Serotonergic neurotransmission and lapses of attention in children and adolescents with attention deficit hyperactivity disorder: availability of tryptophan influences attentional performance

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Abstract
Deficiencies in serotonergic (5-HT) neurotransmission have frequently been linked to altered attention and memory processes. With attention deficit hyperactivity disorder (ADHD) being associated with impaired attention and working memory, this study investigated the effects of a diminished 5-HT turnover achieved by rapid tryptophan depletion (RTD) on attentional performance in children and adolescents with ADHD. Twenty-two male patients with ADHD (aged 9–15 yr) received the RTD procedure Moja-De and a tryptophan (Trp)-balanced placebo (Pla) in a randomized, double-blind, within-subject crossover design on two separate study days. Lapses of attention (LA) and phasic alertness (PA) were assessed within the test battery for attentional performance under depleted and sham-depleted conditions 120 (T1), 220 (T2) and 300 (T3) min after intake of RTD/Pla. At T1 there was a significant main effect for RTD, indicating more LA under intake of a Trp-balanced Pla compared to diminished 5-HT neurotransmission. For T2/T3 there were no such effects. PA was not affected by the factors RTD/Pla and time. Interactions of 5-HT with other neurotransmitters as possible underlying neurochemical processes could be subject to further investigations involving healthy controls as regards altered attentional performance in children and adolescents.

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Key words: ADHD, lapses of attention, phasic alertness, RTD, serotonin.

Introduction
Altered attention and memory processes were shown to be related to changes in serotonergic (5-HT) neurotransmission, with evidence coming from studies in adults and animals. Patients with attention deficit hyperactivity disorder (ADHD) frequently present with attention problems and deficits in working memory, with these symptoms most likely being associated with changes in catecholaminergic neurotransmission, in particular as represented within a changed dopaminergic turnover. However, there are currently only a few studies examining the effects of changes in 5-HT neurotransmission in children and adolescents. This also applies to ADHD, a condition with deficient attention and other cognitive problems frequently observed in children and adolescents of different ages. Regarding the effects of 5-HT neurotransmission on different attentional processes in patients and healthy subjects the studies published so far indicate effects for 5-HT regulating attentional
modulation of early cortical stimuli (Ahveninen et al. 2003), involuntary attention shifting (Ahveninen et al. 2002), repetition priming (Burgund et al. 2003), memory consolidation (Harrison et al. 2004; Riedel et al. 2003), pre-attentive auditory change detection and the earliest pre-attentive phases of auditory processing (Kahkonen et al. 2005; Kahkonen & Ahveninen, 2002). However, diminished 5-HT neurotransmission as indexed by rapid tryptophan depletion (RTD) did not to have an impact on sustained and divided attention or attentional set-shifting (Mendelsohn et al. 2009). In view of the reduction of central nervous 5-HT it has also been suggested that it leads to altered neuromodulation of cortical and also subcortical regions mediating aspects of associative learning, e.g. the orbitofrontal cortex, the striatum and anterior temporal structures, whereas exteroceptive stimuli could acquire an altered incentive motivational value (Rogers et al. 1999).

The RTD technique has frequently been employed to study the effects of diminished central nervous 5-HT neurotransmission in humans. It allows a lowering of central nervous 5-HT synthesis in humans over a short period of time by administration of an amino-acid drink lacking tryptophan (Trp), the physiological precursor of 5-HT (Bell et al. 2005; Gessa et al. 1974, 1975; Gessa & Tagliamonte, 1974; Hood et al. 2005; Moja et al. 1988). The administered amino acids compete with endogenous Trp in plasma on uptake over the blood–brain barrier as they use the same amino-acid transporter, which in turn results in a diminished central nervous synthesis rate of 5-HT. Research has indicated that RTD could affect mood and cognition within two different pathways as indexed by mood regulation and the processing of emotional information on the one hand, and also a further trajectory for the processing of neural information on the other (Booij et al. 2005). As outlined by Booij et al. (2005) the first trajectory may be more important for the discrimination of a vulnerability to impaired 5-HT neurotransmission, i.e. as achieved by RTD. With respect to specific brain areas being affected by RTD there are also data supporting a model in which a projection of the habenula to the raphe represents a convergent feedback pathway controlling the release of 5-HT throughout the brain, with patients who were sensitive to RTD during different cognitive tasks also showing attenuated task-specific responses in the left amygdala and the left anterior cingulate under RTD (Morris et al. 1999). However, it should also be noted that there are findings not supporting a relationship between RTD and changes in attentional performance as well as verbal and visuo-spatial learning, memory, executive function and other cognitive processes (Gallagher et al. 2003; Hughes et al. 2002, 2003; Shansis et al. 2000).

Within current neuroscientific models of attention independent neural networks and neuromodulators are assumed to subserve different attentional functions, such as alerting, orienting/reorienting, and executive control (Posner & Petersen, 1990). Generally, alerting is defined as achieving and maintaining an alert state. Intrinsic alertness represents the cognitive control of wakefulness and arousal, and is typically assessed by simple reaction times to targets without a preceding warning stimulus and by intra-individual variability of task performance along with lapses of attention (LA). In contrast, phasic alertness (PA) is called for in reaction-time tasks in which a warning stimulus precedes the target, and it represents the ability to increase response readiness subsequent to external cueing. On the brain level, the alerting system has been associated with a network involving the locus coeruleus as the origin of the noradrenergic system (Aston-Jones et al. 1994) as well as with right hemisphere frontal and parietal regions in which the anterior cingulate gyrus and the dorsolateral frontal cortex intrinsically control the brainstem noradrenergic activation system via the reticular nucleus of the thalamus. Recently, it has been shown that boys with ADHD showed reduced neural activation in the right anterior cingulate gyrus but increased brainstem activation during an alertness task, including the locus coeruleus (Konrad et al. 2006). In addition, results from a current pharmaco-fMRI study with healthy adults indicated that 5-HT modulated neural activity in selective brain areas including the thalamus and caudate nucleus during sustained attention (Wingen et al. 2008). These data suggest that neural networks of alertness can be modulated not only by noradrenaline but also by 5-HT in subjects with ADHD, and that neurochemical alterations of these networks might result in behavioural performance changes associated with alertness.

The published data available on changed 5-HT neurotransmission in children and adolescents are rather limited. In previous original publications we reported influences of a diminished central nervous 5-HT synthesis achieved by RTD on aggressive behaviour, reaction time and behavioural disinhibition in children and adolescents with ADHD (Zepf et al. 2008a, b, d). Moreover, we investigated the effects of RTD on mood ratings in children and adolescents with ADHD, indicating no clear effects on emotional state in these patients (Zepf, 2009; Zepf et al. 2009b). However, there are currently no data available
investigating the effects of a diminished central nervous 5-HT synthesis achieved by RTD on attentional performance in children and adolescents with ADHD. In the present study we examined the effects of RTD on attention performance as indexed by LA and PA in a group of male children and adolescents with ADHD at different time-points after RTD and placebo (Pla) intake.

Methods

Sample

The analysed sample comprised 22 male subjects of which 17 had been receiving treatment with methylphenidate, comorbid conduct disorder was also tolerated (n=6). The complete recruitment procedure has been described elsewhere (Zepf et al. 2009b). Diagnostic inclusion criteria were a diagnosis of ADHD according to ICD-10 criteria, and age between 9 and 15 yr. Exclusion criteria were IQ < 85, developmental disorders, substance abuse and any other psychiatric and medical conditions. With the half-life of methylphenidate in children and adolescents being < 3 h medication was omitted on the day preceding each examination day and was taken as prescribed between study days (Swanson & Volkow, 2002). The study was assessed and approved by the Ethics Commission of the Faculty of Medicine of the J. W. Goethe University, and was carried out in accordance with the Helsinki Declaration. The patients and their parents were given a complete description of the study, and written and verbal informed consent were obtained from parents and children. The characteristics of the study sample are presented in Table 1.

Study design

The study design was a double-blind, within-subject, crossover design, with the administration of RTD and a Trp-balanced Pla on two different days. The intake of RTD/Pla was a within-subject repeated-measures factor, and was administered in a randomized and counterbalanced manner by an independent supervisor (RTD intake on day 1 vs. day 2). The patients received the RTD/Pla amino acids in an amino-acid drink on the morning of each study day. Attentional performance was assessed by LA and PA in the test for PA of the test battery for attentional performance (TAP; Zimmermann & Fimm, 2002) at 120 (T1), 220 (T2) and 300 (T3) min after drink intake on each study day. Additional behavioural baseline data (T0 = before RTD/Pla intake) on LA and PA were obtained on each day of the study in order to control for effects of exercise (see Data analysis section).

Depletion procedure

The RTD procedure used in this study, designated Moja-De, was developed for use in children and adolescents (Stadler et al. 2007; Zepf et al. 2008a-d, 2009a,c; Zepf & Poustka, 2008). The boys received Moja-De in an amino-acid drink on one day, on a further day they received a Trp-balanced Pla containing the same amino acids plus Trp. The quantities of the RTD procedure Moja-De are given in Table 2.

Assessment of attention performance

Attention was assessed by LA and PA in the PA test of the TAP which consisted of four trial blocks. LA were defined as significant longer reaction times in all trials indexed by responses exceeding the individual mean reaction time plus 2.35 standard deviations (Zimmermann & Fimm, 2002). The alertness reaction as assessed by the t values for PA which is defined as the subject’s ability to shorten their own reaction time for those blocks/trials with ‘x’ being preceded by a signal tone according to Zimmermann & Fimm (2002). In the first and the last block of the four-block set (blocks 1 and 4, with each block consisting of 20 trials),

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Table 1. Demographic characteristics of the study sample (n = 22) with mean and standard deviation (s.d.)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.9 ± 1.8</td>
<td>40.9 ± 9.2</td>
<td>17.6 ± 2.1</td>
</tr>
</tbody>
</table>

Table 2. Quantities of RTD Moja-De (in grams) as administered in an amino-acid drink containing phenylalanine, leucine, isoleucine, methionine, valine, threonine, and lysine, dosage per 10 kg body weight

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Dosage per 10 kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-Phenylalanine</td>
<td>1.32 g</td>
</tr>
<tr>
<td>l-Leucine</td>
<td>1.32 g</td>
</tr>
<tr>
<td>l-Ileucine</td>
<td>0.84 g</td>
</tr>
<tr>
<td>l-Methionine</td>
<td>0.5 g</td>
</tr>
<tr>
<td>l-Valine</td>
<td>0.96 g</td>
</tr>
<tr>
<td>l-Threonine</td>
<td>0.6 g</td>
</tr>
<tr>
<td>l-Lysine</td>
<td>0.96 g</td>
</tr>
</tbody>
</table>

RTD, Rapid tryptophan depletion.
the boys had to press a button once the symbol ‘x’ appeared on a computer screen. For blocks 2 and 3 the task was again to press the same button once the symbol ‘x’ appeared on the screen, except that the symbol ‘x’ was preceded by a signal tone indicating that ‘x’ would soon be appearing.

**Data analysis**

The level of statistic significance was set and kept at \( p = 0.05 \). Normality of data was assessed using Kolmogorov–Smirnov’s goodness-of-fit test, indicating a normal distribution of data for LA under RTD/Pla at T2 and for the \( t \) values for PA at T1, but no normal distribution for LA under RTD/Pla at T1 and T3 as well as PA for Pla intake at T2 and T3. For PA a total 19 datasets were analysed because of missing data. Attentional performance as indexed by LA and PA under RTD and Pla was compared to the difference from RTD to Pla. When the data for a specific time-point were normally distributed (T1 for PA, T2 for LA) a paired \( t \) test (two-tailed) was implemented for comparison of the effects of the treatment factor RTD/Pla on LA and PA. When the data for a specific time-point did not have a normal distribution a two-tailed Wilcoxon’s test for matched pairs was implemented (T1 and T3 for LA, T2 and T3 for PA). Regarding possible effects of time two-tailed Wilcoxon’s tests were used in order to compare the different time-points as each comparison of subsequent time-points included at least one time-point at which the data for the respective variable was not normally distributed. Baseline data (T0 = before intake of RTD/Pla) were also obtained in order to control for effects of learning and exercise using a paired two-tailed \( t \) test and Wilcoxon’s test (two-tailed), with PA showing a normal distribution (day of RTD and Pla intake) and LA showing no normal distribution at T0 (day of RTD and Pla intake). There were no significant differences between T0 and T1 for LA (day of RTD administration: \( Z = -1.542, p = 0.123 \); day of Pla administration: \( Z = 1.562, p = 0.118 \) and PA (day of RTD administration: \( t = -1.062, p = 0.318, \text{d.f.} = 1, 18 \); day of Pla administration: \( t = -0.150, p = 0.882, \text{d.f.} = 1, 18 \)), indicating no effects of exercise. Moreover, there were no differences in LA (\( Z = -0.963, p = 0.336 \)) and PA (\( Z = -0.447, p = 0.632 \)) at T0 when comparing the time-points before intake of RTD/Pla. The findings were also controlled for possible effects of order as regards RTD/Pla administration using two-tailed Mann–Whitney \( U \) tests (groups: RTD on day 1 vs. RTD on day 2). There were no significant differences observed in LA for T1 (RTD and Pla, n.s.), T2 (RTD and Pla, n.s.) and T3 (RTD and Pla, n.s.) regarding the order of RTD/Pla administration. There were also no effects of order for PA for T1 (RTD and Pla, n.s.), T2 (RTD and Pla, n.s.) and T3 (RTD and Pla, n.s.). Data on errors of anticipation, errors of omission and reaction-time data are presented on a descriptive level in Table 3. We also report Cohen’s \( d \) scores for an estimation of effect sizes (see Table 3). Because of the exploratory approach of this study the data did not receive alpha-adjustment.

**Results**

**Effect of time**

There was no significant difference observed in LA from T1 to T2 (RTD: \( Z = -0.845, p = 0.398 \); Pla: \( Z = -1.154, p = 0.248 \)) and from T2 to T3 (RTD: \( Z = -0.162, p = 0.871 \); Pla: \( Z = -0.145, p = 0.885 \)) for each treatment condition. For PA there was also no significant difference from T1 to T2 (RTD: \( Z = -1.113, p = 0.266 \); Pla: \( Z = -0.363, p = 0.717 \)) and from T2 to T3 (RTD: \( Z = -0.222, p = 0.824 \); Pla: \( Z = -0.440, p = 0.660 \)) under both treatment conditions (Figs 1 and 2).

**Effect of RTD/Pla on LA**

For T1 there was a significant effect for the treatment factor as there were more LA under Pla vs. RTD (\( Z = -2.691, p = 0.007 \), see Fig. 1). At T2 there was no such relationship (\( t = -0.568, p = 0.576, \text{d.f.} = 1, 21 \)) indicating no significant changes in LA under diminished 5-HT neurotransmission compared to Pla intake (see Fig. 1). Moreover, for T3 there were no such relationships (Wilcoxon’s test: \( Z = -0.660, p = 0.509 \)).

**Effect of RTD/Pla on alertness**

For T1 (\( t = 0.442, p = 0.664, \text{d.f.} = 1, 18 \), T2 (\( Z = -0.501, p = 0.616 \)) and T3 (\( Z = -0.026, p = 0.979 \)) there was no significant effect of RTD/Pla administration on \( t \) values for PA in the TAP.

**Discussion**

The data of the present study provide preliminary evidence that Trp-related changes in 5-HT neurotransmission influence attentional processes in children and adolescents with ADHD on the precursor level with respect to the factor time after depletion. These findings are in line with results in adults indicating improved attentional control under Trp depletion as well as under dopamine depletion (Scholes et al. 2007). Following this, reduced tonic central nervous 5-HT activity within specific neural
Table 3. Mean reaction time, errors of anticipation, errors of omission, lapses of attention and t values for phasic alertness (all for whole test) assessed with the test battery for attentional performance for all three time-points of assessment T1, T2 and T3

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RTD (mean ± S.D.)</th>
<th>Min</th>
<th>Max</th>
<th>Mean ± S.D.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td>0.19</td>
<td>321.66 ± 69.46</td>
<td>206.94</td>
<td>520.55</td>
<td>309.05 ± 61.08</td>
<td>222.43</td>
<td>517.20</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>314.99 ± 74.49</td>
<td>218.91</td>
<td>575.35</td>
<td>305.27 ± 60.77</td>
<td>214.90</td>
<td>409.02</td>
</tr>
<tr>
<td></td>
<td>0.28</td>
<td>302.20 ± 54.45</td>
<td>212.51</td>
<td>411.21</td>
<td>319.29 ± 66.73</td>
<td>202.45</td>
<td>440.12</td>
</tr>
<tr>
<td>Errors of anticipation</td>
<td>T1</td>
<td>0.16</td>
<td>2.55 ± 3.67</td>
<td>0</td>
<td>16</td>
<td>3.32 ± 5.96</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.52</td>
<td>2.36 ± 2.46</td>
<td>0</td>
<td>7</td>
<td>4.23 ± 4.81</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.34</td>
<td>2.14 ± 2.69</td>
<td>0</td>
<td>11</td>
<td>3.14 ± 3.15</td>
<td>0</td>
</tr>
<tr>
<td>Errors of omission</td>
<td>T1</td>
<td>n.a.</td>
<td>0.82 ± 1.37</td>
<td>0</td>
<td>5</td>
<td>0.82 ± 1.40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.05</td>
<td>0.45 ± 0.74</td>
<td>0</td>
<td>2</td>
<td>0.41 ± 0.91</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.03</td>
<td>0.86 ± 1.06</td>
<td>0</td>
<td>4</td>
<td>0.90 ± 1.26</td>
<td>0</td>
</tr>
<tr>
<td>Lapses of attention</td>
<td>T1</td>
<td>0.94*</td>
<td>2.64 ± 0.73</td>
<td>1</td>
<td>4</td>
<td>3.41 ± 0.91</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.18</td>
<td>2.86 ± 1.17</td>
<td>0</td>
<td>2</td>
<td>3.09 ± 1.31</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.15</td>
<td>2.81 ± 0.75</td>
<td>2</td>
<td>4</td>
<td>2.95 ± 1.07</td>
<td>1</td>
</tr>
<tr>
<td>Phasic alertness</td>
<td>T1</td>
<td>0.12</td>
<td>59.16 ± 14.42</td>
<td>30</td>
<td>80</td>
<td>57.47 ± 14.42</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.12</td>
<td>57.42 ± 11.67</td>
<td>41</td>
<td>80</td>
<td>56.16 ± 9.42</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.16</td>
<td>55.47 ± 7.57</td>
<td>40</td>
<td>71</td>
<td>56.89 ± 10.53</td>
<td>40</td>
</tr>
</tbody>
</table>

Data are presented with mean ± S.D. with minimum (Min) and maximum (Max). Cohen’s d scores are presented for comparison. Rapid tryptophan depletion (RTD) vs. placebo; n.a., not applicable.
* Indicates significant effects for the treatment factor (RTD/placebo).

Fig. 1. Lapses of attention (with mean and s.d.) within the test battery for attentional performance under rapid tryptophan depletion (■) and placebo (□) at time-points T1, T2 and T3 (* p < 0.01).

Fig. 2. t values for phasic alertness (with mean and s.d.) within the test battery for attentional performance under rapid tryptophan depletion (■) and placebo (□) at T1, T2 and T3.
circuits (i.e. the striatum, anterior cingulate, or prefrontal cortex) may have a critical role in attentional control, possibly by improving gating of information via reducing noise in monoaminergic systems (see Scholes et al. 2007).

The availability of Trp as the physiological precursor amino acid of 5-HT seems to play a decisive role with regard to attentional processes, with the administration of the Trp-balanced Pla resulting in increased LA. An advantage of the methodology used (Moja-De) is that the RTD procedure can be considered as being rather specific, leading to a decrease in central nervous 5-HT synthesis of ~90% within just 1 h after intake (Kewitz, 2003). However, although these data are directly related to the depletion of Trp plasma stores and the directly related reduction in central nervous 5-HT synthesis they cannot help to explain the negative findings observed at T2 and T3 as the mentioned 90% reduction in central nervous 5-HT synthesis remains around this level of reduction for >5 h, which is after T2 and T3. Nevertheless, the present findings add to the existing literature as attentional processes in ADHD were shown to be predominantly related to changed dopaminergic neurotransmission, particularly in frontal areas of the brain. A possible explanation for the present findings could be that a compensatory dopamine release after RTD could have resulted in a short-term improvement in attentional performance. However, this explanation is only speculative, and further investigations using positron emission computer tomography with dopaminergic tracers in combination with RTD could be useful in order to further investigate this particular relationship regarding 5-HT–dopamine interactions. Moreover, it should be noted that the effects of the Pla administration on LA were only detected at one time-point. Following this, the findings need to be replicated in future studies with healthy subjects as well as in different patient populations, which is also a major limitation in this investigation. Moreover, it should also be noted that despite the fact that LA were influenced by changed Trp availability only LA, and no other parameters for attentional performance such as t values for PA, were affected by changes in Trp administration. Regarding further limitations of the study, it should be taken into account that only male subjects were included, prompting the question of whether such findings are also found in female subjects – this will be the subject of a future study at our department. Moreover, at this stage it is unclear if the present findings in children and adolescents can be explained by the factor ADHD as a diagnosis because of the lack of an adequate control group in this investigation. Finally, task-specific characteristics as represented within the TAP may also have contributed to the effects found, making further studies with other attention tasks of particular relevance. The fact that PA was not influenced by RTD could also give rise to task-specific and methodological considerations. This in particular refers to the method used in the present study as it differed from procedures previously used in other investigations studying the effects of changed 5-HT neurotransmission on attentional parameters such as sustained attention (Mendelsohn et al. 2009). Finally, the TAP is only indirectly related to the neuroscientific model of attention as proposed by Posner (see also Posner & Petersen, 1990), which underlines the need for future studies on changed 5-HT neurotransmission and its relationship to changed attentional processes.

In sum the findings of the present study indicate increased LA under PLA intake, but no clear effects of RTD on PA. The relationship between ADHD and disturbed alerting functions has been investigated extensively in a wealth of studies (Brown & McMullen, 2001; Cao et al. 2008; Cortese et al. 2006, 2007, 2008; Duane, 1993; George et al. 2005; Hanisch et al. 2004; Konrad et al. 2004; Lecendreux et al. 2000). In particular, patients with ADHD presented with a higher error rate and a larger within-subject reaction-time variability (Cao et al. 2008). Moreover, imaging studies indicating less activation in frontal brain regions such as the middle and superior frontal gyrus, and decreased activation in parietal brain regions as represented by the inferior parietal lobe and the precuneus were found (Cao et al. 2008). In addition, diminished activity in the putamen was detected in ADHD (Cao et al. 2008). Regarding the neuroanatomical position of intrinsic and PA one study indicated that both cognitive parameters were associated with the right hemisphere, in particular the anterior cingulate, the dorsolateral cortex and the brainstem (Sturm et al. 1999). These findings combined suggest deficits in alerting functions in ADHD, and that these deficits could be associated with disturbed activations in frontal and parietal regions related to top-down attention-control processes. In view of the neurochemical underpinnings related to ADHD and disturbed alerting functions it should be noted that noradrenergic activation in particular, rather than 5-HT, is associated with attentional performance as indexed by the maintenance of arousal (Biederman & Spencer, 1999). Moreover, brain-imaging data indicate a dysfunction in fronto-subcortical pathways in ADHD with an underlying noradrenergic dysregulation. Finally, noradrenergic functioning was shown to modulate higher cortical functions such as attention, alertness, vigilance...
and executive functions (Biederman & Spencer, 1999). In the light of these findings the data on the RTD effect on PA in the present study are somewhat plausible from a neurochemical viewpoint. However, further investigations combining imaging techniques with challenge procedures such as RTD and following behavioural (alertness) assessment could be useful in order to further disentangle the relationship between disturbed alertness processes and changes in noradrenergic as well as serotonergic neurotransmission in ADHD. Interestingly, we previously found that within a treatment trial with sertraline in children with anxiety disorders, contrary to findings in adults, no negative effects on attentional performance could be observed (Gunther et al. 2005). Thus, it can be speculated that there are age-dependent differences in the modulation of attentional processes by manipulations of the serotonergic system.

In summary, the present study showed deficiencies in attentional performance under changed administration of the 5-HT precursor amino-acid Trp in children and adolescents with ADHD. Future research is warranted in order to address the effects of 5-HT and Trp on attentional processes in ADHD as a predominantly catecholaminergic disorder, particularly with regard to 5-HT–dopamine interactions and related compensatory processes, and also in comparison with healthy controls.

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