Early Regulatory Problems in Infancy and Psychopathological Symptoms at 24 Months: A Longitudinal Study in a High-risk Sample

Anna Sidor* Cristina Fischer and Manfred Cierpka
Department of Psychosomatic Cooperation Research and Family Therapy, Heidelberg University Hospital, Heidelberg, Germany

Abstract

**Background:** This study investigates the association between regulatory disorders in infants at five months and the development of early childhood problems at 24 months.

**Methods:** The sample was made up of 223 mother-child dyads from multi-problem families who participated in German family support research project “Nobody slips through the net”: These families faced psychosocial risks (e.g. poverty, excessive demands on the mother and mental health disorders of the mother, measured with the risk screening instrument Heidelberger Belastungsskala-HBS) and maternal stress, determined with the Parental Stress Index (PSI-SF). The children’s psychopathologic symptoms and possible early regulatory problems were evaluated by means of Child Behavior Checklist (CBCL 1 1/2-5) and a German questionnaire assessing problems of excessive crying, along with sleeping and feeding difficulties (SFS).

**Results:** A statistically significant association between excessive crying, whining and sleeping problems of 5-month-old infants and both externalizing and internalizing problems of the same infants at age 2 (accounting for 17% and 15% of the variance, respectively) was found after controlling for maternal education, maternal status and infant sex. Feeding problems had no effect on the subsequent development of early childhood problems. Both externalizing and internalizing difficulties were associated with concurrent maternal distress (15% and 12% of the variance) and maternal assessment of the child as being a “difficult child” (14% and 5%, respectively), whereas concurrent maternal depressive symptoms contributed only marginally to the variance explanation (2% for both CBCL scales) at child’s age of 24 months.

**Conclusion:** The results show that infants’ regulatory problems contribute substantially to an increased risk of both externalized and internalized psychologic problems in early childhood in the high-risk sample. Easily accessible support services provided by family health visitors (particularly to the so-called “at-risk families”) are strongly recommended to help prevent the broadening of children’s early regulatory problems into other areas of behavior.

**Keywords:** Early regulatory problems; Psychopathologic symptoms; Maternal stress; Mother-child-interaction; Families at risk

Introduction

Early regulatory disorders are understood as difficulties infants have in adjusting to the environment, regulating their behavior and arousal and in self-calming. These difficulties reveal themselves in symptoms characteristic of age and developmental stages, such as crying or sleeping and feeding problems [1]. Crying in the first three months is regarded as the expression of the usual difficulty experienced in initial adjustment to childhood development [2]. However, according to the guidelines of the German Association for Child and Youth Psychiatry excessive crying/whining beyond the first 3 to 4 months of life is seen as a regulatory problem in early infancy, pertaining to interaction and regulatory contexts, such as self-calming, sleeping and feeding. In such a case, the infant would fuss or cry inconsolably and to an excessive degree [3]. The symptoms typically appear two weeks postnatal, peaking in the sixth week and generally decreasing at the end of the third month [4,5]. As for the prevalence of excessive crying in the first three months, frequencies between 5 and 19% were determined [6]. Persistency of crying beyond the third month was reported in 5.8% of the cases and beyond the sixth month in 2.5% of them [7]. An estimated 5% of all excessive crying cases have organic causes, such as gastrointestinal problems (gastrointestinal reflux, colic), atopy or neuropediatric disorders [5].

Around the third month, most children’s self-regulation abilities improve in a surge of development. Excessive crying can be replaced during the course of early childhood development by other symptoms (e.g. sleep disorders) [8]. A study by von Kries et al. [7] showed that ongoing sleep and feeding problems among children who still cried excessively at 6 months had increased by a factor of 6 to 9.

As with increased crying, the temporary problems relating to the sleep-wake cycle represent normal postnatal adjustment difficulties. According to the guidelines for the diagnosis of regulatory disorders, non-organic sleep disorders are only diagnosed from the 6th month, since the day-night and sleep-wake cycles are still establishing themselves in the first half of the first year of life [6]. In the second half of the first year (between the 7th and the 9th months), the so-called reorganisation processes set in, which lead to an accumulation of sleep problems involving waking and crying at night [9]. Characteristic problems include falling and/or staying asleep (generally accompanied by crying). Sleeping problems are seen as being related to parental support for falling (and re-falling) asleep: The children are unable to

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fall asleep on their own. The estimated prevalence of early sleeping disorders in the first two years of life ranges between 10 and 30% [6,10].

Feeding problems are also frequently temporary disorders that occur during weaning and introduction of pureed and solid food to the diet. According to the guidelines of the German Association for Child and Youth Psychiatry, a feeding disorder is said to be present when feeding is perceived by the parents as stressful, a meal requires more than 45 minutes, and/or the interval between meals is less than 2 hours [3]. The parent-child interaction during feeding is also strained. Due to fear of malnutrition, parents put pressure on the child, contributing to the perpetuation of feeding problems. Since meals in such cases require a great deal of time, the child is fed very frequently, and even during sleep, which results in infants/toddlers lacking hunger as a motivation to eat [6]. Zero to Three [1], a diagnostic system that classifies psychopathological pictures in the first three years of life, distinguished six diagnostic subtypes of feeding disorders, defined by symptoms and clinical course: “feeding disorder of state regulation”, “feeding disorder of caregiver-infant reciprocity”, “infantile anorexia”, “sensory food aversion”, “posttraumatic feeding disorder” and “feeding disorder associated with a concurrent medical condition”.

The prevalence of mild to moderate feeding disorders in the first two years of life is estimated at approx. 15-25% and of serious disorders at 3-10% [11].

Influence of regulatory problems on later behavioural problems

Regulatory disorders that persist longer than the first 3 to 4 months present a potentially unfavorable factor for further childhood development. The persistence and “broadening” of the child’s regulatory disorders into other areas of behavior contribute to an increased risk of further social-emotional and cognitive impairment in infancy. However, the negative influence does not seem to be strong [8,12]. Negative reactivity and “difficult temperament” during toddlerhood are reported to be mediated by maternal variables, such as maternal involvement and sensitivity [13]. Stifter and Spinrad [14] reported that excessively crying infants had higher levels of negative reactivity and a lower capacity for self-regulation at 5 and 10 months during a laboratory examination compared to “typical criers”. The lower capacity for self-regulation applied, however, only to boys. Wurmser et al. [9] reported that infants with a diagnosis of excessive crying at the age of 4 months were judged to be temperamentally more “difficult” at 30 months, in comparison to other children. In addition, a greater frequency of both externalizing and internalizing problems (CBCL 2-3) were found among children who had cried excessively as babies.

In the study of Wolke et al. [15], the negative influence was found until the primary school age (8-10 years); parents judged the temperament of children who had cried excessively as babies higher on the “emotional-negative” and “difficult” scale. Above that, a greater frequency of externalizing disorders, such as hyperactivity and behavioral problems, was observed. In addition, teachers judged the learning progress of such children lower compared to the control group (particularly in relation to hyperactivity).

Similarly, Desantis et al. [16] found an association between duration of whining and unease in the first weeks of life, emotional reactivity and externalizing disorders from the ages of 3 to 8.

The data on sleeping disorders and later behavioral disorders are more limited. Scher and Zuckerman [17] found an association between frequent night waking in the first year of life and a higher CBCL score at 3 1/2 years of age. However, the predictive validity of sleeping disorder accounted for only 3% of the behavior problem variance.

In a study by Schmid et al. [18] persistent multiple regulatory disorders (increased crying, sleeping and feeding disorders in the 5th month) predicted adjustment difficulties and a lack of social skills for pre-school children (56 months). This association applied, however, only to boys.

The results of the Mannheim Child Risk Study point to a more favorable overall prognosis for isolated regulatory disorders: the rate of behavioral problems in later childhood was only slightly higher than among children from the control group [19]. Children with multiple regulatory disorders showed significantly higher rates of subsequent disorders, both internalizing and externalizing. These multiple regulatory disorders, nevertheless, played a minor role in comparison to the psychosocial pressures on the families included in the study: the highest rate of mental disorders was found among children who had suffered multiple regulatory disorders as infants and who were also subject to high psychosocial risks.

According to the meta-analysis conducted by Hemmi et al. [20], persistent excessive crying has the greatest effect on subsequent symptoms: on externalized problems (d=0.51) and internalized problems (d=0.50), and on ADHD (d=0.42). Feeding problems (d=0.21) and multiple regulatory disorders (d<0.45) were only held in connection with general behavioral disorders. Infant sleeping problems in this study had only a small influence on internalized disorders (d=0.24) and general behavioral disorders (d=0.42), while the effect for ADHD was substantial (d=1.30).

With regard to the long-term effects of early regulatory disorders on cognitive development, there is only limited evidence to date and the studies carried out showed only small or very small effects [21,22].

Link between child’s behaviour problems and maternal well-being

Some findings report significant correlations between the infant’s behaviour problems and parental well-being. St. James-Roberts et al. [13] report higher rates of maternal depression and maternal stress at children’s age of 15 months. Wake et al. [12] report higher maternal scores on PSI scales “parental distress” and “difficult parent-child-interaction”, as well as maternal depressive symptoms at children’s age of 24 months, but only if the infant’s problems were persistent. Wurmser et al. [9] found a positive association between the CBCL scores for both externalized and internalized problems in former crying/fussing babies and their mothers with depressive symptoms at the child’s age of 30 months. Lam et al. [23] reported higher maternal depression scores and CBCL scores in 3- and 4-year-old children with current sleep disorders. Some results suggest a negative influence of maternal depressive symptoms on children’s psychological outcomes [24].

The present study involved children raised in high-risk families, and thus, more vulnerable to further stressors and maladaptive outcomes [25]. Laucht et al. [19] found the highest rate of mental problems among children who had suffered multiple regulatory disorders as infants, they were also found to be susceptible to high psychosocial risks.

This study is part of the controlled intervention study “Nobody slips through the net” (KfdN) that investigates effects of the early
The data for the controlled intervention study “Nobody slips through the net” (KfdN)¹ and acted as an intervention (IG) or comparison (CG) group. All of these families are in a stressful situation through psychosocial risks, such as poverty or low maternal education levels, have an additional effect on the child’s externalized and internalized problems. If any evidence of a negative impact of early regulatory problems on a child’s psychopathologic symptomatic could be found around the child’s second birthday, it would emphasize the importance of early preventive measures in the first years of the child’s life, particularly, for those in high-risk families.

As the children involved in our study are raised in high-risk families, we seek to investigate to what extent the occurrence of psychosocial risks, such as poverty or low maternal education levels, have an additional effect on the child’s externalized and internalized problems. If any evidence of a negative impact of early regulatory problems on a child’s psychopathologic symptomatic could be found around the child’s second birthday, it would emphasize the importance of early preventive measures in the first years of the child’s life, particularly, for those in high-risk families.

The present study builds uniquely upon previous research by examining externalized and internalized problems, in the context of regulatory disorders in a group of younger children raised in high-risk families up to the age of 24 months.

Methods

Participants

The sample comprised 224 dyads of mothers and their children who participated in the German family support research project “Nobody slips through the net” (KfdN)¹ and acted as an intervention (IG) or comparison (CG) group. All of these families are in a stressful situation through psychosocial risks, such as poverty (income below €1,000 per household—IG: 69.7%, CG: 35%), lack of social/family support (IG: 33.0%, CG: 27.8%), excessive demands on the mother (IG: 63.5%, CG: 49.3%), mother’s mental health disorder (IG: 36.9%, CG: 31.3%), violence in the partnership (IG 16.9%, CG 5.2%), or underage mothers (IG: 18.7%, CG: 6.2%).

Study design

The data for the controlled intervention study “Nobody slips through the net” (KfdN) were collected at four measurement points: a) at the child’s age of five months (pre-data gathering) and b) at seven months age, c) at 12 months (post-) and d) at 24 months (follow-up data gathering) (for more detail about the study design, procedure and effects of the early prevention program at the child’s age of one year [27]. The data for the present study was collected at two intervals: the first (T1) was at the beginning of the intervention (“Nobody slips through the net” project; see Procedure), when the children were on average 19.04 weeks old (corrected due to prematurity 18.73, SD=2.66), and the fourth (T4) at 24.70 months (SD=0.73). The dropout rate from the first to the fourth time of measurement was 26%. The main reason for dropout was the unavailability of families. Some participants changed their addresses and telephone numbers without informing. In terms of socio-demographic variables, the dropout group does not differ from the remaining study sample. This shows that the dropout was not selective.

As no differences between the two subgroups, “intervention” and “comparison”, were found (Results, descriptive statistic), they were combined in all subsequent analyses.

The study was approved by the Ethics Committee of the Heidelberg University Hospital. Participation in the study was voluntary, and the participants received a small incentive.

The characteristics of the sample are described in Tables 1 and 2.

Measures

The child’s regulatory problems were recorded by means of a parent questionnaire on regulatory disorders in early infancy—“Questionnaire on crying, feeding and sleep (SFS)” [28]. The SFS refers to a “typical week” in everyday family life and can be applied within the first year of the child’s life. The Questionnaire contains 52 items (response mode: "1=never/seldom" to "4=always"): 3 to capture Wessel’s “rule of threes” 24 for crying, whining and sleeping (e.g. cry duration, sleep latency), 13 for feeding (feeding problems, concerns about the child’s weight) [29]. The remaining 12 items assess the co-regulation, i.e. calming strategies that parents use when their child cries, or when it wakes up at night and cannot go back to sleep. The more difficulties children show in terms of crying, feeding and sleeping, the higher the values are in the SFS.

The assessment criteria of the questionnaire, which was constructed on a theoretical and factor-analytic level, were tested on a sample of 642 infants (both clinical and non-clinical subsamples). The factor analysis resulted in three easily interpreted areas: “crying, whining and sleep problems” (Cronbachs α=0.89), “feeding problems” (α=0.82) and “co-regulation” (calming strategies of parents against the child’s crying and sleep problems) (α=0.81). With regard to validity, the SFS distinguished well between the clinical and non-clinical samples. Links were found to exist between the SFS and both diary entries and clinical diagnoses in the clinical sample (parent-infant consultation hours). Because of our interest in regulation problems, rather than strategies, parents’ use when their baby cries, this study did not utilize the co-regulation scale.

Psychic disturbances were assessed with the German Version of the Child Behavior Checklist for ages 1 ½-5 [30,31]. CBCL assesses details of children’s “psychic functioning”, obtaining reports from parents, other close relatives, and/or guardians regarding children’s competencies and behavioural/emotional problems. The checklist consists of 100 items (response mode: “0=not true”, “1=somewhat or sometimes true” to “2=very true or often true”). The following seven syndrome scales are measured: “Emotionally Reactive” (Cronbachs α=0.73), “Anxious/Depressed” (α=0.66), “Somatic Complaints” (α=0.80), “Withdrawn” (α=0.75), “Sleep Problems” (α=0.78), “Attention...
Intervention group | Comparison group | Significance
---|---|---
Age of mothers M (SD) | 24.5 (6.7) | 28.2 (6.4) | p<0.000
n (n%) | n (n%) | p=0.032
Marital status | 29 (24.8%) | 50 (39.1%) | p=0.008
Married | 24 (20.5%) | 29 (22.7%) |
Single mother | 61 (52.1%) | 44 (34.4%) |
Single, a new partner | 3 (2.6%) | 5 (3.9%) |
Education |  |  |  |
Without qualification | 27 (25%) | 13 (10.4%) | p<0.000
Secondary general school | 47 (43.5%) | 47 (37.6%) |
Intermediate secondary school | 25 (23.1%) | 39 (31.2%) |
Technical college entrance qualification | 3 (2.8%) | 5 (4%) |
University entrance diploma | 4 (3.7%) | 13 (10.4%) |
University | 2 (1.9%) | 8 (6.4%) |
Monthly income per household |  |  |  |
< €1,000 | 76 (69.7%) | 41 (35%) | p<0.000
€1,000-€1,500 | 9 (8.3%) | 43 (36.8%) |
€1,500-€2,000 | 15 (13.8%) | 16 (13.7%) |
> €2,000 | 9 (8.3%) | 17 (14.5%) |
Nationality |  |  |  |
German | 94 (83.9%) | 99 (78%) | n. s.
Turkish | 6 (5.4%) | 7 (5.5%) |
Other | 12 (10.8%) | 21 (16.6%) |

Table 1: Sociodemographic data on sample (mothers) at first measurement point (child’s age 19 weeks).

Table 2: Children’s information at birth and at first measurement point T1.

The short form of the German version of the standardized parental questionnaire, PSI–SF ("Parental Stress Index Short Form"), was used to measure maternal stress, quality of mother-child interaction, and child’s "difficult" temperament [32]. This short form consists of 36 items, with the answer format ranging on a five-level scale, from "strongly agree" to "don’t agree at all." The questionnaire is divided into three subscales: the "parental distress" scale (Cronbachs α=0.87), the "dysfunctional parent-child interaction" scale (α=0.80) and the "difficult child" scale (α=0.85).

The Allgemeine Depressionsskala (ADS, General Depression Scale) was used to measure depressive symptoms of the mothers [33]. This is a 20-item screening instrument with a 4-level answer format ("seldom", "sometimes", "often" and "most of the time"). The cutoff value of the instrument for a clinically relevant depressive disorder is 23. The internal consistency with α=.89, the high concordance with Beck Depression Inventory (BDI) and Hamilton Depression Scale (HAM-D), and the fair discriminant validity of the instrument are considered definite.

The general exposure to risk of the families was measured with the help of the "Heidelberger Belastungsskala" [Heidelberg Stress Scale] (HBS) [34]. The HBS was developed for a low-threshold and multi-professional assessment of a family’s stress and resources after the birth of a child. It measures the level of family-functioning in the following five areas: (1) child’s stress: illness, disability, prematurity; (2) parental stress: underage mothers, excessive demands on the parents, mental illness, substance abuse; (3) family stress: lack of family-support, single parent families, chronic or severe illness of a sibling, age difference between siblings lower than 18 months; (4) social stress: poor or no social support, antisocial environment and (5) Material stress: poverty constricted housing conditions.

The responses can be "yes", "probably", "no" or "yes" "no", with values ranging between 0 (no stress) and 100 (very high stress). The following range allocations were set using the HBS: range 0-20: no
load: 21-40: small to moderate load; 41-60: middle load; 61-80: high load; 81-100: extremely high load. The HBS shows an excellent inter-rater reliability within a homogeneous professional group (psychology students) (ICC=0.92). As regards construct validity, significant correlations were found with both maternal sensitivity (CARE Index) \(r=0.20; p=0.001\) and maternal distress (PSI) \(r=0.14, p=0.05\). In terms of the predictive validity, the risk of taking the child into care in case of high stress in the HBS was increased by 4.5 times (ibid.)

**Procedure**

For recruitment of high-risk families, we approached institutions that potentially had contact with pregnant women and mothers (with newborn children) burdened by psychosocial risk factors. We contacted maternity clinics, welfare offices, pregnancy counseling services, midwife practices, pediatricians, family support institutions, counseling centers, etc. in Baden-Württemberg, Rheinland-Pfalz and Hessen. The burdened families in the comparison group lived beyond the KidN intervention areas. Furthermore, the comparison group families were not involved in family support programs that could be compared with the intervention of the family midwives in the project area ("interventions as usual"). Families were asked to participate through cooperating research partners. Following identification of a potential family, we sent relevant contact details to the members of the study group.

As soon as the consent to contact a family was received from the cooperating institutions, the family was contacted by a student assistant, specially trained for family contact and data gathering. The participating mothers were informed about the study and data protection at the first appointment in their personal households. The participating mothers were informed about the study and data protection at the first appointment in their personal households. The families agreed to the data protection terms and conditions and signed the participation consent form. Following this, the stress levels were assessed (HBS, Measurement Instruments) (T0). If all the conditions for participation were met (a sufficiently high stress level-i.e. a HBS value over 20 and adequate language proficiency), the families were contacted again at the first measurement point (T1: child’s age five months) and a set of surveys, including the SFS and PSI-SF was completed.

The next time each family was contacted was around the child’s second birthday. Appointments were sought by telephone for the fourth measurement point (T4), which was conducted in the same way as the first (T1). At Time 4, parents completed a set of surveys including the CBCL, ADS and PSI.

The varying numbers of test participants within the variables presented are the result of varying response rates.

**Statistical Analyses**

For the multivariate prediction of externalised and internalised psychic disturbances and concurrent sleeping problems at T4, regulatory disorder at T1, PSI-scales at T4 and ADS at T4 were entered step by step into a hierarchic regression equation (method enter) intended to account for different contributions to the variance explanation \(R^2\) Change. Potential confounding variables, such as maternal education level, household income, premature birth, infant’s gender and belonging to the group (IG vs. CG), were included in the model and fitted in the equation.

The potential differences between two groups, IG and CG, regarding continuous variables were tested with the Mann-Whitney-U-Test owing to the unfulfillment of the normal distribution requirement (Kolmogorov-Smirnov-Test significant, Table 3).

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| Intervention group | Comparison group | Comparison between groups (U-test) | Normal distribution (whole group) (K-S-Z) |
|--------------------|------------------|-----------------------------------|-----------------------------------------|
|                    | M (SD)           |                                   |                                         |
| SFS "Crying, whining and sleep" T1 | 1.54 (0.31) n=143 | 1.56 (0.30) n=150 | n.s. **                                |
| SFS "Feeding problems" T1 | 1.22 (0.29) n=143 | 1.23 (0.29) n=150 | n.s. ***                                |
| CBCL internalised problems T4 | 7.16 (5.76) n=70 | 6.07 (4.41) n=55  | n.s. **                                |
| CBCL externalised problems T4 | 10.71 (7.14) n=76 | 10.91 (6.76) n=57 | n.s.                                   |
| CBCL sleeping problems T4 | 2.39 (2.43) n=76 | 2.55 (2.12) n=56  | n.s. ***                                |
| ADS T4               | 13.39 (8.89) n=88 | 13.45 (5.61) n=105 | n.s. *                                  |
| PSI "Parental distress" T1 | 2.09 (0.72) n=108 | 2.27 (0.77) n=132 | p<.053 n.s.                            |
| PSI "Dysfunctional parent-child interaction" T1 | 1.43 (0.47) n=100 | 1.39 (0.43) n=131 | n.s. ***                                |
| PSI "Difficult child" T1 | 1.66 (0.65) n=88  | 1.62 (0.55) n=129 | n.s. ***                                |
| PSI "Parental distress" T4 | 2.24 (0.82) n=101 | 2.30 (0.79) n=114 | n.s.                                   |
| PSI "Dysfunctional parent-child interaction" T4 | 1.56 (0.51) n=101 | 1.56 (0.53) n=114 | n.s. ***                                |
| PSI "Difficult child" T4 | 2.04 (0.68) n=100 | 2.09 (0.69) n=114 | n.s. *                                  |

SFS: Questionnaires on Crying, Feeding and Sleeping; ADS: Allgemeine Depressionsskala; PSI: Parental Stress Index; CBCL: Child Behavior Checklist; K-S-Z: Kolmogorov-Smirnov-Test; U-test: Mann-Whitney-U-test; **: p ≤ 0.05; ***: p ≤ 0.01; ***: p ≤ 0.001; n.s.: not significant

Table 3: Descriptive statistics on SFS scales (T1), CBCL 1 ½-5 scales (T4), ADS scales (T4) and PSI scales (T1, T4).
Additionally, for overview of associations between parameters at T4 (CBCL, ADS, PSI), as well as for testing potential multi-collinearity among independent variables, Spearman’s rank correlations were computed. For all calculations, a significance level of 0.05 was determined (two-tailed). The statistical analysis of the data was conducted using the statistics program SPSS for Windows, Version 19.0.

Results

Descriptive Statistics

Table 3 shows descriptive statistics for all variables applied. No differences between two subgroups, intervention and comparison were found.

Correlations between CBCL, ADS, and PSI at T4

Table 4 shows highly significant positive rho correlations between all the tested parameters at T4. Both CBCL scales, external and internal, are associated with maternal depressive symptoms (r=0.52 and r=0.46, respectively), maternal distress (r=0.44 and r=0.33), dysfunctional parent-child-interaction (r=0.31 and r=0.44) and maternal assessment of the child as “difficult” (r=0.49 and r=0.45) (Table 4).

Prediction of the externalised problems (CBCL) at two years by means of regulatory disorder at five months

The SFS scale for “crying, whining and sleep problems” at T1 was a highly significant predictor (Beta=0.43, p=0.000), contributing to 17% of the variance of the children’s externalized problems at T4 ($R^2$ Change=0.17, p=0.000). The inclusion of maternal distress (PSI) and the maternal assessment of the child as “difficult” (PSI) at T4 improved the explanatory power of the model independently and significantly (contribution of “maternal distress” $R^2$ Change=0.15, Beta=0.41, p=0.000; of “difficult child” $R^2$ Change=0.14, Beta=0.70, p=0.000). Maternal depressive symptoms (ADS) at T4 contributed only little additional variance to the model ($R^2$ Change=0.02, Beta=0.19, p=0.053). Feeding problems at T1, “Dysfunctional parent-child-interaction” (PSI) at T4, as well as all maternal and infant’s demographic variables did not contribute to the externalized problems. The final model explained 49% of the variance in the children’s externalised problems.

Table 4: Spearman’s Rho correlations for CBCL scales, maternal depressive symptoms (ADS), maternal stress levels (PSI), dysfunctionality of mother-child interaction (PSI) and “difficult child” scale (PSI) at 2 years (T4).

| CBCL external | CBCL internal | ADS | PSI “Parental distress” | PSI “Dysfunctional interaction” | PSI “Difficult child” |
|---------------|---------------|-----|-------------------------|-------------------------------|-----------------------|
| N=113         | N=128         | N=193| N=125                   | N=215                        | N=214                 |
| .541***       | .422***       | .457***| .333***                 | .440***                      | .487***               |
| N=119         | N=128         | N=120| N=119                   | N=119                        | N=127                 |
| .517***       | .442***       | .459***| .646***                 | .449***                      | .467***               |
| N=113         | N=128         | N=120| N=192                   | N=192                        | N=191                 |
| .333***       | .333***       | .663***| .530***                 | .449***                      | .456***               |
| N=119         | N=125         | N=215| N=215                   | N=215                        | N=214                 |

Table 4: Spearman’s Rho correlations for CBCL scales, maternal depressive symptoms (ADS), maternal stress levels (PSI), dysfunctionality of mother-child interaction (PSI) and “difficult child” scale (PSI) at 2 years (T4).

Table 5: Linear regression analysis for investigating effects of infant regulatory problems at (19 weeks) on child’s externalised problems at 2 years (N=101).
at the fourth measurement point ($R^2=0.55$; corrected $R^2=0.49$; $F=9.92$; $p=0.000$) (Table 5).

### Prediction of the internalised problems (CBCL) at two years by means of regulatory problems at five months

The SFS scale for “crying, whining and sleep problems” at T1 was a highly significant predictor ($\beta=0.40$, $p=0.000$), contributing to 15% of the variance of the children’s internalised problems at T4 ($R^2$ change=0.15, $p=0.000$). The inclusion of maternal stress parameter at T4 as “parental distress” (PSI) ($R^2$ change=0.12, $\beta=0.37$, $p=0.000$), “dysfunctional parent-child-interaction” (PSI) ($R^2$ change=0.05, $\beta=0.30$, $p=0.01$) and maternal assessment of child as “difficult” (PSI) ($R^2$ change=0.05, $\beta=0.41$, $p=0.008$), significantly improved the explanatory power of the model. Separate contribution of maternal depressive symptoms at T4 was very small and statistically marginal ($R^2=0.44$; $F=7.71$; $p=0.000$) (Table 5).

### Prediction of the concurrent sleeping problems (CBCL) at two years by means of regulatory problems at five months

The SFS scale for “crying, whining and sleep problems” at T1 explained 11% of variance of concurrent sleeping problems at two years of age (CBCL) ($R^2$ change=0.11, $\beta=0.33$, $p=0.001$, $F=2.82$, $p=0.014$) after controlling for sociodemographic variables, child variables, PSI scales and ADS scale. All other variables were not significant and made no independent contribution to concurrent sleeping problems.

### Discussion

#### Influence of regulatory disorders in infancy on externalised and internalised problems at two years of age

The aim of this study was to examine the extent to which regulatory disorders in infants at five months account for their psychiatric disturbances at 24 months. In line with other research our findings indicate an association between early regulatory disorders and subsequent children’s psychic problems [8,15,16,19,20]. Our results show a highly statistically significant association between crying, whining and sleeping disorders at five months, and one and a half years later, for both externalized and internalized problems, controlling for the net income per household, mother’s educational level, prematurity and the child’s gender, maternal distress and depressive symptoms, dysfunctional mother-child interaction and the mother’s perception of her child being “difficult”. In 24-month-old children, 17% of the variance in the children’s externalized problems and 15% of the variance in the children’s internalized problems were explained by crying and sleep problems during the 5th month.

Overall, in previous research, the negative influence of the early regulatory disorders did not seem to be strong [8,12]. For instance, in a cohort study, Wake et al. [12] found that persistent sleeping disorders in the first year account for only 1.4% of the variance of CBCL at two years. In their meta-analysis, Hemmi et al. [20] report a medium effect of persistent excessive crying on both externalized ($d=0.51$) and internalized problems ($d=0.50$).

In our study, however, the association between early regulatory disorders and psychological/behavioral problems at two years was quite pronounced. This could speak for a phenomenon specific to our socioeconomically disadvantaged sample. Mothers in a high-risk population are likely to be more challenged by difficulties with their children and have fewer resources, such as social support or

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| Model summary | $R^2$ Change | $R^2$ | Corrected $R^2$ | $F$ | $\beta$ |
|---------------|-------------|-------|----------------|-----|--------|
| Block 1       |             |       |                |     |        |
| Mother’s education | 0.10**     | 0.10  | 0.08           | 4.99** | n.s.   |
| Household income | n.s.       |       |                |     | -0.26**|
| Block 2       |             |       |                |     |        |
| Premature infant | n.s.       | 0.12  | 0.08           | 2.95*  | n.s.   |
| Gender infant  | n.s.        |       |                |     |        |
| Block 3       |             |       |                |     |        |
| Group (IG / CG) | n.s.       | 0.12  | 0.07           | 2.46*  | n.s.   |
| Block 4       |             |       |                |     |        |
| SFS Crying/ Sleep T1 | 0.15***  | 0.27  | 0.22           | 5.45*** | 0.49***|
| Block 5       |             |       |                |     |        |
| SFS Feeding T1 | n.s.       | 0.27  | 0.22           | 4.70*** | n.s.   |
| Block 6       |             |       |                |     |        |
| PSI "Parental Distress’ T4 | 0.12*** | 0.39  | 0.33           | 7.13*** | 0.37***|
| Block 7       |             |       |                |     |        |
| PSI “Dysfunctional parent-child interaction’ T4 | 0.05** | 0.44  | 0.38           | 7.31*** | 0.30** |
| Block 8       |             |       |                |     |        |
| PSI "Difficult Child’T4 | 0.05** | 0.48  | 0.42           | 7.83*** | 0.41** |
| Block 9       |             |       |                |     |        |
| ADS T4        | 0.02+       | 0.51  | 0.44           | 7.71*** | 0.22+   |

$**$: $p \leq 0.001$; $***$: $p \leq 0.01$; $+$: $p \leq 0.10$; n.s.: not significant; SFS: Questionnaires on Crying, Feeding and Sleeping; ADS: Allgemeine Depressionsskala; PSI: Parental Stress Index; IG: Intervention Group; CG: Comparison Group

Table 6: Linear regression analysis for investigating effects of infant regulatory problems at 19 weeks on child’s internalised problems at 2 years ($N=94$).
access to counseling services, in comparison to their more fortunate counterparts. This, in turn, may contribute to the broadening of the children’s initial regulatory problems. Children born into high-risk families appear to be more vulnerable to further stresses and maladaptive outcomes [25,33]. Similarly, Laucht et al. [19] found the highest rate of mental problems among children who had suffered multiple regulatory disorders as infants, and who were also subjected to high psychosocial risks.

It remains unclear why feeding problems at five months show no influence on children’s externalised or internalised symptoms at two years. Feeding disturbances in the 5th month, frequently observed during the introduction of solid food, are fairly common and most likely to be temporary [6,36]. It is possible that the feeding difficulties observed during the 5th month are merely a transitive phenomenon with no clinical implications for the child’s further development. In another study on this sample, we found as well no impact of feeding problems at five months on the child’s development at 12 months [37].

The sociodemographic control variables barely explain the psychic problems suffered by the children. The fact that the high-risk sample belongs to a rather low socioeconomic class, presumably limited the variance. We found only a negative effect of the maternal low income on the children’s internalised problems.

**Link between maternal distress and depressive symptoms, dysfunctionality in mother-child interaction, child’s “difficult” temperament and child’s concurrent sleeping problems at two years**

Both externalized and internalized problems at the age of 24 months were associated with concurrent maternal distress, accounting respectively for 15% and 12% of the variance and maternal assessment of the child as “difficult” (14% and 5% of the variance, respectively), whereas concurrent maternal depressive symptoms contributed marginally to variance explanation (2% of the variance for both CBCL-scales). In bivariate analyses, however, both externalised and internalised problems were found to correlate strongly with concurrent maternal depressive symptoms. In the regression model, PSI scales contributed mostly to the explanation of the variance of children’s externalised and internalised problems, whereas the role of maternal depressive symptoms was marginal as a predictor, probably due to multicollinearity with parental distress. A strong correlation between maternal depressive symptoms and maternal distress (r=0.66) suggests that both self-report methods, ADS and the PSI scale “parental distress”, possibly measure quite similar constructs. Mothers’ distress and dissatisfaction with their life is strongly related to the extent of their depressive symptoms.

Both externalized and internalized problems at children’s age of 24 months were associated with maternal assessment of the child as “difficult” (accounting for 14% and 5% of the variance, respectively), whereas dysfunctional mother-child interaction was linked only to internalized problems. Again, bivariate externalised and internalised problems correlated strongly with dysfunctional mother-child interaction, but in case of external problems, the dysfunctional parent-child interaction was likely redundant as a predictor due to multicollinearity with parental distress.

**Link between crying and sleeping problems at five months of age and sleeping problems at two years of age**

The sleeping and crying disorders at five months explained about 11% of the variance of sleeping problems at two years. This finding suggests a certain, but rather moderate continuity of regulatory problems: 89% variance of the problems at both measurement points was still not common. Since the construction of the SFS scale used to record the early regulation disorders does not allow for a separate view of sleep and crying problems, it is only theoretically possible to gauge whether it is the sleep problems, or rather the crying that had impact on later psychic disturbances. The distinction is not possible diagnostically either: According to guidelines for the diagnosis of regulatory disorders, sleep disorders are only diagnosed from the 6th month since the day-night and sleep-wake cycles are still establishing themselves in the first half of the first year of life [3].

In this study, we found no association between sleeping problems at two years and either maternal stress levels, or the degree of dysfunctionality in mother-child interaction, or the child’s temperamental “difficulty”, which suggests that those concurrent sleeping problems have hardly any negative impact on maternal well-being at two years of age. The other results investigating the same sample only at the first measurement point, however, show a moderate association between crying and sleeping problems at five months and maternal distress: Persistent crying and sleep disorders in early infancy affected both the well-being of parents and the relationship between parents and infant [38]. Persistent sleep problems in children also lead to extreme sleep deprivation in parents [9]. The question remains, why this link at two years is no longer significant. Did these parents in the meantime successfully cope with the children’s problems?

In our study, the association between regulatory disorders at five months and at two years was weaker than the one between early regulatory disorders and externalising or internalising problems at two years. This somewhat perplexing result needs further investigation. Presumably, the mechanisms of sleep disturbances at two years and early crying or sleeping problems in the first half year of age are mostly different. At toddler age, dysfunctional behavioural habits play an important role, inducing, among other things, frequent night-waking. In early infancy, in contrast, difficulties pertaining to arousal regulation, such as coping with overstimulation and problems with calming down, contribute to crying or sleep disturbances.

The etiological mechanisms involved in the long-term effects of early regulatory disorders on subsequent emotional or behavioral problems in children remain unclear. Presumably, serious early regulatory problems could be an expression of a “difficult temperament” with poor adjustment to the environment [8]. Excessive crying beyond three months is regarded as an indicator of dysfunctional regulatory capacities and probably low behavioral inhibition, and an overall predictor of subsequent behavioral problems [15]. Ineffective regulatory mechanisms, stimulus hypersensitivity and deficits in behavior regulation purportedly play an important role in the formation of regulatory disorders [20]. Our results, in line with other findings, demonstrate a strong link between mothers’ assessment of children as “difficult” and psychic problems (r=0.49 for external and r=0.45 for internal problems). In a multivariate analysis, too, we found that both early regulatory problems and mothers’ assessment of children as “difficult” had an independent predictive power, with respect to children’s psychic disturbances at two years. The link to externalized problems, however, was far stronger, accounting for 14% of the variance, than the one to internalized problems (only 5% of the variance was explained). This not-so-surprising result shows that externalized problems, such as aggressive behavior or attention...
disorders, are more strongly linked to temperamental “difficulty” than internalized problems such as being anxious/depressed, withdrawn or somatic complaints.

Although this study did not focus on the effects of the early prevention program KfdN, it is important to mention that the intervention in the first year of the child’s life produced no long-term effects on its behavioral problems at two years. The KfdN-program shows positive effects only in the post-gathering point (T3). Presumably, the intervention was either to short or not intense enough to reveal long-term effects. Furthermore, almost half of the families from the comparison group received social assistance in the first year after their child’s birth, too. This could have interfered with the intervention effects of the KfdN program [27].

Limitations: It should be noted that our study deals with a risk sample, limiting the generalisability of results with respect to other different samples. It can also be assumed that the study subjects who were exposed to psychosocial stress, had difficulties while filling out the questionnaires, which could have contributed to distortions in the response behaviour. Apart from that, the social desirability factor in questionnaires should be taken into account. Besides our selective sampling and the corresponding lack of a normative control sample, the direction of maternal stress and maternal depressive symptoms as predictors of the CBCL scales in the regression model could be questioned.

Conclusion: Our results reinforce existing knowledge about the relationship between regulatory problems in infants and their later psychic disruptions. The results show that infants’ regulatory problems contribute substantially to an increased risk of both externalized and internalized psychic problems in early childhood in the high-risk sample. Externalized and internalized psychic problems are associated with increased maternal stress and dysfunctional mother-child interaction and maternal assessment of the child as “difficult”.

Clinical Implication: Our findings provide evidence for a distinctly negative influence of early regulation problems on children’s psychic health. As a result, the healthcare system—particularly, physicians and midwives employed in the healthcare system, but also family members—should be made more aware of the sensitivities of, and pressures on, young mothers (and probably fathers, too) and additional support should be provided to families. In case of severe regulatory difficulties, it is advisable to draw parents’ attention to the parent-infant advisory services, which not only help improve early childhood regulatory disorders, but also support mother-child interaction and help relieve pressure on young families. It is crucial to improve the awareness of possible long-term effects of early regulatory disorders in the healthcare system. Easily to conduct diagnostic measurements of early regulatory disorders, such as crying and sleeping diaries, completing the SFS-questionnaire or assessing Wessel’s rule of three could help with the identification of these problems. Unfortunately, SFS does not offer cut-of-values yet, so that we rather suggest applying sleeping-crying-diaries and Wessel’s rule as more practicable.

An easy access to support services provided by, e.g. family health visitors is recommended too, particularly in the so-called “high risk families”, as it seems that a negative impact of early regulatory disorders was particular pronounced in the socio-economically disadvantaged sample. Services offering early assistance after childbirth (e.g. the KfdN prevention project or comparable projects) have proved to be effective in improving children’s social development, as well as reducing dysfunctionality in mother-child interaction, and therefore, can be a valuable addition to the outreach initiatives [26,27].

Competing Interests
The authors declare that they have no competing interests.

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References
1. Zero to Three (2005) Diagnostic classification: Diagnostic classification of mental health and developmental disorders of infancy and early childhood: Revised edition (DC: 0-3R). Washington, DC, Zero to Three Presses, USA.
2. Largo RH, Benz-Castellano C (2004) Die ganz normalen Krisen-Fit und Misfit im Kleinkindesalter. In: Regulatoriostörungen der frühen Kindheit, Papoušek M, Schieche M, Wurmser H (Ed.), Verlag Hans Huber, Bern, Germany 17-30.
3. Hofacker N von, Lehmkühl U, Riesch F, Resch A, Papoušek M, et al. (2007) Regulatoriostörungen im Säuglings-und Kleinkindalter. In: Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie und-psychotherapie (eds) Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter.
4. Papoušek M (2006) Frühkindliche Regulatoriostörungen. In: Lehrbuch der Psychotherapie, Band IV: Verhaltenstherapie mit Kindern und Jugendlichen und ihren Familien, Matteja F München (Ed.), CIP Medien 407-420.
5. Helt-Bonacci C, Cierpka M (2012) Exzessives Schreien. In: Frühe Kindheit 0-3 Jahre. Beratung und Psychotherapie für Eltern mit Säuglingen und Kleinkindern. Cierpka M (Ed.), Springer, Berlin, Heidelberg, Germany 171-198.
6. Wurmser H (2009) Schrei-, Schlaf- und Fütterungstörer. Právalenz, Persistenz, Prädiktoren und Langzeitprognose. Monatschrift Kinderheilkunde 157: 574-579.
7. von Kries R, Kalies H, Papoušek M (2006) Excessive crying beyond 3 months may herald other features of multiple regulatory problems. Arch Pediatr Adolesc Med 160: 508-511.
8. Hofacker N von, Jacobell T, Malinowski M, Papoušek M (1996) Diagnostik von Beeinträchtigungen der Mutter-Kind-Beziehung bei frühkindlichen Störungen der Verhaltensregulation. Kindheit und Entwicklung 5: 160-167.
9. Wurmser H, Papoušek M, Hofacker N von (2004) Langzeitrisiken persistierender exzessiven Säuglingsschreisens. In: Regulatoriostörungen der frühen Kindheit, Papoušek M, Schieche M, Wurmser H (Ed.), Verlag Hans Huber, Bern, Germany 311-338.
10. Scholtes K, Benz M, Demant H (2012) Schlafstörungen im Kindesalter. In: Frühe Kindheit 0-3 Jahre. Beratung und Psychotherapie für Eltern mit Säuglingen und Kleinkindern, Cierpka M (Ed.), Springer, Berlin, Heidelberg, Germany 199-218.
11. Hofacker N von (2009) Frühkindliche Regulatoriostörungen. Neuere Entwicklungen und ihre Relevanz für die Praxis. Monatschrift Kinderheilkunde 157: 567-573.
12. Wake M, Morton-Alen E, Poulakis Z, Hiscock H, Gallagher S, et al. (2006) Prevalence, stability, and outcomes of cry-fuss and sleep problems in the first 2 years of life: Propective community-based study. Pediatrics 117: 836-842.
13. St. James-Roberts J, Conroy S, Wilsher C (1998) Stability and outcome of persistierenden exzessiven Säuglingsschreisens. In: Regulationsstörungen der frühen Kindheit, Papoušek M, Schieche M, Wurmser H (Ed.), Verlag Hans Huber, Bern, Germany 171-198.
14. Stifter CA, Spinrad TL (2002) The effects of excessive crying and hyperactivity on the development of emotion regulation. Infancy 3: 133-152.
15. Wolke D, Rizzo P, Woods S (2002) Persistent infant crying and hyperactivity problems in middle childhood. Pediatrics 109: 1054-1060.
16. Desantis A, Coster W, Bigsby R, Lester B (2004) Colic and fussing in infancy, and sensory processing at 3 to 8 years of age. Infant Mental Health J 6: 522-539.
17. Scher A, Zukerman S (2005) Persistent night waking and settling difficulties across the first year: Early precursors of later behavioural problems? J Reproduct Infant Psychol 23: 77-86.
18. Schmid G, Schreier A, Meyer R, Wolke D (2010) A prospective study on the persistence of infant crying, sleeping and feeding problems and preschool behaviour. Acta Paediatr 99: 286-290.

19. Laucht M, Schmidt MH, Esser G (2004) Frühkindliche Regulationsprobleme: Vorläufer von Verhaltensauffälligkeiten des späteren Kindesalters? In: Regulati onsstörungen der frühen Kindheit, Papousek M, Schieche M, Wurmser H (Ed.), Hans Huber Verlag, Bern, Germany 339-356.

20. Hemmi MH, Wolke D, Schneider S (2011) Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: A meta-analysis. Arch Dis Child 96: 622-629.

21. Rao MR, Brenner RA, Schisterman EF, Vik T, Mills JL (2004) Long term cognitive development in children with prolonged crying. Arch Dis Child 89: 989-992.

22. Wolke D, Schmid G, Schreier A, Meyer R (2009) Crying and feeding problems in infancy and cognitive outcome in preschool children born at risk: A prospective population study. J Dev Behav Pediatr 30: 226-238.

23. Lam P, Hiscock H, Wake M (2003) Outcomes of infant sleep problems: a longitudinal study of sleep, behavior and maternal well-being. Pediatrics 111: e203-e207.

24. Luoma I, Tamminen T, Kaukonen P, Laippala P, Puura K, et al. (2001) Longitudinal study of maternal depressive symptoms and child well-being. J Am Acad Child Adolesc Psychiat 40: 1367-74.

25. Wadsworth ME, Achenbach TM (2005) Explaining the link between low socioeconomic status and psychopathology: Testing two mechanisms of the social causation hypothesis. J Consult Clin Psychol 73: 1148-1153.

26. Cierpka M, Keiner fällt durchs Netz® (2005) Wie hoch belastete Familien unterstützen werden können. Familien dynamik 34: 36-47.

27. Sidor A, Kunz E, Eickhorst A, Cierpka M (2013) The effects of the early prevention program “Keiner fällt durchs Netz” (KfdN) [“Nobody slips through the net”] on child, on mother and on their relationship. A controlled study. Infant Mental Health J 34: 11-24.

28. Gross S, Reck C, Thiel-Bonney C, Cierpka M (2013) Empirical basis of the questionnaire for crying, feeding and sleeping. Prax Kinderpsychiatr Kinderpsychosomatik 62: 327-347.

29. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC (1954) Paroxysmal fussing in infancy, sometimes called colic. Pediatrics 14: 421-435.

30. Achenbach TM, Rescorla LA (2000) Manual for the ASEBA preschool forms & profiles. University of Vermont, Research Center for Children, Youth and Families, Burlington, VT, Chittenden.

31. Arbeitsgruppe Deutsche Child Behavior Checklist (2002) Elitenfragebogen für Klein- und Vorschulkinder (CBCL/1 ½-5). Arbeitsgruppe Kinder-, Jugend- und Familien diagnostik (KJFD), Köln.

32. Abidin RR (1995) Parenting Stress Index: Professional manual. (3rd Edn), Psychological Assessment Resources, Lutz, FL, USA.

33. Hautzinger M, Bailer M (1993) Allgemeine Depressions Skala. Manual. Beltz Test GmbH, Göttingen, Germany.

34. Sidor A, Eickhorst A, Stasch M, Cierpka M (2012) Assessing risk exposure in families within the scope of early intervention: The Heidelberg Stress scale (HBS) and its quality criteria. Prax Kinderpsychiatri Kinderpsychosomatik 61: 766-780.

35. Waddell C, Offord DR, Shepherd CA, Hua JM, McEwan K (2002) Child psychiatric epidemiology and Canadian public policy-making: The state of the science and the art of the possible. Can J Psychiatry 47: 826-832.

36. Hofacker H von, Papoušek M, Wurmser H (2004) Fütter- und Gedeihstörungen im Säuglings- und Kleinkindalter. In: Papoušek M, Schieche H, Wurmser H (Eds.), Regulationsstörungen der Frühen Kindheit. Frühe Risiken und Hilfen im Entwicklungskontext der Eltern- Kind-Beziehungen. Hans Huber: Bern, Germany 171-199.

37. Sidor A, Fischer C, Eickhorst A, Cierpka M (2013) Influence of early regulatory problems in infants on their development at 12 months: A longitudinal study in a high-risk sample. Child Adolesc Psychiatry Ment Health 7: 35.

38. Sidor A, Thiel-Bonney C, Kunz E, Eickhorst A, Cierpka M (2012) Persistent, excessive crying in 5-month-old infants and the pre-, peri- and postnatal adversities of their mothers in a high-risk sample. Z Kinder Jugendspsychiatr Psychother 40: 239-250.

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