the complex features of the psychiatric disorder ADHD can be reduced to a single defect in one neurotransmitter (dopamine) and one behavioural abnormality (reward and extinction). The authors seem to be aware of the inherent reductionism of their model, but they claim that ignoring other possible changes will facilitate theorisation and future research. I cannot see the advantage of isolating a still hypothetical (and controversial) aspect of ADHD pathology (i.e., hypofunctioning dopamine systems), by ignoring the interactions of this subcomponent with other components of the pathology (i.e., other neurotransmitters/chemicals and non fronto-striatal brain regions), and then – almost in contradiction to the initial admittance of reductionism – explain every single aspect of the pathology by this isolated sub-segmental dysfunction. If all ADHD behaviour features can be explained by hypodopaminergic fronto-striatal pathways, one wonders what the other neurotransmitters and brain regions are there for? The cautious statement that "the present model may be applicable mainly to a subgroup of ADHD linked to dopamine hypofunction" (sect. 3, para. 2) is a prime example of the logical fallacy of circular reasoning: We provide an explanatory model of ADHD, but it will only apply to those patients who meet the model.

The authors claim that "the majority of findings . . . seem to converge on dopamine in the etiology of ADHD" (sect. 3, para. 2). True, but ADHD research has been excessively biased towards dopamine investigation, and the few studies that have investigated the involvement of other neurotransmitters have been positive. Thus, atomoxetine, a selective noradrenaline inhibitor, has shown to be effective in ADHD symptom relief (Kratochvil et al. 2003), in line with the role of noradrenaline in attention processes and ADHD (Levy & Swanson 2001). Likewise, serotonin has been related to impulsiveness in animals and humans (Krakowski 2003; Robbins 2002) and in the mechanisms of action of stimulant drugs (Gainetdinov et al. 1999; Winstanley et al. 2003), but almost completely neglected in ADHD research (Oades 2002).

Furthermore, although a dopamine dysfunction in ADHD (alongside other neurotransmitter dysfunctions) is likely, at the present state of research it is unclear whether dopamine is hyper- or hypofunctioning (Solanto 1998), whether there is a differentiation of specific dopamine systems being under- (i.e., prefrontal systems) and others over-regulated (i.e., basal ganglia; Castellanos et al. 1997; Rohde et al. 2003), or whether there is a differentiation of hypo- and hyper-dopaminergic striatal systems in ADHD patients depending on symptom severity (Teicher et al. 2000). Other ADHD animal models have found a hyper-trophic rather than hypo-trophic mesocortical dopamine system (Viggiano et al. 2003b). The exhausted theory of hypofunctioning dopamine systems in ADHD has thus in recent years been replaced by a far more sophisticated picture of multiple and divergent monoamine dysfunction.

The authors do not make any attempts to integrate recent brain imaging findings of structural and functional abnormalities in temporal, parietal or cerebellar brain regions (Castellanos et al. 2002; Durston et al. 2003; Rubia et al., in press; Sowell et al. 2003) into their model of fronto-striatal dysfunction. The rather sweeping statement that global functional and structural changes in ADHD may be a result of reduced blood circulation caused by decreased dopamine, is difficult to sustain. I am not aware of a direct link between brain structure and blood circulation. In functional imaging, the effect of dopamine on neural hemodynamic coupling is controversial, apart from the fact that there is no specific effect of dopamine on blood flow over other neurotransmitters (Johnston et al. 2004). Thus, dopamine enhancement as well as reduction has not been shown to have an effect on neural hemodynamic coupling (Esaki et al. 2002; Rao et al. 2000). If anything, there is recent evidence that dopamine antagonists increase fronto-striatal connectivity in healthy adults (Honey et al. 2003), whereas in ADHD, dopamine agonists decrease fronto-striatal and parietal activation (Langleben et al. 2002; Schweitzer et al. 2003; Szobot et al. 2003), which would support a hyperdopaminergic hypothesis of ADHD.

The theory of abnormal reward and extinction processes as a global explanatory model for ADHD, as the authors acknowledge, predicts deficits in learning and memory in ADHD. Contrary to their claim, however, there is hardly any evidence in the ADHD literature for learning or memory deficits, unless, obviously, in comorbidity with learning disorder (or working memory, which is an executive function). The definition of the complex feature of impulsiveness as "responses with short inter-response times" and "the choice of smaller, immediate rewards" reflects the limitation of the rat's model viewpoint: Although this is the only way impulsiveness can be measured in rats, in humans, impulsiveness is more complex, including heterogeneous features such as poor self-control, disinhibition, prematurity, temporal myopia, delay aversion, lack of persistence, increased boredom, sensation seeking, distractibility, inattention, and irritability (Evenden 1999; Rubia 2002). To explain all of these heterogeneous cognitive features by abnormal reinforcement processes seems an oversimplification.

The problem with animal models is that, in order to compare between species at the behaviour level, higher complex human features need to be reduced to motor and limbic components that can be observed in both, and at the anatomical level, complex human neural networks have to be decomposed into simpler motor and limbic pathways. This is exactly what Sagvolden et al. have done: the complex mental disorder of ADHD is being reduced to dopamine mediated limbic reward and extinction processes. Fortunately for us, the human brain is more sophisticated than the rat brain, and I am afraid more sophisticated theories will be needed to do justice to one of the most complex and pleiomorphic disorders of psychiatry that is ADHD.

Is the hypodopaminergic hypothesis plausible as neural bases of ADHD?

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Abstract: The "dynamic developmental theory" is based on hypofunctioning dopamine systems that follow an early overactivity phase. The theory does not consider recent experimental evidences from different attention-deficit/hyperactivity disorder (ADHD) models and the heterogeneity of the disorder. Alternatives are proposed that integrate available information gathered from clinical and experimental studies, with theoretical constructs.

The dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) postulates an early hyperfunctioning followed by hypofunctioning dopamine (DA) systems. Its peculiarity consists in an early overactivity phase of DA neurons that could be the result of different genetic and epigenetic factors. Historically, the use of psychostimulant drugs such as methylphenidate (MPH) and *d*-amphetamines in ADHD over decades has supported the hypofunctioning hypothesis. However, our understanding of the DA systems has increasingly improved as to feedback regulation in the mesencephalon and at target sites (frontal cortex, striatum). For instance, DA neurons control their own firing. In fact, DA D_2 autoreceptors hyperpolarize DA neurons, and in turn reduce their responsiveness and firing rate (see, e.g., Bonci et al. 2003). Furthermore, the membrane transporter protein for DA (DAT) reduces DA neurotransmission by re-uptaking it into the terminal (Wightman et al. 1988).

MPH blocks DAT both in the mesencephalon and target sites, thus increasing synaptic DA (Seeman & Madras 2002). This, in turn, activates DA receptors. However, low doses of MPH mainly act on mesencephalic D_2 autoreceptors, leading to inhibition of DA neuron firing (Brandon et al. 2003; Ruskin et al. 2001).

Therefore, the efficacy of low doses of MPH (Solanto 2002)

does not depend on increased DA availability but rather on reduced excitability and firing frequency of DA neurons. Moreover, DAT blockade reduces the probability of DA neuron firing without reducing tonic DA release. Indeed, the inhibition of phasic DA release during bursts does not allow DA to reach the DA peak level (up to micromolar concentrations vs. the nanomolar range in tonic release; Seeman & Madras 2002). In addition, multiple evidence from animal models of ADHD does not support a hypofunctioning DA systems in juvenile animals (see, e.g., Viggiano et al. 2003a; 2004).

In fact, (1) DAT knockout mice show a hyperdopaminergic state and behavior hyperactivity (Zhuang et al. 2001); (2) juvenile hyperactive Spontaneously Hypertensive rats (SHR) show increased basal DA release in the prefrontal cortex and nucleus accumbens (Carboni et al. 2003; 2004); (3) ADHD children have increased excretion of the DA metabolite homovanillic acid (HVA) (see Castellanos & Tannock 2002). Furthermore, Naples High Excitability (NHE) rats show morphofunctional evidence for hyperplasic DA systems, whereas molecular biology studies suggest in the prefrontal cortex an overexpression of genes associated with cytoarchitecture, metabolism, and signal transduction (Viggiano et al. 2002; 2003b). As a matter of fact, the NHE rats do not show evidence of hypofunctioning DA systems in adulthood. Therefore, the dysfunction of the DA systems in ADHD may also be underpinned by a hyperfunctioning state not limited to an early stage.

The hypofunctioning DA phase that follows the early hyperfunction, as suggested by Sagvolden et al., emerges from experimental studies in the SHR model (de Jong et al. 1995; Russell et al. 1995), that is hyperactive but also suffers from arterial hypertension. However, a hypodopaminergic system does not lead to behavioral hyperactivity, as demonstrated by several knockout and pharmacological DA depletion studies (reviewed in Viggiano et al. 2003a). Since it is well known that the arterial hypertension damages brain architecture, the late hypofunction in SHR is probably associated with it.

Finally, the main branches of the DA systems do not necessarily share the same functional state, depending on local factors. This, in turn, may be responsible for the heterogeneity of ADHD (Biederman & Faraone 2002; Sergeant et al. 2003) and explain its main variants (Sonuga-Barke 2003). Likewise, different animal models may reproduce different clinical variants (Viggiano et al. 2004).

Although a dysfunction of DA systems is associated with ADHD in humans and animal models, this might be a compensatory change to other primary defects (Rubia 2002). In fact, if the system is *hyper*, target neurons will be susceptible to neurotoxicity and neurodegeneration. Therefore, low doses of MPH reduce the phasic DA release, whereas high doses produce a "generalized stimulation" (Seeman & Madras 2002) a biphasic effect that is not predicted by a hypodopaminergic hypothesis. Nonetheless, the amelioration of the ADHD symptoms would be only symptomatic, because the primary defect has not yet been ascertained.

Notwithstanding, the molecular mechanisms by which MPH determines enduring changes in DA neurotransmission remain to be elucidated, as repeated MPH treatment in juvenile SHR exert long-term effects on membrane excitability (Brandon et al. 2003) and transduction mechanisms (Sadile 2000; Andersen et al. 2002).

In conclusion, the dynamic developmental theory appears plausible and interesting; however, it should include the above-mentioned considerations to explain different ADHD variants.

The biopsychosocial context of ADHD

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) represents adaptation to defective neurotransmission – an adaptation seldom with benefit. The resulting behavioural style not only increases vulnerability to adverse experiences, but also creates a context in which encountering adversity is more likely. Furthermore, the fact that ADHD is a highly heritable condition increases the probability of a child with a compromised neurobiological disposition being raised by caregivers with suboptimal resources.

The target article is, to my knowledge, the first serious attempt to present a unified theory expanding from the biology of brain neurochemistry to continuously evolving interaction between a child with attention-deficit/hyperactivity disorder (ADHD) and his or her social environment. It is also noteworthy that the first author, Sagvolden, is a renowned scientist in murine research.

At the basis of the dynamic developmental theory, put forward by Sagvolden et al., is a model of dysfunctional dopamine systems in the brain. Three hypofunctioning dopamine system branches and their behavioural consequences, representing the core symptoms of ADHD, are outlined. These compromised properties result from a combination of intrinsic (genetic) and extrinsic (e.g., drugs and toxins) influences on the developing brain. The altered neurobiological disposition gives rise to two main behavioural processes causing ADHD: altered reinforcement of novel behaviour and deficient extinction of previously reinforced behaviour. According to the theory, ADHD symptoms are a product of a dynamic process of the individual's adaptation to defective neurotransmission.

The authors have construed a coherent account spanning from biochemistry, via behaviour, to a reciprocal interplay between the affected child and his/her biosocial environment. The theory predicts that ADHD behaviour results from, and is continuously modified by, the dynamic context of individual predispositions and interpersonal surroundings well into adulthood. And in the case of many adults, the individual predispositions come to form the interpersonal surroundings of another individual – their child.

The individual predispositions are primarily guided by genes. However, the interplay also starts early – going back (at least) to the intrauterine life (Grossman et al. 2003; Schneider et al. 1998). By the time the child's behaviour reaches the level of abnormality qualifying for ADHD, years of active interaction have taken place. And yet, as Sagvolden et al. note, not all children presenting with the core symptoms of ADHD get identified as maladjusted. This is because the environment has been unusually insightful and supportive in guiding the child's excessive and disorganised activity into constructive creativity. The individual ADHD symptoms at different times in a person's life vary and are influenced by factors exerting either a positive or negative effect. In other words, the environment can either protect from maladjustment, or predispose to it.

Crucial here is the caregiver's ability to adjust the environment to the child's needs for optimal development of adaptive skills. The resulting behavioural style, in turn, determines the long-term consequences of the early interactions. The theory predicts that a child with ADHD finds it hard learning how to match their behaviour to the demands of a given situation. Consequently, there will be few chances for the child to be rewarded for compliant behaviour. Instead, the resulting chaotic behavioural style will only magnify the negative interactions with carers. For optimal upbringing, the caregivers have to adapt to the child's special needs by taking into account the implications of the underlying deficits and adjust their expectations and demands accordingly. As the authors spell out, "a child with ADHD requires exceptional parenting skills" (sect. 4.2, para. 3).