Original Article

A multicentre randomized controlled trial on trans-generational attention deficit/hyperactivity disorder (ADHD) in mothers and children (AIMAC): an exploratory analysis of predictors and moderators of treatment outcome

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Abstract: *Objective:* We examined predictors and moderators of treatment outcome in mothers and children diagnosed with ADHD in a large multicentre RCT. *Method:* In total, 144 mother-child dyads with ADHD were randomly assigned to either a maternal ADHD treatment (group psychotherapy and open methylphenidate medication, TG) or to a control treatment (individual counselling without psycho- or pharmacotherapy, CG). After maternal ADHD treatment, parent-child training (PCT) for all mother-child dyads was added. The final analysis set was based on 123 dyads with completed primary outcome assessments (TG: *n* = 67, CG: *n* = 56). The primary outcome was the change in each child's externalizing symptoms. Multiple linear regression analyses were performed. *Results:* The severity of the child's externalizing problem behaviour in the family at baseline predicted more externalizing symptoms in the child after PCT, independent of maternal treatment. When mothers had a comorbid depression, TG children showed more externalizing symptoms after PCT than CG children of depressive mothers. No differences between the treatment arms were seen in the mothers without comorbid depression. *Conclusions:* Severely impaired mothers with ADHD and depressive disorder are likely to need additional disorder-specific treatment for their comorbid psychiatric disorders to effectively transfer the contents of the PCT to the home situation (CCTISRCTN73911400).

Keywords: Parental ADHD, parent-child training, predictor, moderator, outcome

Eine multizentrische, randomisiert-kontrollierte Studie zur transgenerationalen Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) bei Müttern und Kindern (AIMAC): eine explorative Analyse von Prädiktoren und Moderatoren

Zusammenfassung: *Fragestellung:* Ziel der multizentrischen randomisiert-kontrollierten Studie war die Untersuchung von Prädiktoren und Moderatoren des Behandlungserfolgs bei Müttern und Kindern mit ADHS. *Methodik:* 144 Mutter-Kind-Paaren mit jeweils von ADHS betroffenen Müttern und Kindern wurden zwei unterschiedlichen Bedingungen zur Behandlung der ADHS der Mutter randomisiert zugewiesen (Behandlungsgruppe: Gruppentherapie in Kombination mit offener Medikation mit Methylphenidat; Kontrollgruppe: stützende unspezifische Gespräche). Alle Mutter-Kind-Paare erhielten nach der Behandlung der Mutter zusätzlich ein Elterntraining zur Behandlung der ADHS des Kindes. Die Analysen basieren auf 123 Mutter-Kind-Paaren (TG: *n* = 67, CG: *n* = 56). Primäre Zielgröße war die Veränderung des externalen Problemverhaltens des Kindes. Es wurden multiple lineare Regressionsanalysen durchgeführt. *Ergebnisse:* Die Schwere des externalisierenden Problemverhaltens des Kindes in der Familie bei Baseline sagte unabhängig von der Behandlungsbedingung der Mutter stärkere externalisierende Symptome beim Kind nach dem Mutter-Kind-Training vorher. Kinder von Müttern der Behandlungsgruppe mit komorbider Depression zeigten mehr externalisierende Symptome nach dem Elterntraining als Kinder von Müttern der Kontrollgruppe mit komorbider Depression. Es zeigten sich keine Unterschiede zwischen den Behandlungsbedingungen bei Müttern ohne komorbide Depression. *Schlussfolgerungen:* Schwer beeinträchtigte Mütter mit ADHS und komorbider Depression scheinen eine zusätzliche störungsspezifische Behandlung ihrer komorbiden psychiatrischen Störung zu benötigen, um die Inhalte des Mutter-Kind-Trainings effektiv in den Alltag integrieren zu können (CCT-ISRCTN73911400).

Schlüsselwörter: Elterliches ADHS, Eltern-Kind-Training, Prädiktor, Moderator, Outcome

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a frequent and heritable neurodevelopmental disorder that affects approximately 5% of all children worldwide (Faraone et al., 2006). It is characterized by the core symptoms of inattention, impulsivity, and hyperactivity (APA, 2013). Longitudinal studies have shown that, in approximately 50% of cases, ADHD persists into adulthood (Fayyad et al., 2007). Due to a high heritability of ADHD (Biederman, & Faraone, 2005), both children and their parents are frequently affected by ADHD. ADHD in parents has a significant impact on parent-child interactions, parenting style, and family functioning (Weiss et al., 2000). Parental ADHD seems to be relevant for effective ADHD intervention for the child as well (Chronis-Tuscano, et al., 2016). In many studies, parental ADHD has been found to predict diminished child behavioural treatment responses (for example see Wang et al., 2014). In regard to maternal characteristics, more severe maternal ADHD seems to complicate an improvement of the child's ADHD symptoms after PCT (Parent-child training) (Sonuga-Barke, Daley, & Thompson, 2002). It has also been shown that high levels of maternal depression are linked with negative outcomes of PCT (Hinshaw, 2007; Lee, Niew, Yang, Chen, & Lin, 2012). However, so far, the influence of maternal characteristics has been significantly less investigated than other aspects.

In a multicentre randomized controlled trial (RCT), we investigated the effect of intensive multimodal treatment for mothers with ADHD (group psychotherapy plus open methylphenidate (MPH) treatment) combined with individual PCT, targeting the externalizing symptoms of the child. We found the multimodal treatment approach to be superior to counselling without psychotherapeutic or pharmacological interventions with respect to the improvement of maternal ADHD and related psychopathology. Though the severity of the externalizing symptoms of the children improved in both groups after PCT, there were no significant group differences between the two maternal treatment conditions regarding the child's symptoms (for details please see Jans et al., 2015). However, the variability in each child's outcome was still high, with some children showing more improvement than others, leading to the question of whether predictors and moderating factors of PCT exist, which could have contributed to these varying treatment effects.

Generally, studies focusing on predictor or moderating variables of treatment for children's externalizing behaviour produced, to some extent, conflicting results. For example, some studies found a prognostic influence of a child's age (Ollendick et al., 2016), sex (Fossum, Morch, Handegård, Drugli, & Larsson, 2009; Lavigne et al., 2008) and/or the severity of externalizing symptoms (Hautmann, Eichelberger, Hanisch, Plück, Walter, & Döpfner, 2010; Hemphill, & Littlefield, 2006; Jensen et al., 2001; Lundahl, Risser, & Lovejoy, 2006; Reid, Webster-Stratton, & Baydar, 2004; Stoolmiller, Eddy, & Reid, 2000) on treatment outcomes, whereas others could not replicate these findings, i.e. with respect to age (Arnold, Hodgkins, Caci, Kahle, Young, & Reif, 2015; Lundahl, Risser, & Lovejoy, 2006), sex (Hautmann et al., 2010) or comorbidities (Ollendick, Jarrett, Grills-Taquechel, Hovey, & Wolff, 2008; Owens et al., 2003). The results from the Multimodal Treatment Study of Children with ADHD (Hinshaw, 2007; The MTA Cooperative Group, 1999) suggested that neither sex, comorbid oppositional defiant disorder nor conduct disorder of the child significantly moderated treatment outcome, whereas a comorbid anxiety disorder was a moderator for a more positive treatment response to behavioural intervention in contrast to community care. In contrast, a recent meta-analysis indicated that children with ADHD and other psychiatric comorbidities benefited less from PCT than children with pure ADHD (Lee, Niew, Yang, Chen, & Lin, 2012). The comparability between the various studies is complicated since many of these studies often do not differentiate between different forms of disruptive behaviour disorders (DBD), use different treatment manuals or compare data at different times after the intervention. Although the data generally indicate the superior effectiveness of PCT compared to routine clinical care for children with ADHD (e.g. van den Hoofdakker et al., 2010), the impact of the child's age as a possible moderator of treatment response to PCT in ADHD has not been studied yet. Due to the changing nature of parenting with the increasing age of the child, however, the age of the child might be a variable of interest.

On the other hand, the existing research on maternal factors influencing PCT treatment outcome of children diagnosed with ADHD is quite limited. Regarding individual PCT, targeting infantile ADHD symptoms after maternal ADHD treatment, neither predictor variables (also called "prognostic factors") that refer to a main effect on overall treatment outcome nor moderator variables that inform on whom and under what circumstances different treatments have different effects have been studied so far (Kraemer, Wilson, Fairburn, & Agras, 2002; Papakostas, & Fava, 2008). Therefore, the aim of the present explorative analysis was to examine predictors and moderators of treatment outcome in a multicentre RCT. We investigated the impact of a multimodal treatment for maternal ADHD compared to a less intensive treatment on the efficacy of individual PCT in children with externalizing symptoms. We analysed child and maternal variables as potential predictors and moderators referring to sociodemographic, developmental, and previous treatment features, as well as to ADHD severity and comorbidity at baseline. The results may fuel the development of more specific treatment approaches for mother-child dyads with ADHD and, thus, may lead to higher success rates in treating both the ADHD of the children and of the mothers.

Methods

Study design and participants

This multicentred RCT occurred at five different study sites in Germany: Würzburg, Homburg, Mannheim, Freiburg, and Berlin. Mother-child dyads with ADHD ($N = 144$) were randomly assigned to one of two treatment arms. In the first part of the study the mothers in the treatment group (TG; $n = 77$) received weekly group psychotherapy in addition to pharmacotherapy with MPH for 12 weeks before they participated in the second part, a 12-week PCT (individual weekly sessions). Mothers in the active control group (CG; $n = 67$) received supportive counselling (weekly individual sessions) without specific psycho- or pharmacotherapy over a period of 12 weeks in part one before their participation in the 12-week individual PCT (part two) began. During PCT participation, the study protocol provided group psychotherapy every four weeks, continued MPH treatment for TG mothers, and individual counselling every four weeks for CG mothers. The primary outcome was the change in the children's externalizing symptoms after PCT at week 26 from baseline. Study recruitment and the eligibility criteria are described in detail elsewhere (Jans et al., 2013; Jans et al., 2015). Of the original sample, 123 mother-child dyads participated in primary outcome assessment at week 26 and formed the subsample for our analysis (see Appendix) on predictors and moderators of outcome [$n_{TG} = 67$ (87% of the randomized dyads), $n_{CG} = 56$ (85% of the randomized dyads)]. Sample characteristics are shown in Table 1.

Interventions

Treatment group

In part one, the mothers in the TG received group psychotherapy in the form of a manualized skills training programme based on dialectical-behavioural therapy (Hess-

linger, Philipsen, & Richter, 2004). The efficacy of this manualized skills training programme for adults with ADHD was confirmed with a multicentre feasibility study (Philipsen et al., 2007) and compared to a loosely structured discussion group (Hirvikoski et al., 2011) in which ADHD-related topics were discussed.

In addition to group psychotherapy, mothers in the TG received extended release methylphenidate (MPH; Medikinet retard®), starting with a daily dosage of 10 mg and titrating up to a daily dosage not exceeding 1.3 mg/kg body weight. In a recent RCT in our ADHD network, the combination of MPH medication and group psychotherapy as described above was found to be superior to the combination of placebo and non-specific counselling in adult patients (Philipsen et al., 2015).

Control group

Part one of the treatment of the mothers in the CG included weekly individual, non-specific supportive counselling lasting 15 to 20 minutes that was structured by a predefined checklist. Specific psychotherapeutic interventions, homework assignments or pharmacological treatment with MPH were not allowed.

Parent-child training (TG and CG)

In part two of the treatment, PCT was conducted with all mother-child dyads according to a well-established, structured behavioural psychotherapy programme for children with ADHD and ODD (oppositional defiant disorder) (THOP; Döpfner, Schürmann & Fröhlich, 2007). PCT was administered in individual, weekly one-hour sessions, predominantly with the child and their mother. Additional information is provided by Jans et al. (2007).

Assessment

Mothers and children were diagnosed with ADHD according to the DSM-IV-TR criteria. Children with potential ADHD and comorbid psychiatric disorders were diagnosed using the German versions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), a semi-structured diagnostic interview conducted with both mother and child (Deutsche K-SADS-Arbeitsgruppe, 2001). The summed score of the ADHD-ODD scale, based on the K-SADS-PL assessment of the children's ex-

Table 1. Clinical characteristics of mothers and children (*N* = 123).

	Treatment Group (*n* = 67)	Control Group (*n* = 56)
	M ± *SD* / % (*n*)	*M* ± *SD* / % (*n*)
Mother		
Age at baseline (in years)	38.4 ± 5.0	39.6 ± 5.4
ADHD subtype (ADHS-DC)		
Inattentive	22.4 % (15)	23.2 % (13)
Hyperactive-impulsive	7.5 % (5)	16.1 % (9)
Combined	70.1 % (47)	60.7 % (34)
≥ 1 current or remitted comorbid disorder (SCID-I)	62.7 % (42)	64.3 % (36)
≥ 1 current comorbid disorder (SCID-II)	19.4 % (13)	23.2 % (13)
Child		
Male	73.1 % (49)	75.0 % (42)
Age at baseline (in years)	9.1 ± 1.6	9.8 ± 1.7
ADHD subtype (K-SADS-PL)		
Inattentive	43.3 % (29)	32.1 % (18)
Hyperactive-impulsive	9.0 % (6)	8.9 % (5)
Combined	47.8 % (32)	58.9 % (33)
≥ 1 current or remitted comorbid disorder (K-SADS-PL)	41.8 % (28)	55.4 % (31)

ADHD: Attention deficit and hyperactivity disorder; ADHS-DC: Diagnostic Checklist for Diagnosis of ADHD in Adults (Rösler et al., 2004); SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Axis I and Axis II (Wittchen, Zaudig, and Fydrich, 1997). K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Deutsche K-SADS-Arbeitsgruppe, 2001).

ternalizing behaviour (change from baseline), was the primary outcome measure of the trial (the scale covers the DSM-IV diagnostic criteria of ADHD and ODD). The ADHD-ODD scale was completed at baseline and at week 26 (after 12 weeks of PCT) by an investigator blinded to the treatment assignments. The summed score of the ADHD-ODD scale theoretically ranges from 0 to 26 and reflects the amount of fulfilled DSM-IV-TR criteria (18 ADHD criteria, eight ODD criteria). The psychometric properties of the ADHD-ODD scale were described by Jans et al. (2009).

The mothers were diagnosed using the Diagnostic Checklist for diagnosis of ADHD in adults (ADHS-DC; Rösler et al., 2004), the Wender-Utah-Rating-Scale (German short version, WURS-k; Retz-Junginger et al., 2003) and the Structured Clinical Interview for DSM-IV (SCID-I, SCID-II, German version, Wittchen, Zaudig, & Fydrich, 1997). Moreover, the mothers were examined with the Conners Adult ADHD Rating Scale (CAARS, German version, blind observer-rating; Christiansen et al., 2013) and the Symptom-Checklist (SCL-90-R, German version; Franke, 2002). ADHD diagnoses with subtype specification, as well as the presence of psychiatric comorbid disorders, for both the mothers and the children are listed in Table 1. Additionally, the intelligence of the mothers was assessed with the Multiple Choice Vocabulary Test (MWT-B, screening for verbal IQ; Lehrl, 1977). Finally, the Home Situations Questionnaire (HSQ; Barkley, & Edelbrock, 1987), a parent-report scale, was used to assess behavioural non-compliance of the child in family situations, such as during meal time or while completing chores. The HSQ consists of 16 items and contains a list of different problem situations at home. The mother is asked to indicate whether or not each item is a problem and, if so, to rate its severity on a Likert scale from 1 (mild) to 9 (severe).

For the children and mothers, the socio-demographics and patient histories were assessed by additional semi-structured interviews.

The diagnostic assessments and study interventions for the children were conducted by trained clinicians (experienced physicians or psychologists) of the study centres' child psychiatric units. The diagnostic assessments and study interventions for the mothers were conducted by trained clinicians of the adult psychiatric units.

The variables to be analysed as predictors and moderators of treatment outcome were assessed before the beginning of the treatment (at the time of the screening assessment for study participation or at the baseline assessment, respectively) and correlated to developmental and sociodemographic features and previous treatments as well as to ADHD severity and comorbidity at baseline (see Table 2).

Statistical analysis

Two-step multiple linear regression analyses were conducted with the children's externalizing symptom severity (ADHD-ODD scale) as the outcome variable after 26 weeks.

All the variables that were to be analysed as predictors and moderators were pre-specified in the statistical analysis plan of the multicentre RCT. The variables were dichotomized, e.g. based on sample medians, and for each variable, both predictor and moderator analyses were performed.

Table 2. Predictor and moderator variables.[1]

Child
Age at baseline
Sex
Developmental delay[2] (yes/no)
Regular school type (yes/no)
Regular school attendance (yes/no)
Psychopharmaceuticals (yes/no)
Presence of current comorbidity (K-SADS-PL)
Presence of remitted disorder (K-SADS-PL)
HSQ score at baseline
Mother
Age at baseline
IQ
Advanced college entrance qualification (yes/no)
Marital status: married (yes/no)
Previous psychiatric/psychotherapeutic treatment (yes/no)
ADHD-Index (CAARS) at baseline
Presence of current comorbidity (SCID)
Presence of remitted disorder (SCID)
Global Severity Index at baseline (SCL-90-R)

[1] All predictor and moderator variables were dichotomized and for each variable both predictor and moderator analysis were performed. K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Deutsche K-SADS-Arbeitsgruppe, 2001); HSQ: Home-Situations-Questionnaire (Barkley & Edelbrock, 1987); ADHD: Attention deficit and hyperactivity disorder; CAARS: Conners Adult ADHD Rating Scale (Christiansen et al., 2013); SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Axis I and Axis II (Wittchen, Zaudig, & Fydrich, 1997); IQ: Intelligence Quotient. SCL: Symptom-Checklist (Franke, 2002).
[2] Delay in speech/motor development or urinary/excremental control.

To investigate the effects of these variables as prognostic factors for treatment outcome independent of intervention (predictors), the linear models of step one included the children's baseline ADHD-ODD symptoms score, centre, treatment group, and the respective dichotomized predictor variable. In step two, each variable's interaction with treatment (TG vs. CG) was added to examine the moderating effect on treatment outcome. ADHD-ODD summed scores obtained at week 26, as opposed to the corresponding change from baseline, were modelled as outcomes in order to communicate the ADHD-ODD levels achieved at that time. Owing to the adjustment for baseline values, the resulting predictor and moderator effects were identical for both approaches. The significance level was set to .05. Due to the explorative nature of the study, no adjustment for multiple testing was performed.

Results

The patient characteristics of the TG and the CG were similar and showed only minor differences (see Table 1). The differences between the groups were related to the maternal ADHD subtype; TG mothers were more frequently affected by the combined subtype than CG mothers. Compared to children in the TG, children in the CG were slightly more frequently affected by the combined ADHD subtype and their comorbidity rates were slightly higher. Similar baseline characteristics were also found in the full analysis set (FAS) of all randomized dyads (Jans et al., 2015).

Predictor analyses

Table 3 shows the results of the regression analyses examining child- and mother-related variables as predictors for treatment outcome at week 26, independent of the maternal intervention group. A tic disorder diagnosis of the child was a significant predictor for more externalizing child behaviour at week 26. More externalizing child problem behaviour in the family at baseline, as measured with the HSQ, was also a significant predictor for more externalizing child symptoms at week 26. The other child-related variables did not predict treatment outcome. None of the maternal characteristics were predictors of the treatment outcome of the child.

Moderator analyses

Table 4 shows the results of the moderator analyses. None of the child-related variables moderated treatment outcome of the child after PCT at week 26 (see Figure 1). The presence of a psychiatric comorbid disorder in the mother was associated with more externalizing symptoms in the child after PCT in the TG. More specifically, treatment outcome was significantly moderated by the presence of depression in the mother, with more symptoms in the children of mothers with ADHD and depression (see Figure 2). In the TG, children of mothers with comorbid depression did not show any improvement in externalizing symptoms after PCT. None of the remaining maternal characteristics moderated the treatment effect.

Discussion

The aim of our analyses was to explore predictors and moderators of treatment outcome in the RCT-AIMAC trial by comparing the effects of two treatment options for mothers with ADHD on the effect of individual PCT on children's externalizing symptoms.

Regardless of the maternal intervention group, the severity of the externalizing behaviour of the child in the family (measured with the HSQ) was a predictor for more externalizing symptoms after PCT. In addition, we found a comorbid tic disorder of the child as a second negative predictor for treatment outcome. Interestingly, none of the maternal characteristics predicted the treatment outcome.

Our results are in line with the findings of longitudinal studies, which indicated the high rate of chronic courses of externalizing symptomatology from childhood to adolescence (Bussing, Mason, Bell, Porter, & Garvan, 2010; Holbrook et al., 2016; Roy et al., 2016). Moreover, it replicates the assumption that the extent of externalizing behaviour strongly predicts future externalizing behaviour in school-aged children with ADHD (Bussing et al., 2010; Holbrook et al., 2016; Miranda, Colomer, Fernandez, Presentacion, & Rosello, 2015; Roy et al., 2016). Thus, this result likely is related to the severity and chronicity of ADHD and ODD symptoms, which seemed to be unchanged by the PCT intervention of the present study. However, there are studies that have found higher levels of externalizing symptoms to be associated with a greater change in problem behaviour after PCT (Hautmann et al., 2010; Hemphill, & Littlefield, 2006; Jensen et al., 2001; Lundahl et al., 2006; Reid et al., 2004; Stoolmiller et al., 2000). These contradicting findings might be caused by different therapeutic manuals or other methodological differences. In the current study, for example, the severity of the externalizing behaviour of the child was assessed by the HSQ as "behavioural non-compliance in the family", which significantly predicted less symptom improvement by PCT. In addition, we controlled for the children's externalizing behaviour at baseline by using the ADHD-ODD scale. The result of a si-

Table 3. Therapeutic outcome in week 26 by predictor: Mean number of ADHD/ODD symptoms (least squares means).

Predictors	*n*[1]	Mean (95 % CI)	Predictor effect (95 % CI)[2]	*t*-value (df)	*p*-value
Child					
Age at baseline					
≤ 9.5 years	64	10.7 [9.5, ,11.8]	0.5 [−1.1, 2.2]	0.6 (116)	.522
> 9.5 years	59	10.1 [9.0, 11.3]			
Sex					
Male	91	10.2 [9.2, 11.1]	−1.0 [−2.8, 0.9]	−1.0 (116)	.304
Female	32	11.1 [9.5, 12.7]			
Comorbidities (K-SADS-PL)					
Any					
No	70	10.5 [9.4, 11.6]	0.3 [−1.4, 2.0]	0.3 (116)	.757
Yes	53	10.3 [9.0, 11.5]			
ODD or CD					
No	88	10.6 [9.7, 11.6]	0.7 [−1.1, 2.6]	−0.8 (116)	.437
Yes	35	9.9 [8.4, 11.4]			
Tic disorder					
No	116	10.2 [9.4, 11.0]	−4.4 [−7.8, −0.9]	−2.5 (116)	.014
Yes	7	14.5 [11.2, 17.9]			
Any remitted disorder					
No	103	10.4 [9.5, 11.3]	0.1 [−2.1, 2.4]	0.1 (116)	.914
Yes	20	10.3 [8.3, 12.4]			
School attendance					
No	27	9.8 [8.0, 11.5]	−0.8 [−2.8, 1.2]	−0.8 (116)	.422
Yes	96	10.6 [9.7, 11.5]			
Psychopharmaceuticals					
No	30	10.2 [8.6, 11.9]	−0.2 [−2.2, 1.7]	−0.3 (116)	.804
Yes	93	10.5 [9.5, 11.4]			
Developmental delay					
No	60	10.6 [9.4, 11.8]	0.4 [−1.3, 2.0]	0.5 (116)	.647
Yes	63	10.2 [9.1, 11.4]			
Regular school type					
No	16	11.0 [8.7, 13.3]	0.7 [−1.8, 3.1]	0.5 (116)	.588
Yes	107	10.3 [9.5, 11.2]			
HSQ score at baseline					
≤ 52	62	9.7 [8.5, 10.8]	−1.9 [−3.7, 0]	−2.0 (110)	.044
> 52	55	11.6 [10.3, 12.8]			
Mother					
Age at baseline					
≤ 39 years	64	10.6 [9.4, 11.7]	0.3 [−1.4, 2.0]	0.4 (116)	.726
> 39 years	59	10.3 [9.1, 11.5]			

Table 3. continuation

Predictors	*n*[1]	Mean (95 % CI)	Predictor effect (95 % CI)[2]	*t*-value (df)	*p*-value
ADHD-Index (CAARS) at baseline					
≤ 19	65	10.3 [9.1, 11.4]	−0.4 [−2.0, 1.3]	−0.4 (113)	.679
> 19	55	10.6 [9.4, 11.8]			
Comorbid disorders					
No	87	10.1 [9.1, 11.0]	−1.2 [−3.0, 0.6]	−1.3 (116)	.208
Yes	36	11.2 [9.7, 12.7]			
Depression					
No	107	10.2 [9.3, 11.1]	−1.7 [−4.3, 0.9]	−1.3 (116)	.191
Yes	16	11.9 [9.5, 14.3]			
Anxiety					
No	110	10.3 [9.5, 11.2]	−1.0 [−3.7, 1.7]	−0.7 (116)	.472
Yes	13	11.3 [8.8, 13.8]			
Any personality disorder					
No	97	10.4 [9.5, 11.3]	−0.1 [−2.1, 1.9]	−0.1 (116)	.927
Yes	26	10.5 [8.7, 12.3]			
Any remitted disorder					
No	58	10.6 [9.5, 11.8]	0.4 [−1.2, 2.1]	0.5 (116)	.616
Yes	65	10.2 [9.1, 11.3]			
Remitted disorder: depression					
No	73	10.7 [9.7, 11.8]	0.7 [−0.9, 2.4]	0.9 (116)	.378
Yes	50	10.0 [8.7, 11.3]			
Previous treatment					
No	56	9.7 [8.5, 10.9]	−1.4 [−3.0, 0.3]	−1.6 (116)	.103
Yes	67	11.0 [9.9, 12.1]			
Marital status: married					
No	44	10.3 [8.9, 11.7]	−0.2 [−1.9, 1.5]	−0.3 (116)	.806
Yes	79	10.5 [9.5, 11.5]			
Advanced college qualification					
No	93	10.7 [9.7, 11.6]	1.0 [−0.9, 3.0]	1.0 (116)	.307
Yes	30	9.7 [8.0, 11.3]			
IQ					
≤ 107	70	11.1 [10.0, 12.2]	1.6 [0.0, 3.3]	1.9 (116)	.057
> 107	53	9.5 [8.3, 10.7]			
SCL Global Severity Index at baseline					
≤ 0.65	61	9.6 [8.5, 10.8]	−1.4 [−3.1, 0.2]	−1.7 (113)	.094
> 0.65	59	11.1 [9.9, 12.2]			

ADHD: Attention deficit hyperactivity disorder; ODD: Oppositional defiant disorder; CI: Confidence interval; K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Deutsche K-SADS-Arbeitsgruppe, 2001); CD: Conduct disorder; HSQ: Home-Situations-Questionnaire (Barkley, and Edelbrock, 1987); CAARS: Conners Adult ADHD Rating Scale (Christiansen et al., 2013); IQ: Intelligence quotient; SCL: Symptom-Checklist (Franke, 2002).

[1] N: Number of mother-child-dyads with non-missing predictor and non-missing outcome at week 26.

[2] Predictor effect: A difference < 0 for predictor (upper line) minus predictor (bottom line) favours the group with the predictor value of the upper line.

Table 4. Therapeutic outcome in week 26 by moderator and intervention group: Mean number of ADHD/ODD symptoms (least squares means).

Moderators	Group (*n*)[1]	Mean (95 % CI)	Treatment effect: difference TG-CG (95 % CI)[2]	Modifier effect: difference of treatment effects[2]		
				difference A-B (95 % CI)[3]	*t*-value (df)	*p*-value
Child						
Age at baseline						
≤ 9.5 years	TG (38)	11.3 [9.8, 12.7]	1.2 [−1.1, 3.6] A	0.3 [−3.0, 3.6]	0.20 (115)	.845
	CG (26)	10.0 [8.2, 11.8]				
> 9.5 years	TG (29)	10.6 [8.9, 12.3]	0.9 [−1.4, 3.3] B			
	CG (30)	9.7 [8.0, 11.3]				
Sex						
Male	TG (49)	10.9 [9.6, 12.1]	1.4 [−0.5, 3.3] A	1.0 [−2.7, 4.8]	0.54 (115)	.589
	CG (42)	9.5 [8.1, 10.9]				
Female	TG (18)	11.4 [9.2, 13.5]	0.4 [−2.9, 3.6] B			
	CG (14)	11.0 [8.6, 13.4]				
Comorbidities (K-SADS-PL)						
Any						
No	TG (41)	11.1 [9.7, 12.5]	1.1 [−1.1, 3.3] A	0.0 [−3.3, 3.4]	0.02 (115)	.985
	CG (29)	10.0 [8.3, 11.7]				
Yes	TG (26)	10.8 [9.0, 12.6]	1.1 [−1.4, 3.6] B			
	CG (27)	9.7 [8.0, 11.5]				
ODD or CD						
No	TG (48)	10.8 [9.5, 12.0]	0.2 [−1.7, 2.1] A	−3.4 [−6.9, 0.2]	−1.86 (115)	.065
	CG (40)	10.6 [9.2, 12.0]				
Yes	TG (19)	11.6 [9.5, 13.6]	3.5 [0.5, 6.6] B			
	CG (16)	8.0 [5.8, 10.3]				
Tic disorder						
No	TG (63)	10.9 [9.8, 12.0]	1.4 [−0.2, 3.1] A	5.9 [−1.0, 12.7]	1.70 (115)	.091
	CG (53)	9.4 [8.2, 10.6]				
Yes	TG (4)	12.7 [8.3, 17.1]	−4.4 [−11.0 2.2] B			
	CG (3)	17.1 [12.1, 22.2]				
Any remitted disorder						
No	TG (58)	11.1 [9.9, 12.2]	1.2 [−0.6, 3.0] A	0.6 [−3.8, 5.1]	0.27 (115)	.786
	CG (45)	9.8 [8.5, 11.2]				
Yes	TG (9)	10.6 [7.5, 13.7]	0.6 [−3.5, 4.7] B			
	CG (11)	10.0 [7.2, 12.7]				
School attendance						
No	TG (14)	10.6 [8.1, 13.0]	1.6 [−1.9, 5.2] A	0.6 [−3.4, 4.7]	0.31 (115)	.755
	CG (13)	9.0 [6.4, 11.5]				
Yes	TG (53)	11.1 [9.8, 12.3]	1.0 [−0.9, 2.9] B			
	CG (43)	10.1 [8.7, 11.5]				
Psychopharmaceuticals						
No	TG (17)	10.8 [8.5, 13.0]	1.1 [−2.3, 4.5] A	−0.1 [−4.0, 3.8]	−0.05 (115)	.960
	CG (13)	9.7 [7.2, 12.2]				

Table 4. continuation

Moderators	Group (*n*)[1]	Mean (95 % CI)	Treatment effect: difference TG-CG (95 % CI)[2]	Modifier effect: difference of treatment effects[2]		
				difference A-B (95 % CI)[3]	*t*-value (df)	*p*-value
Yes	TG (50)	11.1 [9.8, 12.4]	1.2 [−0.7, 3.1] B			
	CG 43)	9.9 [8.5, 11.3]				
Developmental delay						
No	TG (35)	11.2 [9.6, 12.7]	1.1 [−1.3, 3.5] A	0.0 [−3.3, 3.3]	0.0 (115)	.999
	CG (25)	10.1 [8.2, 11.9]				
Yes	TG (32)	10.8 [9.2, 12.4]	1.1 [−1.2, 3.4] B			
	CG (31)	9.7 [8.1, 11.3]				
Regular school type						
No	TG (10)	11.5 [8.6, 14.4]	0.9 [−3.7, 5.6] A	−0.2 [−5.2, 4.8]	−0.07 (115)	.942
	CG (6)	10.5 [6.9, 14.2]				
Yes	TG (57)	10.9 [9.7, 12.1]	1.1 [−0.6, 2.9] B			
	CG (50)	9.8 [8.5, 11.0]				
HSQ score at baseline						
≤ 52	TG (30)	9.8 [8.1, 11.6]	0.4 [−1.8, 2.7] A	−0.9 [−4.2, 2.4]	−0.55 (109)	.586
	CG (32)	9.4 [7.9, 11.0]				
> 52	TG (32)	12.2 [10.6, 13.8]	1.3 [−1.1, 3.7] B			
	CG (23)	10.9 [9.0, 12.7]				
Mother						
Age at baseline						
≤ 39 years	TG (38)	11.4 [9.9, 12.9]	1.8 [−0.5, 4.1] A	1.5 [−1.8, 4.7]	0.88 (115)	.382
	CG (26)	9.6 [7.8, 11.4]				
> 39 years	TG (29)	10.4 [8.8, 12.1]	0.4 [−2.0, 2.7] B			
	CG (30)	10.1 [8.4, 11.7]				
ADHD-Index (CAARS) baseline						
≤ 19	TG (37)	11.5 [10.0, 12.9]	2.6 [0.3, 4.8] A	2.7 [−0.6, 6.0]	1.61 (112)	.110
	CG (28)	8.9 [7.2, 10.6]				
> 19	TG (27)	10.5 [8.8, 12.3]	−0.1 [−2.5, 2.3] B			
	CG (28)	10.7 [9.0, 12.3]				
Comorbid disorders						
Any						
No	TG (47)	10.1 [8.8, 11.4]	0.0 [−1.9, 1.9] A	−3.8 [−7.3, −0.2]	−2.11 (115)	.037
	CG (40)	10.1 [8.7, 11.5]				
Yes	TG (20)	13.0 [11.0, 15.0]	3.8 [0.8, 6.7] B			
	CG (16)	9.2 [7.0, 11.4]				
Depression						
No	TG (57)	10.4 [9.2, 11.5]	0.3 [−1.4, 2.0] A	−5.8 [−11.00 −0.8]	−2.30 (115)	.024
	CG (50)	10.0 [8.8, 11.3]				
Yes	TG (10)	14.5 [11.5, 17.5]	6.1 [1.5, 10.8] B			
	CG (6)	8.4 [4.8, 12.0]				

Table 4. continuation

Moderators	Group (*n*)[1]	Mean (95 % CI)	Treatment effect: difference TG-CG (95 % CI)[2]	Modifier effect: difference of treatment effects[2]		
				difference A-B (95 % CI)[3]	*t*-value (df)	*p*-value
Anxiety						
No	TG (60)	10.8 [9.7, 12.0]	1.0 [−0.7, 2.7] A	−1.2 [−6.5, 4.1]	−0.45 (115)	.652
	CG (50)	9.8 [8.5, 11.1]				
Yes	TG (7)	12.4 [8.9, 15.8]	2.2 [−2.8, 7.3] B			
	CG (6)	10.1 [6.4, 13.9]				
Any personality disorder						
No	TG (54)	10.9 [9.6, 12.1]	0.9 [−0.9, 2.8] A	−1.1 [−5.1, 2.9]	−0.54 (115)	.591
	CG (43)	10.0 [8.6, 11.3]				
Yes	TG (13)	11.5 [9.0, 14.0]	2.0 [−1.6, 5.6] B			
	CG (13)	9.5 [6.9, 12.0]				
Remitted disorders						
Any						
No	TG (32)	11.4 [9.8, 13.0]	1.6 [−0.8, 4.0] A	1.0 [−2.4, 4.3]	0.57 (115)	.572
	CG (26)	9.8 [8.0, 11.6]				
Yes	TG (35)	10.6 [9.0, 12.1]	0.7 [−1.6, 2.9] B			
	CG (30)	9.9 [8.3, 11.5]				
Remitted depression						
No	TG (41)	11.3 [9.9, 12.7]	1.2 [−0.9, 3.3] A	0.2 [−3.1, 3.5]	0.14 (115)	.888
	CG (32)	10.1 [8.5, 11.7]				
Yes	TG (26)	10.5 [8.7, 12.2]	1.0 [−1.6, 3.5] B			
	CG (24)	9.5 [7.7, 11.3]				
Previous treatment						
No	TG (31)	9.7 [8.1, 11.3]	0.0 [−2.4, 2.4] A	−2.2 [−5.4, 1.1]	−1.32 (115)	.191
	CG (25)	9.7 [8.0, 11.5]				
Yes	TG (36)	12.1 [10.6, 13.6]	2.1 [−0.0, 4.3] B			
	CG (31)	9.9 [8.3, 11.5]				
Marital status: married						
No	TG (27)	10.6 [8.9, 12.4]	0.6 [−2.2, 3.4] A	−0.9 [−4.4, 2.6]	−0.51 (115)	.613
	CG (17)	10.1 [7.9, 12.3]				
Yes	TG (40)	11.2 [9.8, 12.7]	1.5 [−0.6, 3.5] B			
	CG (39)	9.8 [8.3, 11.2]				
Advanced college qualification						
No	TG (49)	11.4 [10.1, 12.7]	1.5 [−0.4, 3.4] A	1.3 [−2.6, 5.2]	0.67 (115)	.506
	CG (44)	9.9 [8.5, 11.3]				
Yes	TG (18)	9.8 [7.7, 12.0]	0.2 [−3.2, 3.6] B			
	CG (12)	9.6 [7.0, 12.2]				
IQ						
≤ 107	TG (40)	11.8 [10.4, 13.2]	1.4 [−0.8, 3.5] A	0.8 [−2.5, 4.1]	0.49 (115)	.622
	CG (30)	10.4 [8.8, 12.0]				
> 107	TG (27)	9.8 [8.0, 11.5]	0.6 [−1.9, 3.0] B			
	CG (26)	9.2 [7.5, 11.0]				

Table 4. continuation

Moderators	Group (*n*)[1]	Mean (95 % CI)	Treatment effect: difference TG-CG (95 % CI)[2]	Modifier effect: difference of treatment effects[2]		
				difference A-B (95 % CI)[3]	*t*-value (df)	*p*-value
SCL Global Severity Index at baseline						
≤ 0.65	TG (34)	9.5 [8.0, 11.1]	−0.3 [−2.6, 2.0] A	−3.0 [−6.3, 0.4]	−1.76 (112)	.080
	CG (27)	9.8 [8.1, 11.6]				
> 0.65	TG (30)	12.4 [10.7, 14.1]	2.7 [0.3, 5.0] B			
	CG (29)	9.7 [8.1, 11.4]				

ADHD: Attention deficit hyperactivity disorder; ODD: Oppositional Defiant Disorder; TG: Treatment group; CG: Control group; CI: Confidence interval; K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Deutsche K-SADS-Arbeitsgruppe, 2001); CD: Conduct disorder; HSQ: Home-Situations-Questionnaire (Barkley & Edelbrock, 1987); CAARS: Conners Adult ADHD Rating Scale (Christiansen et al., 2013); IQ: Intelligence quotient; SCL: Symptom-Checklist (Franke, 2002).

[1] *N*: Number of mother-child-pairs with non-missing moderator and non-missing outcome at week 26.

[2] A difference TG-CG < 0 favours the TG.

[3] A difference A-B < 0 indicates a more favourable or less unfavourable outcome of TG versus CG in subgroup A than in subgroup B.

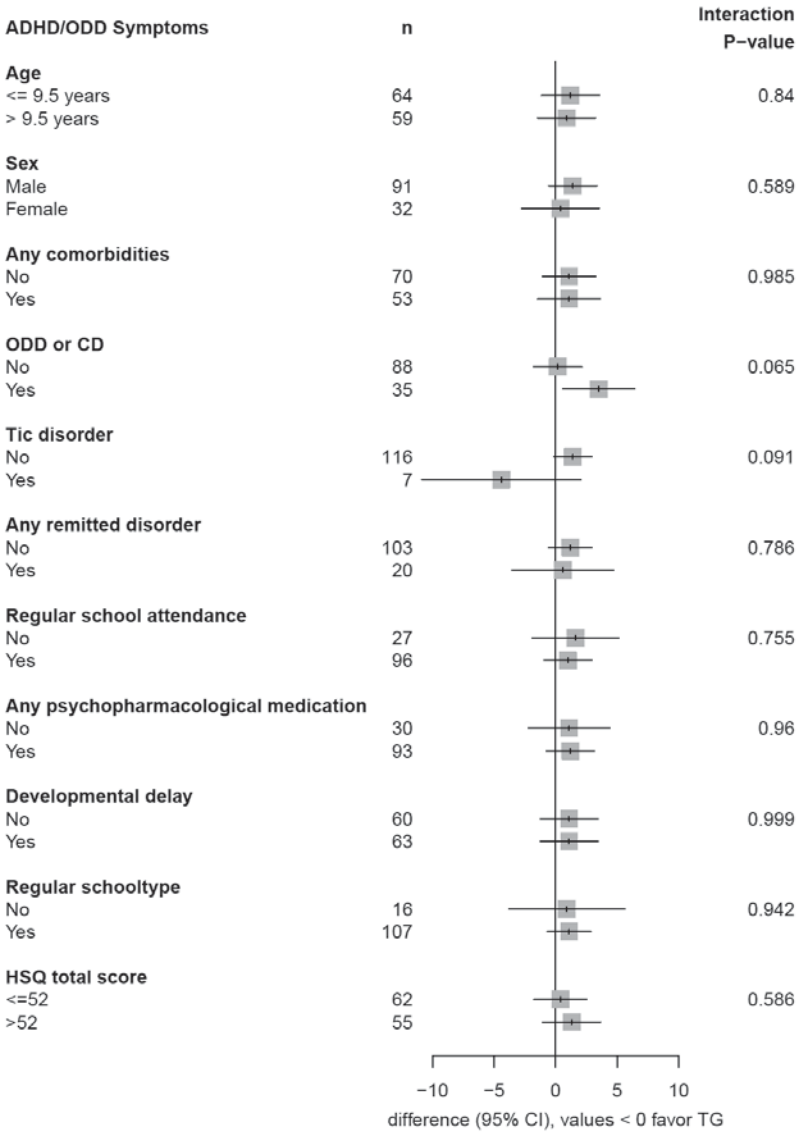

Figure 1. Child moderators of treatment effects. Treatment effects on ADHD/ODD symptoms within subgroups based on child moderator variables, analyzed by randomized treatment in mother-child-pairs with non-missing moderator variable and non-missing ADHD/ODD outcome at week 26, with 95 % confidence interval. A difference below 0 favors the treatment group (TG). The linear model includes baseline ADHD/ODD symptoms score, center, treatment, moderator and the interaction beaween treatment and moderator.
CI confidence interval; ADHD attention deficit hyperactivity disorder; ODD oppositional defiant disorder; K-SADS-PL Kiddie-SADS Present and Lifetime Version (SADS: Schedule for Active Disorders and Schizophrenia); CD conduct disorder; HSQ home-situations-questionnaire.

gnificant prognostic value of the baseline HSQ scores, in spite of controlling for externalizing symptom severity as conducted in our study, points to the need for differentiating ADHD and ODD symptom severity from externalizing behaviour in family life.

The predictor analyses revealed that, irrespective of the maternal intervention group, a tic disorder of the child was a significant predictor for more externalizing symptoms after PCT. However, the relevance of this finding is limited due to the small sample size of children with comorbid tic disorders. Concerning outcome moderators, our results aligned with those of other current studies (Lundahl et al., 2006), suggesting that neither sex nor age of the child moderate the treatment outcome of a behavioural PCT. In contrast to the literature (Hinshaw, 2007; van den Hoofdakker et al., 2010), no moderating effects of psychiatric comorbidities in children with ADHD were observed. Possible explanations for these inconsistent results might be differences in study design. In addition, children, as well as their mothers, were all diagnosed with ADHD. This was a significant difference compared to the studies mentioned above, in which only a minor part of the mothers of children with ADHD were also affected by the disorder. Another difference, especially in regard to the MTA study

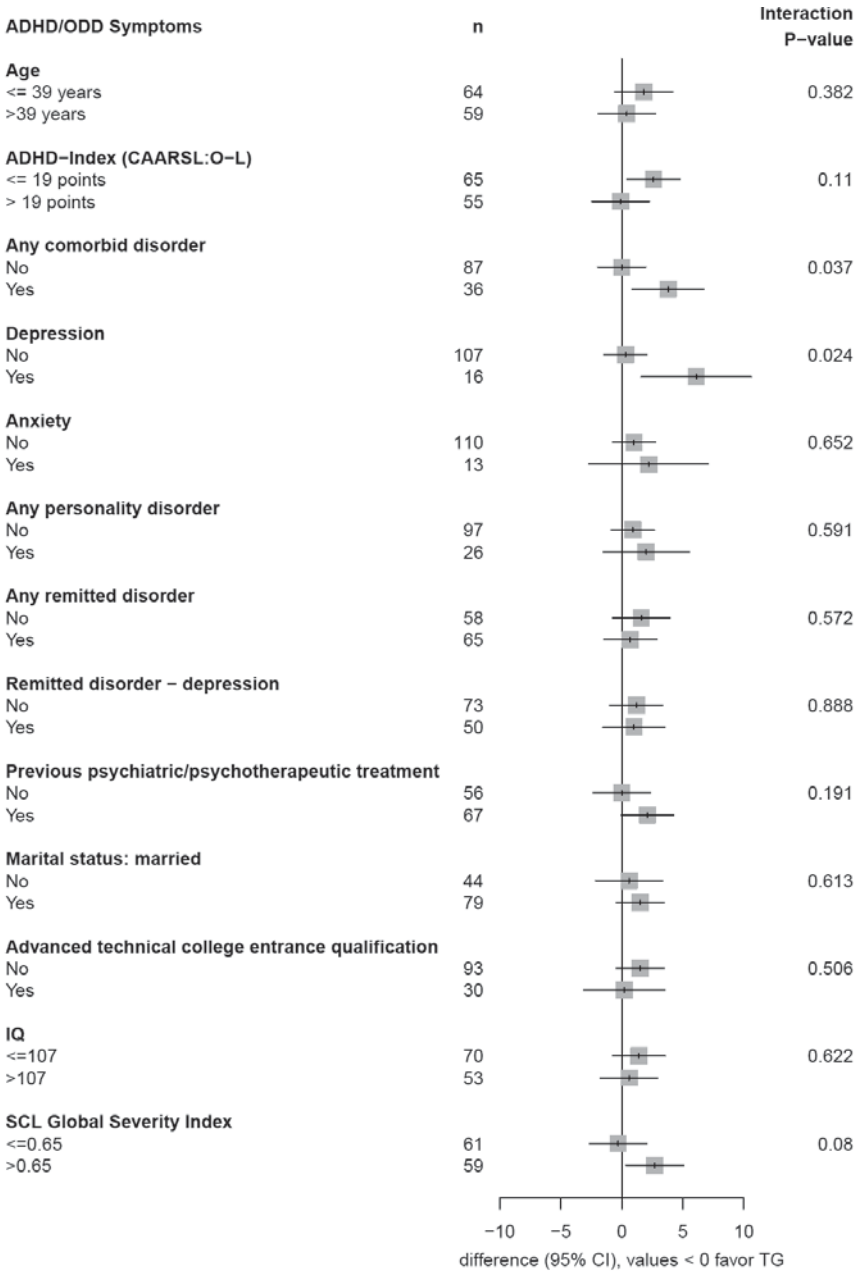

Figure 2. Maternal moderators of treatment effects.
Treatment effects on ADHD/ODD symptoms within subgroups based on mother moderator variables, analyzed as described for figure 1; CAARS-O:L Conners Adult ADHD Rating Scale – Observer-rating Scale, Long Version; IQ intelligence quotient; SCL Symptom-Checklist.

(Hinshaw, 2007), are the distinct therapeutic manuals that have been used. Finally, we did not investigate moderators solely for PCT but rather moderators of the outcome of the treatment of maternal ADHD in addition to PCT.

Regarding maternal characteristics, our results are consistent with previous findings indicating a moderating effect of maternal depression on treatment outcome (Chronis, Chacko, Fabiano, Wymbs, & Pelham, 2004; Hinshaw, 2007). In our study, children of mothers with depression in the TG showed more externalizing behaviour after PCT and, thus, benefited less from the intervention compared to the children of mothers in the CG. This suggested that the severely impaired mothers with ADHD and psychiatric comorbidities (especially depression) do not need the extensive ADHD-specific treatment that was offered to our TG (group psychotherapy plus MPH) to improve the child's response to PCT. Hence, our CG intervention, which included less time-consuming counselling sessions offering the opportunity to discuss individual topics with the therapist, seemed to be more appropriate and might have allowed the affected mothers to profit, e.g. by addressing non-ADHD problems. This is an important finding as it emphasizes the need for disorder-specific treatment approaches for parents with ADHD and psychiatric comorbidities and debunks the motto "the more, the better". Based on our findings, one could conclude that a modular treatment programme flexibly covering comorbidity profiles seems to be more appropriate than the fixed programme, focusing primarily on ADHD, provided in the clinical trial.

In contrast to previous findings (Sonuga-Barke et al., 2002), we did not observe any moderating effect of maternal ADHD symptoms at baseline. In this context, the study of Sonuga-Barke et al. (2002) found high levels of maternal ADHD symptoms to limit the effect of PCT. These divergent results might be due to methodological differences between the studies. A main difference lies in the therapy of maternal ADHD. While in the aforementioned study mothers participated in PCT only, in the present study affected mothers also received ADHD treatment before participating in PCT. In both groups this additional therapeutic approach for the mothers resulted in decreased maternal ADHD severity and might, therefore, have prevented a negative impact on PCT's efficacy. Furthermore, maternal ADHD symptoms in the previous study (Sonuga-Barke et al., 2002) ranged from low to high and were not diagnosed according to the DSM-IV-TR, whereas in the present study mothers had well-diagnosed ADHD with consistently high symptom levels. Due to the high homogeneity of maternal ADHD severity in our sample, we likely failed to show a moderating impact on the treatment outcome of the child.

The findings of the present study have to be interpreted in the context of several limitations. First, due to the exploratory approach of this study, an α-error correction for multiple testing was not conducted. Therefore, the likelihood of incorrectly rejecting the null hypothesis (Type I error) was increased and the statistically significant predictor and moderator effects found in our study must be interpreted with caution. Second, although the primary outcome (ADHD-ODD scale) was assessed in blinded interviewer ratings based on information from both mothers and children, this score highly correlates with the mother's point of view (Jans et al., 2009). Hence, the primary outcome can be considered a proximal outcome measure with restricted validity. Moreover, our study results were limited as the majority of measures based on maternal reports. Due to multiple interventions for maternal ADHD, the interpretation of the present findings is limited. The DBT group psychotherapy as well as the MPH medication could have had an impact on maternal depression. For example, DBT interventions could have improved depressive symptoms, whereas side effects of MPH could have had contrary effects. A further limitation was the fact that the variables analysed as potential predictors or moderators were dichotomized based on the sample medians. The dichotomization of continuous variables can either artificially inflate or deflate power to detect interaction effects (Frazier, Tix, & Barron, 2004). Nevertheless, we pre-specified this approach with the explicit intention to explore the effects in clinically meaningful patient subgroups, while keeping the extent of data exploration, model-building, model complexity, and interpretation per variable at bay. In addition, our results are limited by the exclusion of dropouts from the present analysis. Our main strategy in the design of the present exploratory analysis of a substantial number of pre-specified predictors/moderators was to keep model building and modelling assumptions at an absolute minimum by using simple, entirely pre-specified models. Therefore, we did not apply the multiple imputation approach we used in the main outcome analysis of our trial to our present analysis of predictors. The theory of multiple imputation requires that all factors investigated during the analysis step must also be included in the preceding multiple imputation step. Simultaneous inclusion of all considered factors (including interactions with treatment for step two) during the imputation step would have overstrained the linear model assumption. Multiple imputation with each single factor included, in turn, would have generated different imputed data for each factor. Instead, we decided to use the same data set for all analyses and added the respective dichotomized predictor, each in turn to the variables used in the Jans et al. 2015 paper (baseline ADHD-ODD symptoms score, centre, treatment group). This regression strategy uses the information contained in all of the factors included in the model to correct for potential bias due to missing outcomes. Thus it produces fair treatment comparisons if missingness occurs at random given these factors – a much weaker statistical assumption than

"missing completely at random" warranted for direct, unadjusted comparisons in the presence of missing outcomes (Carpenter & Kenward, 2013). A further advantage is that no data dredging was done – dichotomization of continuous predictors was pre-specified.

In spite of these limitations, this is, to our knowledge, the first RCT investigating the efficacy of the treatment of mothers and children diagnosed with ADHD on the child's externalizing symptoms that analysed both potential predictors and moderators of treatment outcome. Most of the investigated variables failed to show such effects, suggesting that the symptom improvements seen in both maternal treatment groups were robust and generalizable. Clinicians should anticipate the possibility of lower symptom improvement in children with higher externalizing problem behaviour in the family and should address the need for individualized treatment approaches accounting for comorbid disorders.

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Compliance with Ethical Standards

Conflict of interest

C. Jacob received speakers' honoraria from Novartis and Medice and is a member of the adult ADHD Advisory Board of the latter company. S. Gross-Lesch received speakers' honoraria from Medice, and Lilly. S. Matthies received speakers' fees from Janssen-Cilag and was involved in the clinical trials conducted by Janssen-Cilag and Lilly in the years 2008–2010. M. Rösler is a member of the Medice and Shire speakers' bureaus, is a member of Lilly, Shire, and Medice, advisory boards, and performed clinical trials for Medice and Lilly. W. Retz received speakers' honoraria from Medice, Novartis, and Shire. He is involved in clinical trials for the German Ministry of Education and Research (BMBF), Novartis, Medice, and Vifor. E. Sobanski was on advisory boards, was involved in Phase-III studies or investigator-initiated trials, and presented lectures for Medice, Shire, Eli Lilly, and Novartis within the last three years. B. Alm was involved in Phase-III studies for Medice, Eli Lilly, and Novartis and was on Eli Lilly's advisory board. L. Poustka received speakers' honoraria from Eli Lilly and Shire during the last three years. M. Colla was on advisory boards, received speakers' honoraria, and participated in Phase-III studies for Shire, Eli Lilly, and Novartis within the last three years. A. Häge received speakers' honoraria, conference attendance support and participated in clinical trials from Shire, Lundbeck, and Servier during the last three years. S. Hohmann received speakers' honoraria from Jansen Cilag in 2012. K. Becker received speakers' honorary (independent lecture content) from Shire during the last three years. C. M. Freitag receives royalties for books on ADHD and autism (Kohlhammer-Verlag, Beltz-Verlag). A. Philipsen was on advisory boards, presented lectures, was involved in Phase-III studies, and received travel grants from Eli Lilly, Janssen-Cilag, Medice, Novartis, and Shire within the last three years; she is the author of books and articles on psychotherapy published by Elsevier, Hogrefe, Schattauer, Kohlhammer, and Karger; she is involved in clinical trials funded by the German Federal Ministry of Education and Research.

All other authors declared no conflicting interests (J. Geissler, L. Gentschow, E. Graf, S. Groß-Lesch, B. Haack-Dees, S. Hänig, C. Jaite, T. Jans, V. Kappel, K. Schneider-Mom, B. M. van Noort, T. D. Vloet, A. von Gontard, A. Warnke).

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Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the university's institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/1422-4917/a000602.

ESM 1. Figure.
Consort diagram of sample flow.

References

APA (2013). *Diagnostic and statistical manual of mental disorders* (5th Ed.). Washington, DC.

Arnold, L.E., Hodgkins, P., Caci, H., Kahle, J., Young, S., & Reif, A. (2015). Effect of treatment modality in long-term outcomes in attention-deficit/hyperactivity disorder: A systematic review. *PLoS ONE, 10*(2).

Barkley, R.A., & Edelbrock, C. (1987). Assessing situational variation in children's behavior problems: The Home and School Situations Questionnaires. *Advances in Behavioral Assessment of Children and Families, 3*, 157–176.

Biederman, J., & Faraone, S.V. (2005). Attention-deficit hyperactivity disorder. *Lancet, 366*(9481), 237–248.

Bussing, R., Mason, D.M., Bell, L., Porter, P., & Garvan, C. (2010). Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*, 595–605.

Carpenter, J. & Kenward, M. (2013). Multiple imputation and its application. Chichester: John Wiley & Sons.

Christiansen, H., Hirsch, O., Philipsen, A., Oades, R.D., Matthies, S., Hebebrand, J., et al. (2013). German validation of the conners adult ADHD rating scale-self-report: confirmation of factor structure in a large sample of participants with ADHD. *Journal of Attention Disorders, 17*(8), 690–698.

Chronis, A.M., Chacko, A., Fabiano, G.A., Wymbs, A.B., & Pelham Jr., W.E. (2004). Enhancements to the behavioral parent training paradigm for families of children with ADHD: Review and future directions. *Clinical Child and Family Psychology Review, 7*(1), 1–27.

Chronis-Tuscano, A., Clarke, T.L., O'Brien, K.A., Raggi, V.L., Diaz, Y., Mintz, A.D., et al. (2013). Development and preliminary evaluation of an integrated treatment targeting parenting and depressive symptoms in mothers of children with attention-deficit/hyperactivity disorder. *Journal of Consulting and Clinical Psychology, 81*(5), 918–925.

Chronis-Tuscano, A., Wang, C.H., Strickland, J., Almirall, D., & Stein, M.A. (2016). Personalized treatment of mothers with ADHD and their young at-risk children: a SMART Pilot. *Journal of Clinical Child & Adolescent Psychology, 45*, 510–521.

Chronis-Tuscano, A., Wang, C.H., Woods, K.E., Strickland, J., & Stein, M.A. (2017). Parent ADHD and Evidence-Based Treatment for Their Children: Review and Directions for Future Research. *Journal of Abnormal Child Psychology, 45* (3), 501–517.

Döpfner, M., Breuer, D., Schurmann, S., Metternich, T.W., Rademacher, C., & Lehmkuhl, G. (2004). Effectiveness of an adaptive multimodal treatment in children with Attention-Deficit Hyperactivity Disorder – global outcome. *European Child and Adolescent Psychiatry, 13 Suppl 1*, 117–129.

Döpfner, M., Schürmann, S., & Fröhlich, J. (2007). *Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten: THOP* (4th ed.). Weinheim: Beltz.

Faraone, S.V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine, 36*, 159–165.

Fayyad, J., De Graaf, R., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., et al. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *British Journal of Psychiatry, 190*, 402–409.

Fossum, S., Morch, W., Handegård, B.H., Drugli, M.B., & Larsson, B. (2009). Parent training for young Norwegian children with ODD and CD problems. Predictors and moderators of treatment outcome. *Scandinavian Journal of Psychology, 50*(2), 173–181.

Franke, G.H. (2002). *SCL-90-R – Die Symptom-Checkliste von L.R. Derogatis (2. vollständig bearbeitete und neu normierte Auflage)*. Göttingen: Beltz Test.

Frazier, P., Tix, A.P. & Barron, K.E. (2004). Testing Moderator and Mediator Effects in Counseling Psychology Research. *Journal of Counseling Psychology, 51* (2), 115–134.

Hautmann, C., Eichelberger, I., Hanisch, C., Plück, J., Walter, D., & Döpfner, M. (2010). The severely impaired do profit most: short-term and long-term predictors of therapeutic change for a parent management training under routine care conditions for children with externalizing problem behavior. *European Child and Adolescent Psychiatry, 19*, 419–430.

Hemphill, S.A., & Littlefield, L. (2006). Child and family predictors of therapy outcome for children with behavioral and emotional problems. *Child Psychiatry and Human Development, 36*, 329–349.

Hesslinger, B., Philipsen, A., & Richter, H. (2004). *Psychotherapie der ADHS im Erwachsenenalter: Ein Arbeitsbuch*. Göttingen: Hogrefe.

Hinshaw, S.P. (2007). Moderators and mediators of treatment outcome for youth with ADHD: understanding for whom and how interventions work. *Journal of Pediatric Psychology, 32*(6), 664–675.

Hirvikoski, T., Waaler, E., Alfredsson, J., Pihlgren, C., Holmstrom, A., Johnson, A., et al. (2011). Reduced ADHD symptoms in adults with ADHD after structured skills training group: results from a randomized controlled trial. *Behaviour Research and Therapy, 49*(3), 175–185.

van den Hoofdakker, B., Nauta, M.H., van der veen-Mulders, L., Sytema, S., Emmelkamp, P.M.G., Minderaa, R.B., et al. (2010). Behavioral Parent Training as an Adjunct to Routine Care in Children with Attention-Deficit/Hyperactivity Disorder: Moderators of treatment response. *Journal of Pediatric Psychology, 35*, 317–326.

Holbrook, J.R., Cuffe, S.P., Cai, B., Visser, S.N., Forthofer, M.S., Bottai, M., et al. (2016). Persistence of parent-reported ADHD symptoms from childhood through adolescence in a community sample. *Journal of Attention Disorders, 20*, 11–20.

Jans, T., Graf, E., Jacob, C., Zwanzger, U., Gross-Lesch, S., Matthies, S., et al. (2013). A randomized controlled multicentre trial on the treatment for ADHD in mothers and children: enrolment and basic characteristics of the study sample. *ADHD Attention Deficit and Hyperactivity Disorders, 5*(1), 29–40.

Jans, T., Jacob, C., Warnke, A., Zwanzger, U., Gross-Lesch, S., Matthies, S., et al. (2015). Does intensive multimodal treatment for maternal ADHD improve the efficacy of parent training for children with ADHD? A randomized controlled multicenter trial. *Journal of Child Psychology and Psychiatry, 56*(12), 1298–1313.

Jans, T., Weyers, P., Schneider, M., Hohage, A., Werner, M., Pauli, P., & Warnke, A. (2009). The Kiddie-SADS allows a dimensional assessment of externalizing symptoms in ADHD children and adolescents. *ADHD Attention Deficit and Hyperactivity Disorders, 1*(2), 215–222.

Jensen, P.S., Hinshaw, S.P., Kraemer, H.C., Leonora, N., Newcorn, J.H., Abikoff, H.B., et al., (2001). ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(2), 147–158.

K-SADS-Arbeitsgruppe, D. (2001). *ICD-10, DSM III-R, DSM-IV Fassung der Kiddi-SADS-PL (5. Auflage der deutschen Forschungsversion, erweitert um ICD-10-Diagnostik*. Frankfurt: Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters.

Kraemer, H.C., Wilson, G.T., Fairburn, C.G., & Agras, W.S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry, 59*(10), 877–883.

Lavigne, J.V., LeBailly, S.A., Gouze, K.R., Cicchetti, C., Jessup, B.W., Arend, R., et al. (2008). Predictor and moderator effects in the treatment of oppositional defiant disorder in pediatric primary care. *Journal of Pediatric Psychology, 33*, 462–472.

Lee, P.C., Niew, W.I., Yang, H.J., Chen, V.C., & Lin, K.C. (2012). A meta-analysis of behavioral parent training for children with attention deficit hyperactivity disorder. *Research in Developmental Disabilities, 33*(6), 2040–2049.

Lehrl, S. (1977). *Mehrfachwahl-Wortschatz-Intelligenztest Form B*. Erlangen: Straube.

Leijten, P., Raaijmakers, M.A., de Castro, B.O., & Matthys, W. (2013). Does socioeconomic status matter? A meta-analysis on parent training effectiveness for disruptive child behavior. *Journal of Clinical Child and Adolescent Psychology, 42*(3), 384–392.

Lundahl, B., Risser, H.J., & Lovejoy, M.C. (2006). A meta-analysis of parent training: moderators and follow-up effects. *Clinical Psychology Review, 26*(1), 86–104.

Miranda, A., Colomer, C., Fernandez, M.I., Presentacion, M.J., & Rosello, B. (2015). Analysis of personal and family factors in the persistence of attention deficit hyperactivity disorder: results of a prospective follow-up study in childhood. *PLoS One, 10*.

The MTA Cooperative Group (1999). Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with Attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 56*(12), 1088–1096.

Ollendick, T.H., Greene, R.W., Austin, K.E., Fraire, M.G., Halldorsdottir, T., Allen, K.B., et al. (2016). Parent management training and collaborative and proactive solutions. A Randomized Control Trial for Oppositional Youth. *Journal of Clinical Child and Adolescent Psychology, 45*, 591–604.

Ollendick, T.H., Jarrett, M.A., Grills-Taquechel, A., Hovey, L.D., & Wolff, J.C. (2008). Comorbidity as a predictor and moderator of treatment outcome in youth with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. *Clinical Psychology Review, 28*, 1447–1471.

Owens, E.B., Hinshaw, S.P., Kraemer, H.C., Arnold, L.E., Abikoff, H.B., Cantwell, D.P., et al. (2003). Which treatment for whom for ADHD? Moderators for treatment response in the MTA. *Journal of Consulting an Clinical Psychology, 71*, 540–552.

Papakostas, G.I., & Fava, M. (2008). Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. *Dialogues in Clinical Neuroscience, 10*(4), 439–451.

Philipsen, A., Jans, T., Graf, E., Matthies, S., Borel, P., Colla, M., et al. (2015). Effects of Group Psychotherapy, Individual Counseling, Methylphenidate, and Placebo in the Treatment of Adult Attention Deficit Hyperactivity Disorder. *JAMA Psychiatry, 72*(12), 1199–1210.

Philipsen, A., Richter, H., Peters, J., Alm, B., Sobanski, E., Colla, M., et al. (2007). Structured group psychotherapy in adults with attention deficit hyperactivity disorder. *The Journal of Nervous and Mental Disease, 195*(12), 1013–1019.

Reid, M.J., Webster-Stratton, C., & Baydar, N. (2004). Halting the development of conduct problems in head start children: the effects of parent training. *Journal of Clinical Child and Adolescent Psychology, 33*, 279–291.

Retz-Junginger, P., Retz, W., Blocher, D., Stieglitz, R.D., Georg, T., Supprian, T., et al. (2003). [Reliability and validity of the Wender-Utah-Rating-Scale short form. Retrospective assessment of symptoms for attention deficit/hyperactivity disorder]. *Nervenarzt, 74*(11), 987–993.

Rösler, M., Retz, W., Retz-Junginger, P., Thome, J., Supprian, T., Nissen, T., et al. (2004). [Tools for the diagnosis of attention-deficit/hyperactivity disorder in adults. Self-rating behaviour questionnaire and diagnostic checklist]. *Nervenarzt, 75*(9), 888–895.

Roy, A., Hechtman, L., Arnold, L.E., Sibley, M.H., Molina, B.S., Swanson, J.M., et al. (2016). Childhood Factors Affecting Persistence and Desistence of Attention-Deficit/Hyperactivity Disorder Symptoms in Adulthood: Results from the MTA. *Journal of the Academy of Child and Adolescent Psychiatry, 55* (11), 937–944.

Sonuga-Barke, E.J., Daley, D., & Thompson, M. (2002). Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD? *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(6), 696–702.

Stoolmiller, M., Eddy, J.M., & Reid, M.J. (2000). Detecting and describing preventive intervention effects in a universal school-based randomized trial targeting delinquent and violent behavior. *Journal of Consulting Clinical Psychology, 68,* 296–309.

Wang, C.H., Mazursky-Horowitz, H., & Chronis-Tuscano, A. (2014). Delivering Evidence-Based Treatments for Child Attention-Deficit/Hyperactivity Disorder (ADHD) in the Context of Parental ADHD. *Current Psychiatry Reports, 16* (10), 474.

Weiss, M., Hechtman, L., & Weiss, G. (2000). ADHD in parents. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(8), 1059–1061.

Wittchen, H.-U., Zaudig, M., & Fydrich, T. (1997). *Strukturiertes Klinisches Interview für DSM-IV. Manual zum SKID-I und SKID-II*. Göttingen: Hogrefe.

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