hypofunctional state.	[1,3,6 7,10, 14,30, 43,47]	Psychostimulant medication induces the same behavioral effects, including improved attention, in ADHD and healthy subjects.	[20–22]
	Psychostimulants produce their therapeutic effects by increasing dopamine.	[3,10, 14]	Specific inhibitors of the noradrenaline transporter are as effective as psychostimulants on ADHD symptoms.	[23]
Genetic	Genetic studies confirmed an association of ADHD with the 7-repeat allele of the D_4 dopaminergic receptor and with other genes involved in the dopaminergic systems.	[1,3,7, 14,30]	The most robust finding in ADHD is its association with a polymorphism of the D_4 receptor gene. The 7-repeat allele of the D_4 receptor is more frequent in ADHD patients (23%) than in healthy subjects (17%).	[15–18]
Brain imaging	Functional imaging studies reveal abnormalities in the cortical–striatal–thalamic brain circuits, which gives support to the dopamine-deficit theory.	[3,14, 30]	A meta-analysis taking into account 16 functional imaging studies does not support simpler models, which posit that ADHD is strictly a disorder resulting from deficits of activity in a few isolated brain regions.	[45]
	A binding study with [^{11}C]raclopride reveals depressed dopamine activity in the caudate of adults with ADHD.	[10, 47]	'We cannot rule out the possibility that the blunted dopamine responses to methylphenidate in subjects with ADHD could reflect higher baseline dopamine tone.'	[10]

[a]The reference lists are not exhaustive.

discharge rate of dopaminergic neurons and specific steps of a conditioned behavior. Indeed, dopamine acts on target neurons via G-protein-coupled receptors. Therefore, it is likely that the postsynaptic response of target neurons to a brief change in extracellular dopamine is delayed and prolonged compared with the presynaptic event [57]. Indeed, the effects mediated by dopaminergic D_2 autoreceptors reach their maximum ~0.2 s after the onset of the presynaptic event (i.e. after a phasic dopamine release) and last for ~1 s (i.e. at least for 0.5 s after the complete disappearance of this presynaptic signal) [58,59]. In the prefrontal cortex, the phasic release of dopamine does not serve to transmit a temporally precise signal but might modulate the network activity on timescales of seconds to tens of minutes [60,61]. Therefore, 'it is unlikely that dopamine is in series between a stimulus and a response and that it mediates stimulus-response coupling' [51]. It is striking to note that, except for autoreceptors, we still ignore the kinetics of the effects of released dopamine on target neurons. Fourth, when rats can choose between two levers, one to get intravenous cocaine and another to get sweetened water, they always press the latter [62]. Because cocaine is much more potent than physiological stimuli to enhance extracellular dopamine, this observation questions the view of a positive relationship between the dopamine signal and the intensity of reward [62].

The precise functions of dopamine are still a matter of debate (see later), but the arguments raised earlier and other pieces of evidence show that 'dopamine is not necessary nor sufficient to mediate the hedonic impact of reward' [50]. The dopaminergic theory of reward has often been put forward to explain addiction. Koob and Le Moal [53,63] repeatedly questioned this view. For them, the perception of reward results from the activity of a reward system, which involves dopaminergic neurons in addition to GABAergic and opioidergic neurons, and of an anti-reward system, which involves noradrenaline, CRF and dynorphyn neurons. According to these authors [63], research on the anti-reward system has been neglected 'because of an excessive focus on psychostimulant drugs and reward pathways (largely misattributed to the mesolimbic dopamine system)'.

As discussed earlier, dopaminergic transmission is too slow to directly act as a teaching signal. Moreover, other recent evidence indicates that 'dopamine is not needed for new learning and not sufficient to directly mediate learning by causing a teaching or prediction signal' [50]. Indeed, transgenic mice in which dopamine release is specifically impaired are still able to learn a task reinforced by a reward [64,65]. Conversely, hyperdopaminergic mice, in which the DAT expression has been decreased, exhibit an enhanced extracellular dopamine level but are identical to control mice regarding learning [66]. Therefore, dopamine activation by reward and its prediction is 'a consequence but not a cause of reward learning' [50].

Although there is now a widespread agreement that dopamine does not mediate the hedonic impact of reward and does not directly cause the reward associations involved in learning, it certainly plays a part in some other aspects of the reward processes [50,52]. Mesolimbic dopaminergic neurons seem to be 'a component of the brain

circuitry regulating effort-based functions' [52]. According to Berridge's terminology [50], dopamine is not involved in 'liking' or in learning but it contributes to 'wanting'; it helps to 'motivate the pursuit of rewards'. Therefore, dopamine might modulate complex decision making and learning processes taking place over seconds, but other modulators (e.g. noradrenaline, serotonin) have also been shown to have a role [67]. Consistent with this view, dopamine-deficient mice in their dopamine-depleted state still have a preference for sucrose and can learn the location of food rewards but 'are not motivated to engage in goal-directed behaviors' [65,68].

Positively reinforced learning in ADHD patients

The present understanding of dopamine function is consistent with observations in parkinsonian patients [69] and in healthy adults (for review, see Ref. [50]). Because children with ADHD have learning disabilities, the role of dopamine in reward-directed learning has often been put forward to explain ADHD [14]. However, this interpretation should be re-examined oweing to the fact that dopamine signaling cannot act as a teaching signal. Moreover, 'reinforcement contingencies have a positive impact on task performance and levels of motivation for both children with ADHD and normal controls' [70]. Although reward processing is often thought to be altered in ADHD children, findings have been inconsistent [70]. A recent study that examined the effects of variations in reward magnitude, immediacy, probability and age on preferences for reward observed no differences between ADHD and matched comparison subjects [71]. Therefore, it seems unjustified to rest the neurobiology of ADHD, and its high co-morbidity with drug abuse, on an overly simplistic dopaminergic theory of reward.

Does psychostimulant medication positively affect long-term outcomes?

There is no doubt that psychostimulant medication alleviates the core symptoms of ADHD during treatment [72]. However, it is less clear whether they have beneficial long-term outcomes on the functioning of ADHD patients. This is an important issue because, according to a general consensus, children with ADHD are clearly at risk of later development of antisocial behavior, substance abuse and significant academic underachievement [73,74]. However, regarding antisocial behavior, the follow-up at 3 years of the ADHD children in the Multimodal Treatment ADHD (MTA) study [75] shows that 'by 24 and 36 month, more days of prescribed medication were associated with more serious delinquency'. The same study reported 'we did not find evidence of protective or adverse effects of medication treatment for ADHD on the initiation of substance use' [75]. This is in line with other studies that showed that, among ADHD children, psychostimulant medication does not increase or decrease the risk of subsequent substance use disorders when they reach young adulthood [76,77].

Likewise, the impact of psychostimulant medication on long-term academic outcomes seems to be very little, if any (for review, see Ref. [78]). In particular, the MTA study shows a significant improvement for the core symptoms of ADHD 'but not for academic achievement' assessed by reading scores [79]. However, in a recent, well-controlled and long-term study [80] the authors concluded that their findings 'support the hypothesis that the treatment with stimulant medication is associated with more favorable, long-term school outcomes for children with ADHD'. Nevertheless, this conclusion seems to be rather excessive. Indeed, the authors concluded that 'stimulant treatment of children with ADHD was associated with improved reading achievement', but their data showed that, among the 349 ADHD children of the study, reading scores were significantly enhanced in only one group of 26 children who received daily doses of methylphenidate greater than 40 mg [80]. On average, this study [80] reported 'reading score was similar between the groups of cases that were treated versus not treated with stimulants'. Moreover, this study also showed that 'the proportion of school dropout (i.e. failure to graduate from high school) was similar between treated and non treated cases (22.2% versus 25.8%)' [80] and much higher than in non-ADHD controls (10.0%) [74]. In my opinion this study, rather, supports the view that psychostimulant medication does not improve long-term academic outcomes of ADHD children.

Ethical considerations and concluding remarks

In science, weak theories disappear when better ones replace them. From the point of view of scientific knowledge, there is no reason to fight against the dopaminergic hypothesis of ADHD. Although we have no better theory that might receive a general consensus, some recent studies throw new light on the neurobiology of ADHD. For example, Shaw *et al.* [81] showed that, in contrast to other neuro-developmental disorders such as autism, 'ADHD is characterized by delay rather than deviance in cortical maturation'. Unfortunately, the dopamine-deficit theory of ADHD is so dominant that it discourages the human and financial investments needed to explore alternative theories. Moreover, whatever the hypotheses, neuroscientists should be more aware of the fact that neurobiological theories of ADHD do influence its social representation and, thus, its treatment [82]. The main drawback of the dopamine-deficit theory is that it gives scientific credence to a view that favors psychostimulant medication over other medical, psychological and social approaches to ADHD treatment. Recent evidence-based studies question the view that psychostimulant medication has long-term beneficial effects on ADHD [75,77,78] and point out the interest of psychosocial treatments [83]. Therefore, if we are convinced that the dopamine-deficit theory of ADHD is weak, it is our duty to say so in public. ADHD is a serious concern and we must avoid biasing its evidence-based treatment with a weak scientific theory. In this matter, although it is difficult to accept, no scientific theory is socially preferable to a weak one.

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