

## Dopamine may be 'hyper' with respect to noradrenaline metabolism, but 'hypo' with respect to serotonin metabolism in children with ADHD

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### Abstract

**1. Noradrenaline:** Hechtman /12/ argued for a role for frontal dopamine (DA) and noradrenaline (NA) in ADHD, where Oades /20/ has described lateralised functional impairments. Mechanisms (e.g. via alpha-2 sites) for stimulating low NA activity in ADHD children /9/ in order to promote interactions with mesocortical DA have been discussed /1, 3/.

We described with indicators of overall transmitter metabolism (monoamines, metabolites in 24h urine samples, /22/) significantly lower utilisation ratios (MHPG/NA) in ADHD children with respect to healthy controls. Interestingly, a comparison of between catecholamine levels (DA/NA) showed a correlation with the conditioned blocking measure of selective attention recorded at the time of collection. This measure was negatively associated with blocking in controls. These results are consistent with reports of lower DOPEG and increased DOPAC in ADHD urine /10/ and indicate that the relatively hyperactive DA vs. NA systems may have functional consequences.

**2. Serotonin:** The relevance for ADHD of an association of impulsivity with low serotonin (5-HT) metabolism /34/ has long been played down. Yet, some symptoms have been related to CSF measures of the metabolite 5-HIAA, and in particular the HVA/5-HIAA ratio has been reported to correlate with ratings of activity /3/.

We find that while urinary measures of 5-HIAA are somewhat higher, the ratio HVA/5-HIAA is markedly lower in ADHD children versus controls. In these ADHD children 5-HIAA levels were unenthusiastically related to d-prime measures in a continuous performance task (CPTax), and the HVA/5-HIAA was negatively associated with conditioned blocking. These results suggest a relatively low DA vs. 5-HT activity may have functional consequences, albeit in a subgroup of ADHD. This is consistent with drug-induced prolactin changes reported by Verbaten and colleagues /35/.

**Key Words:** Attention Dopamine, Noradrenaline Serotonin ADHD

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### Introduction:

In view of the dependence of CNS function on the function of biogenic amines as neurotransmitters, astonishingly few studies are published on the parameters that influence amine activity in normal human development or on the changes associated with child and adolescent psychopathology. The difficulties are evident. It is extremely rare

that there is a medical reason for the use of brain imaging techniques with ligands, for access to the nervous tissue involved or the fluids (CSF) that serve as a repository for the products of excess amine synthesis or breakdown. Further as most institutions do not sanction in minors either the pharmacological provocation of symptoms or the use of agents unrelated to the illness

concerned, there is no alternative but to use one of the three strategies remaining.

Strategies: First one can argue by analogy with adult human or animal models, second one can record the effects of drugs administered for the presenting illness, or thirdly one can use measures of amine metabolism in the blood or urine as *indicators* of the general level of their metabolism in the body (where there is no reason to believe there is peripheral organic dysfunction).

### 1. Noradrenaline (NA)

Despite the demonstrated efficacy of psychostimulants in the treatment of many children with ADHD since the 1930s the idea of an altered catecholamine metabolism in these children only caught on 25 years ago /36/. Since then all 3 investigation strategies have been used to demonstrate changes in NA and DA metabolism in ADHD children /16, 12/. It is likely that mesocortical or frontal catecholaminergic changes reflect the more cognitive manifestations of ADHD such as attentional control and working memory /20, 26/, while mesolimbic changes may reflect motor activity and drinking /19, 23/. Yet as Ernst et al. /4/ discuss, not only do the 7 American studies of DA metabolites that they cited, not agree on the direction of change, but even a similar number of neuroimaging studies failed to find consistent or significant changes.

It is the thesis of this article that it is not the absolute level of activity that is significant in eliciting the ADHD symptoms /see also 27/, but rather the relationship of the level of the *activity* of one monoamine to the other that proves psychopathologically significant. In particular in this section I suggest that NA activity is low with respect to DA activity.

NA activity has often been reported to be low in groups of ADHD children /review 19/. More recent results are consistent for low plasma MHPG /9/ and low urinary DOPEG /10/ in ADHD samples. Inconsistencies may be due to subgroups defined by particular complications, such as reading disorder (increased plasma MHPG, /9/), delinquency

(CSF MHPG, /3/) or water balance (plasma/urine monoamine utilisation, /23/).

More important than these absolute measures, it may be that the balance of DA vs. NA activity is critical for ADHD /30/, as of course it is for normal frontal lobe function in attention, working memory and behavioural inhibition /1/. The latter author describes how low doses of DA agonists impair while alpha-2 agonists improve performance on delayed alternation learning in primates, a classic soft sign for frontal function.

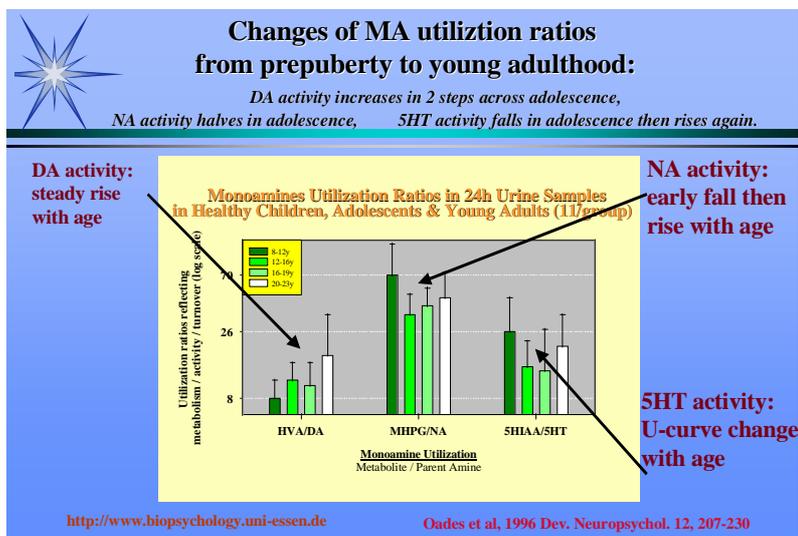
Here I present some of our data to show the importance of using measures that express the ratio of metabolite to parent amine (utilization) or one metabolite to the other. The first important stage of the present discussion is to note that while we confirm for normal subjects widely reported measures that show levels of the monoamine or metabolite alone fall from childhood across adolescence, utilization measures of turnover show different patterns across development /24/. DA activity rises steadily across adolescence, while NA activity drops at puberty before steadily rising to adult levels (figure 1).

For ADHD children NA activity, as reported above, is lower than in healthy controls (figure 2, left). However on the right of the diagram one can see that the ratio to DA activity (HVA/MHPG) is higher than in controls.

This increased ratio HVA/MHPG may reflect low levels of MHPG and/or high levels of unused NA (or both). This may well have functional consequences in the way information is processed. Figure 3 shows that a measure of selective attention, conditioned blocking (CB), correlates positively with DA activity but negatively with the ratio of the amount of DA to NA. This would be explained by relatively low levels of DA – where most DA is utilised. But the correlation is negative for ADHD children where unused NA levels are likely to be high. The ADHD children are poor at developing the ability to show CB with increasing age by comparison with healthy controls /22/. [CB is the delay in learning that stimulus “B” has the same consequences as

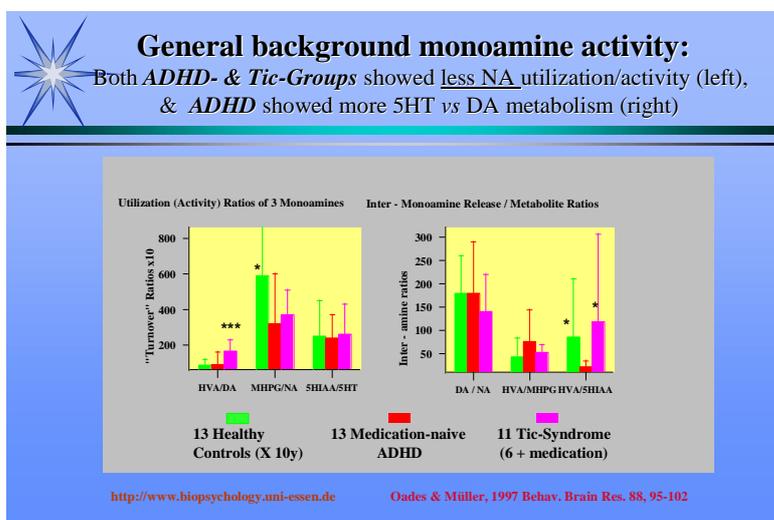
stimulus “A” when it is added during learning about “A” to form the stimulus complex “AB”.]

**Figure 1.**



The development of the turnover or utilization ratios for dopamine (DA), noradrenaline (NA) and serotonin (5-HT) as indicators of general monoamine activity from 24h urine samples across 4 age-groups of healthy children, adolescents and young adults (8-22y-old; see key).

**Figure 2**

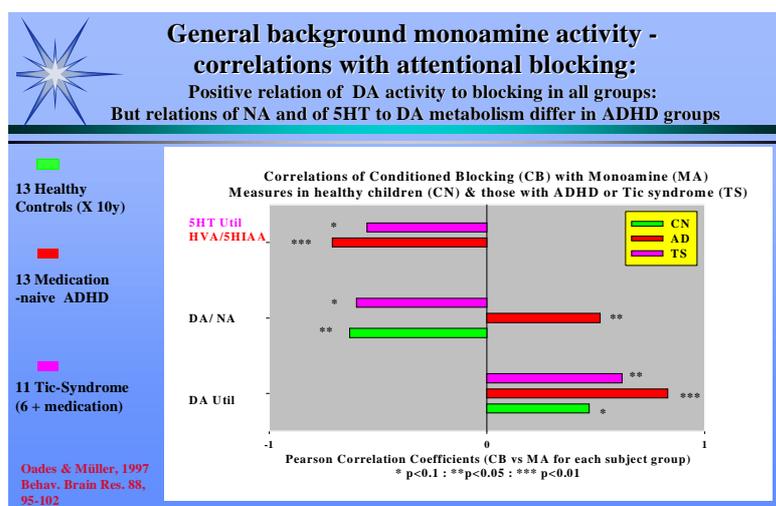


On the left, the turnover or utilization ratios for dopamine (DA), noradrenaline (NA) and serotonin (5-HT) as indicators of general monoamine activity from 24h urine samples are compared for groups of healthy children (mean age 10y), and children with either ADHD or Complex-Tics/Tourette syndrome (see key). On the right, the ratio of the catecholamines, the ratio of their metabolites and the ratio of the dopamine to serotonin metabolites are shown for the same groups.

From these observations I would predict that this change of the *relatively* high DA activity to the *relatively* low level of NA activity would underlie the widely-reported impaired performance of ADHD children on the digit-span task with distracters /26/. At

the root of this problem is the impaired ability to tune in and tune out stimuli that are likely to be relevant to the development of behaviour adaptive to a changing situation /18/.

Figure 3



Correlation coefficients (negative to the left, positive to the right) between conditioned blocking measures of selective attention performance and monoamine levels or activity (metabolite levels or utilization) are shown for healthy children (mean age 10y), , and children with either ADHD or Complex-Tics/Tourette syndrome (see key).

## 2. Serotonin (5-HT)

In the 1980s influential articles concluded that 5-HT activity had little to do with the ADHD clinical picture /28, 37, 19/. This conclusion was based on the inconsistent or negative results obtained from early CSF analyses and later data pertaining to tryptophan treatment, fenfluramine challenge, monoamine oxidase activity and monoamine change in plasma after treatment with psychostimulants. As with NA (previous section) merely Wender's pioneering laboratory reported increased DA and 5-HT metabolites in adult patients not responding to psychostimulants /29/. This dismissal of a role for 5-HT in the ADHD picture is surprising in view of plenty of evidence that decreased metabolism was associated with impulsivity in borderline personality, aggression and suicide /2, 17, 34, 32/. It is not immediately obvious that impulsivity in ADHD is generically different, although a number classifications of impulsive behaviour have been advanced /6/.

More recently evidence is accumulating to support an apparent increase of 5-HT activity from studies investigating parameters in CSF, blood and urine samples: Castellanos et al. /3/

reported increasing metabolite levels in the CSF with increasing delinquency and motor activity, Verbaten et al. /35/ reported increased prolactin levels after presumed blockade of the uptake sites with desipramine - partially consistent with a similar increase of prolactin seen in the study of Halperin et al. /8/ conducted under the specific viewpoint of the correlates of aggressive characteristics – and the association reported by Oades /21/ of poorer signal detection measures with increased excretion of 5-HT metabolite in the urine of ADHD children.

There remain inconsistencies or at least unexpected findings: first, the implication of increased 5-HT metabolism is at odds with an association with impulsivity recorded in non-ADHD contexts. Second, Verbaten et al. /35/ found improved performance on the stop signal paradigm while Oades /21/ reported impaired perceptual thresholds with increased 5-HT metabolism.

The former problem probably reflects the different derivations of "impulsivity" in ADHD and non-ADHD contexts /see 6/. The latter problem is more apparent than real. In animal

studies depletion of 5-HT results in the animals being less able to withhold responses on the no-go component of a Go/no-go task /11/, and “impulsive” responses on a response schedule requiring a fixed number of responses was reduced with the uptake blocker imipramine /5/. These findings support Verbaten on measures of impulsive motor responses where 5-HT may be expected to affect outcome downstream from areas innervated by DA /7/. In contrast 5-HT effects on signal detection measures are likely to involve the auditory cortices that receive marked 5-HT innervation, upstream from regions innervated by DA. It is in the auditory cortices that N1 and P2 event-related potentials are generated, - potentials that are augmenting-reducing sensitive – and have been related to 5-HT activity and sensation-seeking traits /13, 14/. The P2 is often unusually large in ADHD subjects /31, 25/.

Thus, while there can remain little doubt that 5-HT activity may modulate features of the ADHD syndrome, the mechanism requires attention to the locus that may be reflected by study of the precise features under study (e.g. sensation seeking vs. impulsivity or P2 vs. withholding response) and the subgroup of patient concerned. An alternative refinement to the explanation must not be overlooked. The effect of apparently raising or suppressing 5-HT activity may well depend on the status of DA activity.

The study of HVA/5-HIAA ratios in ADHD has certain pitfalls. Figure 1 shows that while DA utilization may gradually increase across adolescence, that for 5-HT may show more of an inverted U-pattern with maturation. Nonetheless if this caveat is put to one side, it may be seen in figure 2 that around 10 years-of-age the HVA/5-HIAA ratio is much depressed compared to the other two groups studied. This could reflect particular increases of 5-HT utilization in the ADHD children, for which there is evidence in studies of other samples (see above), or a decrease of DA activity, as controversially argued by Solanto /33/. While neither of these situations pertained to our study for the monoamines considered alone, there remained a significant suppression of the ratio of the two. This

achieved an apparent functional significance with a marked negative correlation for the development of CB in the ADHD children (figure 3).

### Conclusions:

There is ample evidence that NA and 5-HT activity should be considered in the equation expressing the relations of monoamine transmitter activity to ADHD psychopathology. This in no way reduces the major role for an aspect of DA transmission mechanisms deduced largely from the success of the psychostimulants. The way forward in improving our understanding should involve studies of the relative activity of each monoamine and its contribution to precisely defined features or symptoms of ADHD (cf. anxiety, aggression, sensation seeking and impulsivity) under the realisation that there are likely to be several loci contributing to the overall picture (e.g. upstream/downstream of each other). This paper advances the hypothesis that DA is hyperactive with respect to NA activity, but often hypoactive with respect to 5-HT activity in certain manifestations of ADHD. For therapeutic purposes this means a more serious and widespread consideration of co-treatment or adjunctive forms of therapy. Representative of this point of view Kewley /15/ recently reported a positive experience with adjunctive clonidine or risperidone. The particular agent to be recommended in the future will depend on current investigations of the monoamines to each other and the symptoms that emerge when there are imbalances.

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