Research Report

Methylphenidate normalizes emotional processing in adult patients with attention-deficit/hyperactivity disorder: Preliminary findings

Annette Conzelmanna, Eva Woidicha, Ronald F. Mucha, Peter Weyers, Christian P. Jacob, Klaus-Peter Lesch, Paul Pauli

ARTICLE INFO

Article history:
Accepted 30 December 2010
Available online 6 January 2011

Keywords:
ADHD
Emotion
Methylphenidate
Startle reflex

ABSTRACT

Emotional-motivational dysfunctions may significantly contribute to symptoms of attention-deficit/hyperactivity disorder (ADHD). Hyperactive-impulsive symptoms and sensation seeking could be the result of a search for reinforcers, and cognitive dysfunctions might be due to a low motivational drive. Emotional-motivational dysfunctions could also explain social dysfunctions in ADHD patients because they may lead to misinterpretations of emotional and social clues. Since methylphenidate (MPH) is the first choice as a pharmacological treatment in ADHD, we examined its influence on dysfunctional emotional processes. 13 adult ADHD patients were examined twice, without and after intake of MPH according to their personal medication regimen. The affect-modulated startle paradigm was used to assess physiological (affect-modulated startle response) and subjective (valence and arousal ratings) responses to pleasant, neutral and unpleasant visual stimuli. Healthy controls displayed affective startle modulation as expected, with startle attenuation and potentiation while watching pleasant and unpleasant pictures, respectively. In contrast, unmedicated ADHD patients displayed deficient responses to pleasant stimuli; no startle attenuation during the exposure to pleasant pictures was observed. However, MPH reinstated a normal affective startle modulation, as indicated by attenuation and potentiation associated with pleasant and unpleasant pictures, respectively. Valence and arousal ratings of patients were not affected by MPH. The data suggest that MPH as first choice treatment in ADHD has a positive impact on emotional processes in adult ADHD patients and points to the clinical relevance of emotional-dysfunctions in ADHD.

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* Corresponding author. Department of Psychology, Biological Psychology, Clinical Psychology and Psychotherapy, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany. Fax: +49 931 312733.
E-mail address: pauli@psychologie.uni-wuerzburg.de (P. Pauli).

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1. **Introduction**

With 3–9% of school-aged children suffering from symptoms like hyperactivity, impulsivity, and inattention, attention deficit/hyperactivity disorder (ADHD) is one of the most common diseases during childhood. Thirty to sixty percent of these patients still show residual ADHD symptoms as adults (Barkley, 1990).

The etiology of ADHD is not clearly understood but there is growing evidence that emotional–motivational deficits play an important role. Hyperactivity, impulsivity, and sensation seeking might be interpreted as the search for reinforcers (Johansen et al., 2002) or might result from a steeper and shorter reinforcement gradient (Sagvolden et al., 1998). These ADHD symptoms might also be associated with a reduced reactivity towards punishment or negative consequences (Williams et al., 2008). ADHD patients were reported to have interpersonal problems (Rapport et al., 2002) as well as deficient social and emotional competences. According to Barkley (1997), ADHD patients do have accurate interpersonal perceptual awareness but cannot respond appropriately to emotional clues. However, Casey (1996) pointed out that ADHD children have difficulties in identifying their own emotional expressions compared to healthy controls, and Becker et al. (1993) found evidence for deficits not only in terms of emotional self-regulation but also in terms of interpersonal perceptual awareness. Consequences of these deficits in emotional processes may be lateness, absenteeism, and significantly more errors during work as well as unstable relations and friendships or increased risks of substance or drug abuse (Harpin, 2005). In addition, it was found that executive functions in ADHD can be positively influenced by incentives (Kohls et al., 2009; Andreou et al., 2007) and ADHD patients benefit from emotion regulation trainings and token system in ADHD therapy (Philipsen et al., 2007; Reitman et al., 2001).

We (Conzelmann et al., 2009) recently found clear evidence for emotional dysfunctions in adult ADHD as reflected in a lack of startle attenuation in response to positive stimuli in patients of the combined and the hyperactive types. The latter group also exhibited deficits in startle potentiation in response to negative stimuli. Dopaminergic dysfunctions are supposed to underly these emotional deficits. Generally agreed are ADHD related dysfunctions in the meso-limbic-cortical and in the nigro-striatal dopamine branch (Castellanos et al., 1996; Hesse et al., 2009; Rubia et al., 1999; Vaidya et al., 1998). Confining this assumption, neuroimaging studies revealed increased dopamine transporter level density in adult ADHD patients (Dougerthy et al., 1999; Krause et al., 2000), and never medicated adults with ADHD were found by PET to show diminished F-DOPA reuptake in the left and medial side of the cortex (Ernst et al., 1998). It is speculated that elevated dopamine levels in ADHD patients could lead over lifetime to increased dopamine transporter levels as an adaptive mechanism. Alternatively, initially increased dopamine transporter density could result in a decreased dopaminergic level (Solanto, 2000). Animal studies support both trajectories. Rats with artificially induced dopaminergic hyperfunction show the same hyperactive behavior as animals with induced dopaminergic hypofunction (Castellanos and Tannock, 2002).

Despite several discussions about the etiology of ADHD, there is no doubt about the efficacy of methylphenidate (MPH) treating the major symptoms of ADHD. Like cocaine, MPH increases extracellular dopamine levels by mainly blocking the dopamine transporter (Seeman and Madras, 1998; Volkow et al., 1995). Due to dopaminergic projections of the nucleus accumbens to prefrontal areas, ADHD symptoms like inattention, hyperactivity, and impulsivity improve in children (Kempton et al., 1999; Lawrence et al., 2005) and adults (Medori et al., 2008; Spencer et al., 2005). According to Schultz (1994), the dopaminergic system plays an important role in emotional processing and this may explain ADHD related emotional dysfunctions and a positive impact of MPH on emotional dysfunctions in ADHD. Concerning the impact of methylphenidate on emotional processing, several studies indicated some positive effects in patients suffering from major depressive symptoms and in older, somatically ill patients resulting in a higher quality of life (e.g., Wallace et al., 1995). In bipolar depression, methylphenidate was found to have a stabilizing mood effect (El-Mallakh, 2000). Concerning ADHD, most studies focused on MPH effects on social dysfunctions. Negative social behaviors could be significantly reduced by MPH treatment which also seemed to be more effective than any behavioral training (e.g., Gillberg et al., 1997).

To get objective information about emotional processes, the affect-modulated startle response is a well suited biospsychological measure (Amrhein et al., 2004), also because its neurobiological foundation is well-known (Yeomans and Frankland, 1996). Acoustic startle responses can be measured in humans with electromyography (EMG) of the orbicularis oculi muscle elicited by a sudden noise triggering an eyeblink. Healthy subjects normally exhibit a startle response modulation related to their affective state: the startle response is attenuated during positive and potentiated during negative emotional states. Structures like the nucleus accumbens and the amygdala seem to be relevant for the acoustic affect-modulated startle response (Pissiota et al., 2003) and importantly, both structures are discussed as relevant for emotional–motivational deficits in ADHD (Barkley, 1997). Hence, we used the affect-modulated startle paradigm to examine emotional dysfunctions in ADHD and found deficient emotional processing in adult ADHD patients from the combined and hyperactive/impulsive type (Conzelmann et al., 2009).

To assess whether MPH, the pharmacological treatment of choice for ADHD, affects emotional deficits related to ADHD, we reinvestigated 15 adult ADHD patients; they were firstly examined by Conzelmann et al. (2009) without any medication. These reinvestigated 15 patients were selected on the basis of deficits in startle modulation during the first examination. This strategy seems appropriate as a first step to effectively explore the impact of MPH on emotional processing. Positive findings would justify a large double blind randomized study with all its impact on patients and their treatment. Startle responses and verbal rating data of both test sessions, one with and one without MPH, were compared with the data of matched healthy controls who also took part in the study of Conzelmann et al. (2009). We expected that MPH normalizes the emotional deficits related to ADHD leading to a startle response modulation comparable to healthy controls.
2. Results

2.1. Sample characteristics

As a consequence of the matching procedure, ADHD patients and healthy controls did not differ in age [patients: M = 44.77, SD = 8.318; controls: M = 43.69, SD = 7.696, t = .343, df = 24, p = .735], in IQ (MWT-B) [patients: M = 120.46, SD = 15.83; controls: M = 113.69, SD = 11.41, t = 1.251, df = 24, p = .223] and in gender distribution [x^2(1) = .001, p = 1.000].

2.2. Affective startle modulation

Fig. 1 depicts the affective startle modulation during pleasant, neutral and unpleasant pictures for patients without and with methylphenidate and healthy controls. The effect of methylphenidate on the affective startle modulation is reflected on the one hand by significant valence x group interactions for the comparison between the medicated and unmedicated state of the patients [F(2, 24) = 7.200, p < .004] and between the unmedicated patients and healthy controls [F(2, 48) = 3.671, p = .033], while with MPH the patients and healthy controls did not differ in affective startle modulation [F(2, 48) = 0.112, p = .988].

Further analyses were conducted to clarify the valence x group interaction for the comparison between the unmedicated and medicated state of the patients. The valence effect was significant in the unmedicated [F(2, 24) = 18.270, p < .001] as well as in the medicated condition [F(2, 24) = 8.759, p < .001]. However, post hoc trend analyses of the valence effect in the unmedicated patients revealed a significant linear [F(1, 12) = 12.335, p = .004] as well as a significant quadratic trend [F(1, 12) = 28.748, p < .001]. Under the influence of MPH, the startle modulation of these patients only displayed a significant linear [F(1, 12) = 13.357, p < .003], but no significant quadratic trend [F(1, 12) = 0.213, p = .653]; when medicated, patients showed a decreased startle response due to positive and an increased startle reaction due to negative pictures compared to neutral ones.

Further analyses were conducted to clarify the valence x group interaction of the comparison between the patients unmedicated and healthy controls. The valence effect was significant in controls [F(1, 24) = 8.998, p < .001], who exhibited a significant linear [F(1, 12) = 16.280, p = .002] but no quadratic trend [F(1, 12) = 0.247, p = .628] indicating an increase in startle amplitude as picture valence became more unpleasant. Thus, ADHD patients unmedicated, who showed a linear and quadratic startle modulation, differed from both, their reactions with MPH and healthy controls, while their reactions with MPH with a linear startle modulation only did not differ from the controls.

Concerning the main effect group, neither the comparison of the medicated and unmedicated states of the patients [F(1, 12) = 3.771, p = .076] nor the comparison of healthy controls and patients unmedicated [F(1, 24) = 0.933, p = .344] and healthy controls and patients medicated [F(1, 24) = 1.208, p = .283] did reveal any significant difference.

2.3. Habituation and baseline startle response

Analyses revealed no main group effects and no group x time interaction, only time effects were significant (medicated compared to unmedicated state of the patients, F(5, 60) = 20.448, p < .001; patients unmedicated compared to healthy controls, F(5, 120) = 11.971, p < .001; and patients medicated compared to healthy controls, F(5, 120) = 7.685, p < .001). These results indicate that overall the mean baseline startle magnitude declined over time, indicating normal startle responses and their habituation.

2.4. Affective rating

Fig. 2a depicts valence ratings and Fig. 2b displays arousal ratings for the emotional picture categories of all groups.

The ANOVAs for the valence rating showed only significant valence effects for all performed analysis (all ps < .001; no other effect reached significance).

Overall, valence ratings given by the patients unmedicated and medicated and healthy controls corresponded with a priori categories. Trend analysis revealed in all cases a linear (patients without MPH: [F(1, 12) = .44.309, p < .001]; patients with MPH: [F(1, 12) = .65.630, p < .001]; and healthy controls: [F(1, 12) = .135.064, p < .001]) as well as a quadratic trend (patients without MPH: [F(1, 12) = 4.402, p = .058]; patients with MPH: [F(1, 12) = 5.829, p = .033] and healthy controls: [F(1, 12) = 15.348, p = .002]).

ANOVAs assessing arousal ratings also displayed results as expected. Only the valence effects were significant (all ps < .001; no other effects reached significance). Trend analysis revealed no significant linear trend for the patients unmedicated [F(1, 12) = 1.260, p = .284] and medicated [F(1, 12) = 3.545, p = .084] but a significant linear trend for healthy controls [F(1, 12) = 7.015, p = .021]. With or without MPH the patients and the healthy controls displayed a significant quadratic trend (patients without MPH: [F(1, 12) = .21.427, p = .001]; patients with MPH: [F(1, 12) = 12.946, p = .004]; and healthy controls: [F(1, 12) = 90.272, p < .001]) with higher ratings for both emotional stimuli compared to neutral pictures.

3. Discussion

The present work is a first attempt to assess the impact of methylphenidate (MPH) on emotional deficits in adult ADHD

![Fig. 1 - Affect-modulated startle response. Mean (± SE) affect-modulated startle response during presentation of pleasant, neutral and unpleasant pictures of ADHD patients without and under the influence of methylphenidate and healthy control subjects.](image-url)
patients as indicated by the affect-modulated startle paradigm (Conzelmann et al., 2009). A subsample of patients with deficits in affective startle modulation firstly assessed by Conzelmann et al. (2009), was reassessed after the intake of MPH. MPH did eliminate the previously observed emotional deficit.

With MPH, the ADHD patients’ affective startle modulation was comparable to the modulation shown by the healthy control subjects, while without MPH the patients differed from the controls due to the lack of startle attenuation related to pleasant stimuli.

These findings deliver hints that MPH does have a positive impact on emotional dysfunctions in ADHD. Results are in line with the assumed dopaminergic dysfunctionality in ADHD (Castellanos et al., 1996) and the fact that dopamine is a key neurotransmitter in emotional processing (Nieoullon and Coquerel, 2003). Accordingly, MPH presumably ameliorates emotional dysfunction due to its impact on dopaminergic functionality (Seeman and Madras, 1998).

Several studies found a positive impact of MPH on the major ADHD symptoms of inattention, hyperactivity and impulsivity in adult patients (Medori et al., 2008; Spencer et al., 2005). Others demonstrated positive effects of this stimulant on emotional processes in depression (Joyce, 1986; Kaufmann et al., 1984; Wallace et al., 1995) as well as in ADHD (Gadow et al., 1995; Gillberg et al., 1997; Hinshaw et al., 1992).

Yet the present study found effects on objective biological parameters (startle modulation) assessing emotional processes.

MPH had no effect on the emotional ratings, where untreated ADHD patients are also not impaired. Accordingly, objective biopsychological data indicate that emotional deficits of ADHD patients improved due to the intake of their MPH supplement, whereas subjective ratings did not change. This dissociation in findings between the biological measure “startle response” and the verbal ratings may be related to the fact that verbal reports are mostly based on cognitive evaluations and social requirements, factors which may ameliorate group differences.

The validity of our results is supported by the general comparability of groups. Patients and healthy controls did not differ in age, gender and baseline startle responses. Moreover, the affect-modulated startle responses displayed by healthy controls and the patients with the intake of MPH are in line with the literature (Geyer and Braff, 1982; Lang et al., 1990), as well as the startle habituation of healthy controls and of ADHD patients (Ornitz et al., 1997). These findings indicate that all participants were compliant and attentive, explaining that the observed deficits in affective startle modulation in the patients unmedicated are emotion specific and not due to general effects.

Given that our study examined a very small sample size, we mainly focused on high arousing stimuli. Furthermore, the ADHD participants were not tested blind in a cross-over design. In addition, we compared existing data of patients and controls with new data of the same patients medicated with MPH about 2 to 3 years later where they were still in our medical care because of their ADHD symptoms. Therefore, our findings should be seen as preliminary.

However, our approach is justifiable as a first proof of efficacy. The present positive findings justify the next step, a double-blind, cross-over, placebo-controlled design realized with a larger sample of ADHD patients. With this preliminary study proving our paradigm and MPH effects, future research in this field is justified.

Our preliminary findings suggest a positive impact of MPH on emotional processing in adult ADHD patients which might contribute to the decrease in ADHD symptoms by MPH. As MPH is the first choice treatment in ADHD, the results at the same time point to the clinical relevance of emotional–motivational dysfunctions in ADHD. Further investigations might unravel the relevance of our findings for the etiology of ADHD and thus might help to find new interventions.

4. Experimental procedures

4.1. Participants

Fifteen adult ADHD patients were chosen from the sample examined by Conzelmann et al. (2009) on the basis of deficits in the affect-modulated startle response without MPH. In addition, 15 age and gender matched control participants were selected from this sample. Of these 15 patients, 14 (6 female) had the combined type and one patient (female) had the
hyperactive type. These patients, still in our medical care, were reinvited to participate in a second assessment 2 to 3 years later but this time under MPH. Two patients (2 males of the combined type) had to be excluded due to a high number of zero startle responses (more than 2.5 standard deviations from the samples’ mean) during the second examination. In order to keep a matched control group, the two matched healthy controls were also excluded.

All patients were in- or outpatients of the Department of Psychiatry and Psychotherapy and met full DSM-IV diagnostic criteria for both current and childhood ADHD. All participants completed the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II) for axis I and II psychiatric disorders. For patients, inclusion criteria were childhood and adult ADHD according to the DSM-IV symptom list and onset before the age of 7 years. Exclusion criteria for patients as well as for control subjects were: Age below 18 and above 60 years, IQ level below 80 (Lehrl, 1989: Mehrfachwahl-Wortschatz-Intelligenztest MWT-B.), severe somatic disorders or hearing problems, or alcohol or drug consumption before the study. Additional exclusion criteria for controls were a life-time or a current SCID-I or SCID-II diagnosis.

For the first session, all patients did withdraw MPH medication at least four days in advance. For the second session, all patients took their normal prescribed form and dose of MPH medication one hour before assessment (including immediate release and extended release capsules; see Table 1). We did not change the medication since this preliminary study was designed to ensure a minimum of impairment for the patients and because a clinically optimal dose appeared to be an interesting starting point to investigate MPH influences on the assumed underlying emotional dysfunctions. We investigated the patients one hour after medication intake as it is known that at this time point the efficacy of methylphenidate is ensured in immediate but also sustained release capsules. For the sustained release capsules this means a sudden release of MPH of 22% for Concerta and 50% for Medikinet retard (Benkert and Hippius, 2007).

Participants got the advice not to eat or drink at least two hours previously to the final session. Written informed consent was obtained from all participants for each experimental session separately.

4.2. Procedure

All participants underwent the same experimental procedure, ADHD patients twice, first without MPH (see Conzelmann et al., 2009) and a second time with their normal MPH doses taken one hour before the investigation; controls were only examined once, (see Conzelmann et al., 2009).

The experimental procedure was as follows: After familiarization with the experimental procedure, the startle experiment commenced. 18 pleasant, 18 neutral and 18 unpleasant pictures from the International Affective Picture System (IAPS; Lang et al., 2005) were accompanied by startle probes (50 ms of 95 dB white noise with an instantaneous rise time presented with Beyerdynamic DT 331 headphones, Heilbronn, Germany). Six pictures of each valence category were of low, medium and high arousal, respectively. Additional six positive, neutral and unpleasant pictures were presented without a startle probe to reduce its predictability. Pictures were shown for 8 s and startle probes were presented 2.5, 4.0, or 5.5 s after picture onset. Pictures were separated by variable intervals with an average of 25 s with 18 startle probes 8 or 12 s after picture offset equally distributed across the study. In order to enable the comparison of valence and arousal levels for men and women, 81% of the pictures were exactly the same or of comparable content, while 19% of the pictures differed due to their sex specific content. Six pseudo randomized picture orders were used with not more than two consecutive pictures of the same valence or the same startle onset.

Then, pictures were presented again in a free-viewing condition and subjects were asked to rate the pictures’ valence (1=highly unpleasant, and 9=highly pleasant) and arousal (1=calm, and 9=excited) using SAM scales (Self-Assessment-Manikin) (Lang, 1980).

A 60 dB white background noise was present continuously during the whole experiment (white noise generator, Lafayette Instruments Co., Lafayette, Indiana). To ensure that participants accomplished the picture processing task, subjects were monitored via camera. All experimental procedures were run by ERTS (Experimental Run Time System, Version 3.32, Berisoft Cooperation, Frankfurt, Germany).

4.3. Physiological recordings

Startle response EMG was measured from the left orbicularis oculi muscle with a Vitaport II system (Becker, Karlsruhe,
Germany; sampling rate 512 Hz with high- and low-pass filter of 0.015 s and 2200 Hz). Startle magnitude was quantified as the difference between the highest peak 19.5 to 151.5 ms after and the average across 19.5 ms before startle probe presentation. Before analyzing the data with an interactive program (Matlab, The MathWorks, München, Germany), the signals were rectified, stored at 256 Hz and smoothed with a time constant of 100 ms. Then, physiological recordings were individually z-standardized (mean = 0, standard deviation = 1) and T-transformed (mean = 50, standard deviation = 10) for the affect-modulated startle response data. To assess baseline startle reactions, the habituation data for startle stimuli in the intertrial intervals refer on unstandardized raw data. For further details see Conzelmann et al. (2009).

4.4. Data analysis

Socio-demographic data were evaluated with t-tests with group (patients and controls) as between-subject factor. Analyses of the experimental data were focused on the six high arousing stimuli of each valence category. This was done as it is known that affect-modulated acoustic startle response is larger with an increase in arousal (Cuthbert et al., 1996; Geier et al., 2000), and our small sample size only allows detecting rather strong effects. Affect-modulated startle, valence and arousal ratings were analyzed with repeated measures ANOVAs with picture valence (pleasant, neutral, and unpleasant) as a within-subject factor. Using this statistical method, we compared the patients unmedicated and medicated with the ANOVA and the additional within-subject factor group (repeated measurement). Furthermore, we compared the data of the patients medicated and unmedicated with the controls with the ANOVA and the additional between-subjects factor group. Significant valence effects were further examined for linear and quadratic trends to register alterations of responses in relation to the emotional stimulus material.

Baseline startle response (assessed in the intertrial intervals, ITIs) and its habituation were evaluated with an ANOVA with measurement time (T1 to T6; the 18 ITI startle responses were divided in 6 measurement times each being the mean of three consecutive startle responses) as within-subject factor. For the comparison between the patients’ data medicated and unmedicated the additional within-subject factor group was used and for the comparison with controls the factor group functioned as a between-subjects factor. Significant time effects were evaluated by trend analyses. Alpha level was set at .05, using Greenhouse–Geisser corrections where appropriate. We also conducted all analyses additionally including the between-subjects factor gender. However, as gender never influenced our found group effects, we report the analyses without the factor gender.

Statement of interest

All authors reported no biomedical financial interests or potential conflicts of interests.

Ethical considerations

This study is in line with the Declaration of Helsinki and each subject gave written informed consent before they took part.

Acknowledgment

This work was supported by the German Research Foundation (DFG; KFO 125/1).

Appendix A

The following were the 72 pictures by the International Affective Picture System (IAPS) number separated for females and males. Women: 7820, 6160, 2120, 5460, 9920, 3170, 7010, 7200, 1811, 7190, 4660, 2057, 7020, 3150, 7050, 2205, 9520, 7175, 2221, 4680, 8370, 7000, 7205, 8030, 5830, 9700, 4640, 4641, 1270, 5533, 6550, 7270, 4510, 7004, 7237, 6312, 5621, 6530, 6241, 9250, 5629, 7950, 9160, 3062, 2750, 8490, 1090, 2691, 4613, 8180, 1590, 2720, 2200, 7185; Filler Pictures: 9910, 7182, 7160, 5480, 3080, 7283, 9620, 7002, 5660, 1540, 4572, 8034, 7031, 9008, 6360, 9440, 2480, 8496. Men: 7820, 6160, 2120, 5460, 9920, 3170, 7010, 7200, 1811, 7190, 4660, 2057, 7020, 3150, 7050, 2205, 9520, 7175, 2221, 4680, 8370, 7000, 7205, 8030, 5830, 9700, 4650, 4674, 1274, 5534, 3530, 7330, 4290, 7080, 7187, 6370, 8080, 3010, 6230, 3140, 5260, 7110, 9410, 3000, 4180, 2053, 6150, 3103, 7180, 5700, 7550, 8510, 7130, 9040; Filler Pictures: 9910, 7182, 7160, 5480, 3080, 7283, 9620, 7002, 5660, 1540, 4572, 8034, 7031, 9008, 6360, 9440, 2480, 8496.

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