Behavioural Brain Research 88 (1997) 95–102

The development of conditioned blocking and monoamine metabolism in children with attention-deficit-hyperactivity disorder or complex tics and healthy controls: an exploratory analysis

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Abstract

Conditioned blocking (CB) measures the transient suppression of learning that a new stimulus, added during learning, has the same consequences as the conditioned stimulus already present. Normal CB increases between the age of 8 and 20 years (Oades, R.D., Roepcke, B. and Schepker, R., A test of conditioned blocking and its development in childhood and adolescence: relationship to personality and monoamine metabolism, *Dev. Neuropsychol.*, 12 (1996) 207–230). In the present study CB development is compared between healthy children (CN), children with attention deficit (ADHD) and those with complex tics or Tourette's syndrome (TS) with mean ages of 10–11 years. All children needed fewer learning trials with increasing age: the ADHD group showed a slight impairment. Only controls improved CB with increasing age. A trend for worse CB in the TS than the other groups was significant for those over 11 years. While ADHD children over 11 years showed less CB than controls, younger ADHD children showed more. A correlational analysis of the status of monoamine metabolism in 24 h urine samples showed a positive relationship for CB with dopamine metabolism in controls and TS children, but a negative relationship in ADHD children. In contrast, increases of serotonin metabolism were negatively related to CB in TS but positively in ADHD patients. In conclusion, when selective information processing abilities reflected by CB start to develop at puberty-onset, there is a relative worsening in ADHD patients. But TS patients show an impairment independent of age. Changes in the balance between dopamine and serotonin systems may contribute to normal and abnormal cognitive development. © 1997 Elsevier Science B.V.

Keywords: Selective attention; Conditioned blocking; Attention-deficit-hyperactivity disorder; Tourette's syndrome; Dopamine; Serotonin

1. Introduction

Attention has been usefully and succinctly described as the 'selective aspect of perception' [29]. In children with attention-deficit-hyperactivity disorder (ADHD) the impairment is widely understood to refer to a poor ability to maintain or sustain attention (review in [6]; but see [31] for a different view) and has been associated more with poor perceptual detection thresholds (in signal detection terms, d-prime) than identification thresholds (beta-criterion). Nonetheless a minority of studies have reported an impairment of beta in ADHD patients [6,10]. A changed signal-detection strategy could reflect a selective attention deficit. Investigations of this usually concentrate on measures of target discrimination in the presence of distractors [30], that can show an increased number of target-omission errors in ADHD children [14]. An alternative explanation of the attention deficit, namely an ability to suppress actively the processing of and response to irrelevant stimuli has rarely been examined. For this purpose the learned inattention paradigm is particularly appropriate.

This paradigm includes latent inhibition (LI) and conditioned blocking (CB) tests. LI refers to the delay in conditioning to a stimulus following preexposure to it, without consequence: CB refers to the transient

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suppression of learning about a stimulus added during conditioning to another cue. We are aware of only one research group reporting on LI-testing of children [12,16] and two reporting CB-performance in children [11,21,22]. LI was reported in younger (5–6 years) but not in older children (6–7.5 years) [12,16]. In the latter study, a comparison group of ADHD children also failed to show LI. However, the results were difficult to interpret, partly because of the poor learning performance of one of the groups, and partly because of the apparent need for a masking task to enable the phenomenon to be seen in older children. Nonetheless, if Lubow's suggestion that ADHD children were failing to process irrelevant information is correct [16], then a normal development of CB in ADHD children would also not be expected.

Recently Oades et al. [21] demonstrated CB in young adults in a computer task where sites on an apartment-house plan were associated with colour cues presented at the start of each trial. Success in moving a 'mouse' to the appropriate site within a given time was rewarded with positive points and failure incurred negative points. Compared to adults, 14 and 17 year old adolescents showed less CB and 10 year-old children showed only modest CB. In a further study, these authors [22] showed that this test was sensitive to psychopathology. Young OCD patients showed normal CB, young paranoid schizophrenics demonstrated CB after the initial trial and nonparanoid schizophrenics showed no CB. Reminiscent of the results of manipulating dopaminergic (DA) function in animals (review, [22]), these authors found that measures of the urinary status of DA metabolism correlated positively with CB in young and old healthy subjects but negatively in the nonparanoid patients. However, CB correlated positively with noradrenergic activity in adults but negatively in young children.

Given these results and those of Lubow and colleagues on LI [12,16] it is important to examine more closely the onset of maturation of cognitive strategies reflected in CB, and to contrast these in two groups of children with an attentional impairment (ADHD and Tic/Tourette's syndrome) in whom catecholaminergic dysfunction is well-documented (e.g. review [18]) and delayed development has been proposed [27].

We predicted, first a replication of modest CB in healthy children that would improve with age and correlate with DA activity. Secondly, based on the LI data and evidence of increased incidental learning in ADHD children [4], an impairment of CB was anticipated. (A report on the presence of CB in a sample of 9 year-old ADHD children was published at the end of our study [11]). We expected that if psychopathology resulted from a trait (e.g. genetic, [8]) ADHD children would be impaired across the whole age range, or if the syndrome reflected delayed cognitive development [27], then only young children would be impaired. Thirdly, the status of NA activity, usually depressed in ADHD children, was expected to be low in those with impaired CB [18]. Lastly, it was expected that if TS patients were impaired on CB, that this would reflect their adventitious attention-deficit symptoms, as increased DA activity, normally treated with neuroleptics, would be positively associated with CB.

2. Methods

2.1. Subjects

Subjects were 13 children with ADHD, 11 with complex tic or Tourette syndrome (TS) and 13 healthy controls (CN). The ADHD children were consecutive admissions with a primary DSM IIIR diagnosis from two clinicians of attention deficit disorder with/without hyperactivity (314.01 ($n=7$), 314.00 ($n=6$)) [1]. There were 11 boys and two girls (age-range 7.4–14.3 years, mean 10.5 S.D. 2.0) and were free of medication. Comorbid diagnoses concerned affect/fear (313, $n=5$ plus two cases of enuresis or encoporesis), coordination development (315, $n=3$) and five cases with degrees of conduct problems (312). Patients were excluded if the dominant problem diagnosed was not one of attention deficit or if they had a low IQ score (<70: mean Raven's SPM = 96, S.D. 11). Brief Conners parent-teacher assessments were given to the parents and one of the ward staff (mean 1.8 S.D. 0.3); their scores did not overlap with those for the healthy group (see below).

The TS group was recruited to help determine if the CB results were specific to ADHD-like symptoms or the dominant diagnosis. Ten of the children were male and four were inpatients (age-range 8.2–15.2 years, mean 11.8 S.D. 2.1). The mean IQ (101 S.D. 19) did not differ significantly from the other groups. With two exceptions they were not severely ill (tic severity/frequency ratings averaged 2.1/1.7 on a scale of 1–4, derived from the Tourette-Syndrome global assessment scale, [9]; six had a primary diagnosis of multiple tics (307.22) and five of Tourette syndrome (307.23). The Conners rating scores were similar to those of the AD group (mean 1.5, S.D. 0.3), but these symptoms were considered secondary to the diagnosis. Exclusion criteria were the same as for the ADHD group as long as tics were the major problem diagnosed. Six patients were free of medication at testing, two received pimozide (1–1.5 mg/day) and three tiapride (200–400 mg/day).

Thirteen healthy children (CN, 9 boys, 4 girls, age-range 8.2–14.2 years, mean 11.0 S.D. 1.6) were matched pairwise with the ADHD children for age within 10 months and for Tanner ratings of sexual

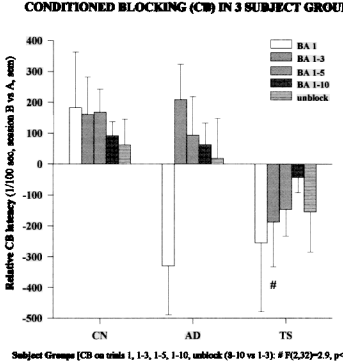

Fig. 1. Relative latency measures of conditioned blocking (CB, S.E.M.) across the first, first three or five or ten test trials (BA 1, 1–3, 1–5, 1–10, unblock = BA (1–3) – (8–10) for healthy children (CN) and those with a diagnosis of ADHD (AD) or Tourette/tic syndrome (TS).

maturity within one level on the scale of 1–6. Their mean IQ (112 S.D. 17) was higher than in the ADHD but not the TS patients (t 2.7, $P < 0.02$; $t = 1.5$, $P < 0.2$, respectively). They were reported to be free of psychiatric illness requiring consultation (past or present), a history of organic disorder and medication. Conners ratings by the parents, though not directly comparable with those from the patients, indicated an absence of relevant problems in this group as there was no overlap of the scores (mean 0.6, S.D. 0.3) and all were below the criterion of 1.5 [10].

Testing followed approval of the protocol by the clinic management, agreement of the therapists and nursing staff to the tests in principle and the time-point in each case and the cooperation, understanding and consent of the child and the legally responsible adult.

2.2. CB task

CB was measured in a learning task presented on a PC color monitor with a joystick for response. The 'mouse-in-house' game took 5–20 min to perform (details and Fig. 1 in [21,22]; software obtainable from the first author). A 'house' was divided into two 'rooms' by a wall with a door in the center and each room was divided into four areas by walls, through which the mouse could not pass. One to three color panels (18 × 7 mm) appeared, centred above the house at the start of each trial. Small panels displayed the minus and plus points scored during the task.

Session A was the subject's own learning control session and B was the CB session. Subjects were asked to bring the cursor from either room to one of two possible goal spots in the other room. The safe-spot would shimmer yellow and +15 points were awarded (inter-trial interval, 2 s). This was demonstrated during joystick calibration. At the start of each trial one of two sets of color cues associated with the two goals lit up for 1 s. In A there was a set of three colors throughout training. If the subjects did not reach the goal within 8 s they received 5 minus points for each additional second. On attaining the learning criterion (88% in 8 trials without minus points), they proceeded to 21 test trials when the first and third colors were presented alone for response (XYYX design, Table 1). The main measure was the latency to find the goal after the color originally presented on the right minus that on the left. In Session B there were two pairs of colors. After achieving a 50% criterion over eight trials (first phase), a third color was added until the full learning criterion had been reached (second phase). CB would be expected in the response latency to the third (added) color when presented alone in the test phase with respect to the first color (alone), seen from the start of the session. The start positions to the colors alternated and the color sets were presented in a pseudo-random sequence.

CB was measured by comparing the differential response latencies in A and B: (i.e. B test (3rd minus 1st stimulus) minus A test (3rd minus 1st stimulus). This was calculated for the first pair of test stimuli, BA 1; the mean of the first three pairs, BA 1–3; five pairs, BA 1–5, all ten pairs of stimuli, BA 1–10) and the first

Table 1
Training and test presentation of colour panels (designated with letters)

	Learning		Test
Session 1	A B C (88% learn criterion)		A alone, C alone
(CBA)	D E F		D alone, F alone
Session 2	M N (50% learn criterion)	M N O (88% learn criterion)	M alone, O alone
(CBB)	P Q (CBB1)	P Q R (CBB2)	P alone, R alone

For analysis of learning trials in each session and phase, see Section 3; detailed analysis for lateral bias or overshadowing through stimulus frequency and perceptual salience see [21,22].

versus the last three test trials on B (B(1–3) – (8–10)). Positive scores show CB or in the last case the development of 'unblocking'.

2.3. Urine collection

DA, noradrenaline (NA), serotonin (5HT) and their metabolites (homovanillic acid, HVA; 3-methoxy-4-hydroxyphenylglycol, MHPG; 5-hydroxyindoleacetic acid, 5HIAA) were measured in 24 h urine collections (low monoamine diet) on the day between tests A and B. Acidified samples were frozen until analysis with ion exchange liquid chromatography and fluorescence detection. Volume-adjusted measures were expressed as nanograms per gram creatinine per square metre body area to correct for general somatic metabolic rates and large variations of body size [20].

2.4. Data treatment

For CB measures there was no significant departure from homogeneity of variances (Bartlett Chi-square 0.46–2.98, $P = 0.23$–0.79). Data were not distributed significantly different from normal (Kolmgorov-Smirnov $d = 0.051$–0.069). Data analysis used parametric multivariate analysis of variance with repeated measures or covariate for age where appropriate. The locus of significant effects ($P < 0.05$) or trends ($P < 0.1$) was examined by posthoc Tukey tests. Pearson correlation coefficients (rho) were also calculated for the relationships of age or monamine measures to CB and group comparisons were explored with t-tests.

3. Results

3.1. Associative learning

A MANOVA comparing groups and the number of trials used for learning the different task phases showed a tendency for group differences ($F(6,60) = 2.06$, $P = 0.07$; data not shown). There were no differences in the first session (CBA: $F(2,32) = 0.21$). But there was a marginal difference on the two phases of the second session (CBB1, CBB2: $F(2,32) = 2.89/3.24$, $P = 0.07/0.05$). The ADHD group required more trials than the TS group in both cases ($P = 0.038/0.05$, Tukey). For each group increasing age tended to be associated with fewer trials on the first session ($r = -0.55$ to -0.59, $P < 0.055$), but this did not extend to the second session (CBB). This implies that differences in the CB measures below could reflect the longer exposure of the ADHD group to stimuli on the second session, but did not arise per se out of age-related learning differences in general.

3.2. Conditioned blocking (CB)

Fig. 1 indicates that controls showed more CB on the first-trial measure (BA 1) than the other groups, but taking more trials into consideration (BA 1–3 and BA 1–5) only the TS group showed a CB impairment. A MANOVA for group × CB (first, first three, first five trials and unblocking) in a repeated measures design showed no significant main effect of group ($F(2,33) = 1.71$, $P = 0.20$), of measure ($F(3,99) = 1.43$, $P = 0.24$) nor an interaction ($F(6,99) = 1.17$, $P = 0.33$).

The modest CB in healthy children compared to adolescents or young adults is consistent with our previous report [21]. The apparent difference between these children and healthy adolescents, and with the ADHD/TS groups along with the advocacy of a developmental learning delay in ADHD children [27] suggests a closer look at age effects on CB would be worthwhile. We concentrate on the three-trial blocking measure (BA 1–3) which has been found to be the most consistent measure in related studies [21,22].

3.3. Age and conditioned blocking (CB)

Improved CB with increasing age in controls was notably absent in the other groups (e.g. BA1–3, $r = 0.4$, $P < 0.018$ vs. $r = +0.017$ (TS) and $r = -0.065$ (ADHD)). Analysis of variance with a covariate for age was suggestive of a group difference on the three-trial measure (BA 1–3; $F(2,32) = 2.84$, $P = 0.07$). The locus for this trend proved to be less CB in the TS vs. the ADHD or CN groups, as above ($t = 2.24$ and 1.81, $P < 0.036$ and $P < 0.085$, respectively; Fig. 2).

The performance of subjects under and over 11 years of age was examined. TS patients older than 11 years showed markedly less CB than controls in the same age group (-178 vs. $+473$, $t = 3.4$, $P < 0.006$), while the older ADHD patients showed nonsignificantly less CB than controls (Fig. 2). But ADHD patients younger than 11 years tended to show more CB than the 7 younger controls (318 vs. -107, $t = -2.1$, $P = 0.06$).

In summary, with the gradual appearance of CB in controls across the age range 8–14 years, two features of the performance of the patients emerge. First, the absence of normal CB in the TS group, seen as a trend vs ADHD or CN groups as a whole, was significant for subjects over 11 years of age. Second, while older ADHD children tended to show less CB than age-matched controls, those younger than 11 years of age actually showed more CB. As ADHD patients, independent of age, were exposed to more trials on the second session (CBB) this implies the strategy of deploying attention in this group differed from that of controls (see Section 4).

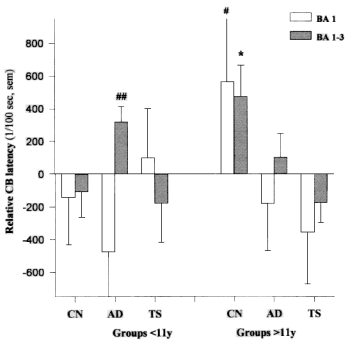

Fig. 2. Relative latency measures of conditioned blocking (CB, S.E.M.) in the first (BA 1) and first three test trials (BA 1–3) in three groups of children (see Fig. 1 legend) under (left) and over 11 years of age (right). # vs. TS, ## vs. CN and TS $0.1 > P > 0.05$, * vs. TS $P < 0.006$.

3.4. Monoamine metabolic status and conditioned blocking (CB)

Could the group differences in cognitive style reflect differences of the status of metabolism of the monoamine neurotransmitters? There were two important metabolic differences between groups (Fig. 3 for data and *t*-tests). First, the ADHD group excreted more 5-HIAA than either the controls or the TS group (Fig. 3, top right): this increases the importance of 5-HT metabolism in the decreased ratio of DA to 5-HT utlization found in this group (HVA/5HIAA ratio; Fig. 3, bottom right): Second, the TS group had double the DA utilization of ADHD or control groups (Fig. 3, bottom left). High DA utilization was a feature of non-medicated TS patients and the HVA/DA ratio was reduced from 20 to 13 in the neuroleptic-treated subgroup (vs. controls t −6.2 to −2.0, $P = 0.0001$ to 0.07; data not shown).

In controls there was an indication of DA metabolism playing a role in information processing related to CB. Increased DA utilization tended to be associated with increased CB (BA1, $r = 0.47$, $P < 0.1$), and an impairment of CB was related with increases of the unmetabolized parent amine (BA 1–5, $r = -0.49$, $P < 0.09$), especially in relation to NA levels (DA/NA, BA 1–3, $r = -0.63$, $P < 0.02$).

In the TS group DA metabolism despite being much higher than in controls, surprisingly showed a similar relationship to CB (BA 1, $r = 0.62$, $P < 0.04$; DA/NA, BA 1–3 and 1–5 $r = -0.6$, $P < 0.07$). However, 5-HT activity related negatively to CB (BA 1, $r = -0.67$, $P < 0.02$; BA 1–3, $r = -0.55$, $P < 0.08$). Separate consideration of medicated and nonmedicated patients informs on these differences. In those free of medication only 5-HT metabolism had a negative association with CB (BA 1, $r = -0.85$ to -0.89, $P = 0.06$–0.04), whereas in those receiving neuroleptic treatment there was an indication that excretion of too much unmetabolized DA, as in controls, had a negative association with CB (BA 1, $r = -0.082$, $P < 0.09$).

The ADHD group provided a contrast to control and TS children with respect to DA and 5-HT activity. Thus, opposite to controls, increasing DA utilization was negatively and increasing DA/NA ratio was positively related to CB (respectively, BA 1, 1–3, 1–5 $r = -0.75$ to -0.83, $P < 0.005$; and BA 1–3, 1–5 $r = +0.52 - 0.59$, $P = 0.08 - 0.04$). Further, contrary to the TS group, ADHD patients tended to show an association between improved CB and excretion of the 5-HT metabolite ($r = +0.5$, $P < 0.1$), especially if this was an increase in relation to DA metabolism (HVA/5HIAA for BA 1–3, 1–5, $r = -0.54$ to -0.71, $P = 0.07$–0.01).

4. Discussion

The main results of this exploratory analysis of the development of CB indicate that, (1) a modest degree of CB develops in normal children at the time of puberty onset (about 11 years of age), (2) CB is not evident in TS children, and that, (3) while young ADHD patients show modest CB (vs. controls), development is impaired with respect to that of controls in the 11–14 year olds. This pattern precludes any simple explanation in terms of IQ differences between ADHD and CN groups, especially as TS patients' IQ did not differ significantly from either of these groups.

At first sight the need or the ability to suppress transiently the processing of added cues in the CB task seems to develop rather late in normal children. This becomes less surprising if one considers that classical conditioning with discrete stimuli can be shown in children under 18 months old, but trace conditioning with overlapping stimuli is only effective as late as 8–9 years of age [32]. Oades et al. [21] in their discussion of developmental changes in the brain that might account for these related cognitive, conditioning functions point to the need for a dialogue between frontal and limbic cortices in controlled attention processes. Limbic cortices, essential in animals for CB [26], mature between 8 and 9 years of age but frontal, cingulate and limbic myelination lags by another 3–4 years [2].

The importance of frontal and cognitive development in this age category is supported by a recent report on

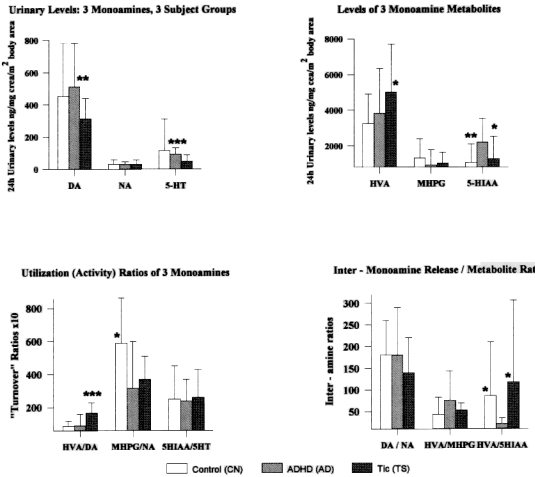

Fig. 3. Monoamine measures (S.D.) in 24 h urine samples from healthy children (CN), or with a diagnosis of ADHD (AD) or Tourette/tic syndrome (TS). Upper left, monoamine levels; upper right, metabolite levels; lower left, utilization ratios; lower right, ratios of catecholamines and monoamine metabolites. The *t*-tests result from a comparison of the extreme values shown for each respective measure: * $0.1 > P > 0.05$, ** $0.05 > P > 0.01$, *** $0.01 > P > 0.001$.

functional MRI measures of frontal function reflecting the expression of working memory [3]. In a small group of 9–11 year-old healthy children, these authors reported that not only the inferior frontal gyrus was activated specifically during the working memory requirement, but that the difference in the signals elicited by the two tasks, absent in the youngest subject (115 months), gradually doubled across subjects spanning the next 2 years of development (118–139 months). The authors advanced explanations encompassing both known developmental decreases in synaptic density and metabolism as well as changes in cognitive strategy. Neuropsychological and topographic event-related potential recording studies have shown that much refinement of frontal inhibitory function occurs after 6 years of age, and particularly between 8 and 12 years of age [5,19,23,25]. Lastly, bearing in mind that monoamine metabolism in children decreases sharply across this age-group, it is of interest that Oades et al. [24] reported that the disruption of frontal DA systems in animals can interfere with the normal expression of CB.

A comparison of our data with the LI data from Lubow and colleagues [12,16] indicate three possible stages in the development of learned inattention styles. The mature information processing strategy of transiently suppressing extra information before learning about it develops between 11 and 18 years of age (here and [21]). Prior to this age (i.e. the 6–11 year age group), novelty attracts, and the subject learns about both stimuli: the consequence is that overall task learning takes longer and CB and LI do not appear (here and [16,21]). But in the 5–6 year olds, under information load, LI appears to occur as result of a lack of capacity or resources to process the channels in parallel. The earliest phase may represent automatic attention processes [15]. Mature LI or CB represent controlled attententional processing [21,22]. The middle phase of development may actually represent a transition from automatic to controlled processing for we see an 'automatic' response to the added cue on the first trial measure (BA 1): the negative values here decrease from younger to older ADHD children. The response over succeeding trials actually incur a modest level of CB, suggesting a delayed activation of controlled processing, as was described and discussed for paranoid schizophrenics [22].

In ADHD children we propose that the earliest phase is delayed. The consequence is that ADHD children aged about 7 to 11 years show better CB than age-matched healthy children. Following this delay, in the

11–14 year old age group ADHD children show the second developmental phase where CB is absent. The proposal that impaired cognitive processes in ADHD children represents delayed development rather than an enduring psychopathological trait remains a matter of active debate (e.g. arguments for a 2 year delay [27]; mixed features [23]; against a delay [28]). Our hypothesis emphasizing the delay predicts that adults with the residual attention deficit syndrome would show normal CB.

The finding of CB in ADHD children by Jones et al. [11] are not inconsistent with our results and interpretation. Their task presentation consisted of three main phases with the 'added-stimlus' present in two of these. Compared to the present study this permitted more time for learning about the added stimulus that is then less 'novel'. This means there would be less difference between groups learning more (e.g. ADHD [4]) and those learning less about incidental or added stimuli (i.e. controls). Further, the ADHD age of 9 years falls into the 7–11 years category of ADHD children that here showed better than average CB.

The important aspect of the CB impairment in TS patients is that it is independent of age and is thus distinguishable from the performance of ADHD patients. This implies that the problem in information processing is more trait-related (i.e. reflects primary diagnostic problems) and less state-related (i.e. the secondary features of attention-deficit symptoms). Among the measures taken, the main feature of the TS group separating them from both ADHD and CN groups was their high rate of DA metabolism. However, this cannot explain the performance difference in a simple way. First, neuroleptic treatment reduced this difference; second, DA utilization was positively associated with CB in control and TS groups alike. However, there are indications that there is an optimum range for the relationship between DA metabolism and CB. Too little activity may impair—in controls there was a negative relationshp with unmetabolized DA levels. Too much activity may impair—unmedicated TS patients with high DA metabolic levels showed less CB than the medicated with decreased DA metabolism.

A crucial, potentially homeostatic mechanism may lie with 5-HT metabolism, considering that it is an inhibitory transmitter impacting on the DA system at the presynaptic level in many parts of the brain [7,17]. Not only was the HVA/5HIAA ratio very high in the TS group, but 5-HT utilization was negatively associated with CB. We propose that the positive association of 5-HT metabolism with CB in the ADHD group may reflect the action of homeostasis, keeping DA activity strictly within normal limits, where there was a tendency for increased DA activity to correlate negatively with CB.

This was an exploratory study and our proposals are tentative. However, they are open for test and an increase of statistical power by replicating the study with more subjects covering a larger age range more densely. A variation in the design could include taking plasma monoamine measures, that may reflect central activity more accurately [13], and taking high and low monoamine activity levels as independent variables in the study of information processing strategies.

Acknowledgements

We are grateful to Dr H. Bussemass and his assistants at the Dr Eberhard Laboratory, Dortmund for the monoamine analysis, J. Altree-Williams and E. Kuske for programming assistance and Dr U. Schall and Professor G. Sartory for their discussion. We thank Dr R. Schepker and Professor C. Eggers for their interest and clinical help. The work was supported in part by the German Research Council (DFG OA 1/4-1).

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