Crying and Feeding Problems in Infancy and Cognitive Outcome in Preschool Children Born at Risk: A Prospective Population Study

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ABSTRACT: Objective: To investigate whether regulatory problems, i.e., crying and feeding problems in infants older than 3 months of age, predict cognitive outcome in preschool children born at risk even when controlled for confounding factors. Methods: A prospective longitudinal study of children born in a geographically defined area in Germany. N = 4427 children of 6705 eligible survivors (66%) participated at all 4 assessment points (neonatal, 5, 20, and 56 months of age). Excessive crying and feeding problems were assessed at 5 months. Mental development was measured with the Griffiths Scale at 20 months, and cognitive assessments were conducted at 56 months. Neonatal complications, neurological, and psychosocial factors were controlled as confounders in structural equation modeling and analyses of variance. Results: One in 5 infants suffered from single crying or feeding problems, and 2% had multiple regulatory problems, i.e., combined crying and feeding problems at 5 months. In girls, regulatory problems were directly predictive of lower cognition at 56 months, even when controlled for confounders, whereas in boys, the influence on cognition at 56 months was mediated by delayed mental development at 20 months. Both in boys and girls, shortened gestational age, neonatal neurological complications, and poor parent-infant relationship were predictive of regulatory problems at 5 months and lower cognition at 56 months. Conclusion: Excessive crying and feeding problems in infancy have a small but significant adverse effect on cognitive development.

single RP occurring together, has been found in the range of 2% to 7% in the general population of infants and toddlers.\textsuperscript{2,18,35,36}

Although crying/fussing and/or sleeping problems are usually transient in early infancy,\textsuperscript{18,37} there is an increasing evidence that persistent excessive crying beyond the colic period (i.e., older than 3 months of age) is predictive of increased attention-hyperactivity problems, lower fine motor function, and poorer educational, language, or cognitive outcome.\textsuperscript{35,38} Up to 80% of children with persistent crying problems referred for treatment had also either sleeping or feeding problems or both.\textsuperscript{39,40}

Thus, it appears that the presence of multiple RP rather than the individual regulation difficulties may be associated with an increased risk for delays in motor, language, and cognitive development.\textsuperscript{41}

Conceptually, persistent crying or feeding problems indicate a lack of inhibition of behavior, e.g., the inability to alter state and stop crying, or to inhibit the tendency of neophobia (acceptance of new food). Similarly, solving tasks in cognitive tests requires self-regulation, i.e., both in attending to tasks and inhibiting inappropriate impulsive responses.\textsuperscript{42,43} Thus, persistent early RP in infancy may continue as self-regulation problems when solving cognitive problems in childhood. Furthermore, early problems in behavior regulation and cognitive scores in childhood have shown to be predicted by neonatal neurological problems, shortened gestational age, and poor parent-infant relationship.\textsuperscript{38,44–49} The socioeconomic status is the most frequently reported major influence on cognitive development,\textsuperscript{50–55} and continued breastfeeding has been associated with higher cognitive scores in childhood.\textsuperscript{56–58} Thus, these factors need to be considered when evaluating the contribution of early persistent crying and feeding behavior to cognitive development. Finally, gender differences have been found with respect to self-regulatory competencies in newborns,\textsuperscript{59,60} infant RP,\textsuperscript{9,20,30,61,62} and pathways of infant self-regulation to lower mental development.\textsuperscript{59}

Previous studies of the long-term outcome of RP have some limitations. They were either based on referred samples,\textsuperscript{58} were small in sample size,\textsuperscript{55,65} or included only a limited range of possible confounder variables.\textsuperscript{41} Furthermore, there is a continuous debate whether RP in infancy are causal precursors of adverse outcomes, an indicator of delayed maturation, or the result of neurodevelopmental problems,\textsuperscript{35} an indicator of general family adversity or of poor parenting,\textsuperscript{2,63} or due to the accumulation of risk. The findings are thus tentative.

This prospective study investigated a whole geographically defined population sample of neonatal at risk infants. We addressed the question whether infant RP, i.e., persistent excessive crying and/or feeding problems are predictive of cognitive outcome in preschool children\textsuperscript{35} even when controlled for a range of neurological, psychosocial, and parenting factors. And in addition, we focused especially on gender differences.

**METHODS**

**Sample**

This epidemiological cohort sample is part of the Bavarian Longitudinal Study\textsuperscript{64,65} and consists of all infants born at risk in a geographically defined area in Southern Bavaria (Germany) during a 15-month period in 1985 to 1986 who were admitted to 1 of 16 children’s hospitals within 10 days after birth (n = 7505 of N = 70,600 life births, 10.6% of all life births, Fig. 1). None of the outpatients were included in the study. The overall aim of the Bavarian Longitudinal Study was to identify the relationship between pre-/perinatal risk factors and developmental disorders, e.g., cerebral palsy, epilepsy, visual and hearing defects, mental retardation, and behavior problems. Prenatal data were coded from the medical histories in the obstetric units, whereas peri-, neo-, and postnatal data were collected prospectively. At that time, all newborns who experienced birth complications, Caesarean section, low APGAR scores, neonatal complications (e.g., neonatal jaundice), or were born preterm were admitted to a children’s hospital neonatal unit. The treatments ranged from observation of the neonates to intensive neonatal care. The average stay was 13.1 ± 21.0 days compared with a 5- to 7-day stay in the obstetric unit for normal postnatal care. Parents were approached within 48 hours of the infant’s hospital admission, the study aims were explained, and the parents were asked to give written informed consent to participate, and 7000 of the parents consented.

![Flow-chart](https://example.com/flowchart.png)

**Figure 1.** Flow-chart—participants and dropouts.
participate. Ethical approval was obtained from the University of Munich Children’s Hospital.

This report includes all children who had participated at all 4 measurement points, i.e., neonatal, 5, 20, and 56 months of age (n = 4427, 66.0% of n = 6705 eligible survivors). Figure 1 shows the frequencies of participants, dropouts (=children with missing data at one or more assessment points), and of those who had died within the course of the study or failed to provide informed consent.

Those with missing data (dropouts) came more often from single parent families were of lower socioeconomic status or were not born to German parents compared with participants. In addition, dropouts lived more often in cities, and mothers and fathers were slightly younger than participants’ parents. Participants were more likely to be born by means of Caesarean section, and their gestational age was slightly lower. Moreover, they had experienced more neonatal problems (intensity of neonatal treatment index [INTI] score), and their head circumference was smaller compared with dropouts. There were no differences between participants and dropouts in the prevalence of regulatory problems (RP) at 5 months (Table 1).

Measures

Regulatory Problems (5 months)

As part of a neurodevelopmental assessment, parents received a standard interview by study pediatricians. Crying and feeding behaviors and problems with these behaviors at 5 months of age were recorded in a standard format. The definitions of crying and feeding problems are shown in Table 2. Crying problems were diagnosed when at least 1 of the 4 criteria were fulfilled. For feeding problems at least 1 of the 3 symptoms had to be present.

Sleeping problems at 5 months of age were assessed but not considered for the RP score as sleeping problems should not be diagnosed in infants younger than 6 months of age.11

Outcome Measures (20 and 56 Months)

At 20 months of age, the mental development was evaluated using the Griffiths Scale66,67 that assesses the following 5 dimensions: locomotor development, personal-social development, hearing and speech, hand and eye coordination, and performance. A total developmental quotient across the 5 domains was computed according to the German norms66: developmental quotient = (developmental age score/age at assessment) × 100. The Griffiths Scale is widely used in Europe,68 and both reliability and validity have been demonstrated.59–71

At 56 months, the cognitive development was assessed using the following instruments: the Columbia Mental Maturity Scale (CMMS), the Active Vocabulary Test (AWST), and the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI). All cognitive assessments were carried out by trained research pediatricians.

The CMMS assesses the general reasoning ability of children between the ages of 3 and 10 years.72,73 The CMMS consists of 8 age-specific levels, each contains between 51 and 65 pictorial and figural classification items. The child has to select from a series of drawings one drawing that is out of place. The CMMS is computed as a deviation score (mean = 100, standard deviation = 15). The reliability for the CMMS is high,64 and it has been shown to be a valid assessment of nonverbal intelligence quotient.74–76

The AWST evaluates the expressive vocabulary of preschool children.77 It was developed for German-speaking countries and is similar to the widely used and valid Peabody Picture Vocabulary Test.75,78–80 The AWST consists of 82 drawings, and the child has to name the presented item. Again, a deviation score is computed (mean = 100, standard deviation = 15). Both high reliability and good concurrent and prognostic validity of the AWST have been reported.81

The Beery-Buktenica Developmental Test of VMI measures the integration of visual and motor abilities. In the VMI, short version 15 drawings of geometric forms are arranged in order of increasing difficulty that the child is asked to copy.82,83 Each drawing is evaluated using predefined scoring criteria, i.e., task solved versus not solved, and a sum score is computed, ranging from 0 to 15. A higher score indicates better performance. The VMI has been shown to be reliable and a valid measure of VMI.83–87

The assessments at 5 and 20 months were carried out corrected for prematurity and the 56 months assessment at chronological age.

Other Predictor Variables (Confounders)

Gestational age was determined from maternal dates of the last menstrual period and serial ultrasounds during pregnancy. When the estimates from these 2 methods differed by more than 2 weeks, Dubowitz et al88 examination result was used.

Neonatal neurological problems were assessed by the method of Casae and Eggermont.89–91 Daily assessments of (1) care level, (2) respiratory dependency, (3) feeding dependency, and (4) neurological status, i.e., mobility, muscle tone, and neurological excitability, were carried out from day 1 after birth. Each of the 6 variables was scored daily on a 4-point rating scale (0 = normal/good state to 3 = worst state). The INTI score was computed as the mean of daily ratings during the first 10 days of life or until a stable clinical state was reached sooner. The INTI score could range from 0 to 18 (higher scores indicate more problems).

The socioeconomic status was obtained by a standard interview with the infant’s parents in the first 10 days of life and computed as a weighted composite score of maternal highest educational qualification, paternal highest educational qualification, and occupation of the head of the family according to Bauer.92 The socioeconomic status
scores were recoded into the following 3 categories: 1 = lower class, 2 = middle class, and 3 = upper class.

The Parent–Infant Relationship Index was evaluated both by a standard interview with the parents and by study nurses’ observations. It consisted of 8 items, covering attachment-related parental concerns and feelings, and current or anticipated relationship problems (Table A1).64 Seven of the 8 items were assessed neonatally, and 1 item at 5 months of age (Table A1). Items were rated on 3- to 5-point rating scales and dichotomized as 0 (no concern or problem) or 1 (problem as defined by item). The sum score ranged from 0 (good parent–infant relationship) to 8.
(poor parent–infant relationship). The reliability and validity for study nurses’ observations were assured via standardized training sessions.

Breastfeeding was assessed at the age of 5 months. The mother was asked about current and/or past breastfeeding. A score was constructed ranging from 0 to 3, i.e., 0 “infant has never been breastfed,” 1 “was breastfed in the past,” 2 “still partly breastfed,” and 3 “still fully breastfed.”

Head circumference at 5 months of age was measured by research nurses during follow-up visits using a pre-defined protocol and standard tapes for head circumference measurement. Head circumference was measured twice, and the mean score was recorded (in cm).

### Statistical Analyses

Statistical analyses were conducted with SPSS 11.0 and AMOS 5.0. The criteria of normal distribution were violated in the Parent–Infant Relationship Index and in the Griffiths Scale. The former was logarithmically transformed (as both skewness and kurtosis were positive), and the latter was reflected and then logarithmically transformed (as skewness was negative and kurtosis positive). High values in the transformed Parent–Infant Relationship Index indicate poor parent–infant relationship, and high values in the transformed Griffiths Scale indicate low mental development.

Nonparametric χ² tests and parametric t tests for independent samples were conducted to check for differences between participants and dropouts (Table 1). In addition, nonparametric χ² tests were conducted to evaluate gender differences concerning the prevalence of RP. Frequencies, degrees of freedom (df), and significance levels (p) are reported.

Bivariate correlation analyses (Pearson’s) were conducted to evaluate associations between number of RP and outcome measures at 20 and 56 months of age, respectively. Correlation coefficients (r), significance levels (p) (2-tailed), and effect sizes according to Cohen (small effect if r ≥ .10; medium effect if r ≥ .30; large effect if r ≥ .50) are reported for the whole sample and separately for boys and girls (Table A2).

According to the findings in the literature, a structural equation model was constructed and tested using the maximum likelihood estimation method (Fig. 2). Two latent variables were specified, namely neonatal problems (i.e., INTI score and gestational age), and cognition (i.e., AWST, CMMS, and VMI) at 56 months. The adequacy of the model was assumed if the Bentler Comparative Fit Index and the Bentler-Bonett Normed Fit Index were ≥0.90, and the Root-Mean-Square Error of Approximation ≤0.08. In addition, unstandardized path coefficients (B), SE, critical ratios, standardized path coefficients (β), and significance levels (p) are reported (Fig. 2; Table 3). The effect sizes of the standardized path coefficients can be classified as follows: small effect if β ≥ 0.10, medium if β ≥ 0.30, and large if β ≥ 0.50. In a multigroup analysis, we checked whether there were significant differences between the models for boys and girls. The unconstrained model, i.e., the model in which the coefficients are allowed to differ between boys and girls, was compared with more restricted models, i.e., models with constant parameters for boys and girls (Table A3).

Using analyses of variance, the main effect of RP (0 = no RP at 5 months; 1 = single crying or feeding problem, 2 = multiple, i.e., crying and feeding problems), the main effect of infant’s gender, and the interaction effect of RP × infant’s gender on mental (Griffiths Scale at 20 months) and cognitive development (CMMS, AWST, and VMI at 56 months) were evaluated. All analyses of variance were adjusted for confounders (gestational age, INTI score, Parent–Infant Relationship Index, socioeconomic status, head circumference, and breastfeeding). For the main and interaction effects F values, degrees of freedom (df), and significance levels (p) are reported (Table 4). If the main effect of RP was significant, post hoc tests (Bonferroni, adjusted for confounders) were conducted, and if the interaction term (RP × infant’s gender) was significant, the post hoc tests were conducted separately for boys and girls. Means (±standard deviations), significance levels (p), and effect sizes (Cohen’s d) are reported. According to Cohen, the effect is small, if d is ≥0.2 and <0.5, the effect is medium for d ≥0.5 and <0.8, and large if d ≥0.8.

### RESULTS

**Prevalence of Regulatory Problems at 5 Months of Age**

About one fifth of the sample (20.8%) suffered from single or multiple regulatory problems (RP) at 5 months of age, namely 6.5% from single crying problems, 12.3%
from single feeding problems, and 2.0% from multiple RP, i.e., both crying and feeding problems.

Boys had more often single crying problems compared with girls (boys: 7.2%; girls: 5.6%; $\chi^2 = 12.14$; $df = 1$; $p < .001$). There were no gender differences concerning single feeding (boys: 11.9%; girls: 12.7%; $\chi^2 = 1.30$; $df = 1$; $p = .26$) or multiple RP (boys: 2.1%; girls: 1.8%; $\chi^2 = 1.51$; $df = 1$; $p = .22$).

**Correlation Analyses**

Table A2 shows that the number of RP at 5 months was significantly correlated with low mental (20 months) and cognitive development (56 months)—both for the whole sample and for the subgroups of boys and girls (Table A2).

**Structural Equation Model**

The fit indices of the conceptual model were acceptable both for the whole sample ($n = 4427$) (Root-Mean-Square Error of Approximation: 0.061; Comparative Fit Index: 0.93; Normed Fit Index: 0.93), and for the subgroups of boys ($n = 2397$) and girls ($n = 2030$) (Root-Mean-Square Error of Approximation: boys: 0.065; girls: 0.060; Comparative Fit Index: 0.93/0.94; Normed Fit Index: 0.93/0.93), respectively. For the whole sample, 46% of the variance in cognition at 56 months was explained by the model, for the boys 47%, and 45% for the girls. In the multigroup analysis, the $\chi^2$ difference test concerning the unconstrained model and more restricted models showed that there are statistically significant differences between boys and girls, except for the measurement weights (factor loadings) (Table A3). Additionally, for the unconstrained model and for model 1 (= model with constant measurement weights across subgroups of boys and girls) the fit indices were good, i.e., both Comparative Fit Index and Normed Fit Index $>0.90$ and Root-Mean-Square Error of Approximation $<0.08$ (Table A3). Thus, Model 1 (constant measurement weights) was adopted.

The estimated model including standardized path coefficients ($\beta$) is shown in Figure 2. In Table 3, unstandardized path coefficients ($B$), SE, critical ratios, and significance levels ($p$) are reported. In girls, the number of RP at 5 months was directly predictive of cognition at 56 months ($\beta = -0.05$; $p = .03$; very small effect), but in boys the direct path was not significant ($\beta = -0.01$; $p =$ ***p < .05; **p < .01; ***p < .001.

*Parent-Infant Relationship Index (PIRI) was logarithmically transformed; high values indicate poor parent-infant relationship.

*Regulatory problems at 5 months of age, i.e., number of regulatory problems: 0 = neither crying nor feeding problems, 1 = single regulatory problem (crying or feeding problems), 2 = multiple regulatory problems (crying and feeding problems).

*Mental development score (20 months) was reflected and logarithmically transformed; high values indicate low mental development.

PIRI, Parent–Infant Relationship Index; VMI, Visual-Motor Integration; AWST, Active Vocabulary Test; CCMS, Columbia Mental Maturity Scale.

Figure 2. Estimated model for boys ($n = 2397$)/girls ($n = 2030$) with Standardized Path Coefficients (boys/girls); Measurement weights assumed as constant across groups.

PIRI, Parent–Infant Relationship Index; VMI, Visual-Motor Integration; AWST, Active Vocabulary Test; CCMS, Columbia Mental Maturity Scale.

Table 2. Regression weights in the structural model for boys and girls ($n = 4427$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circumference</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Mental development</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>PIRI</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Still breastfeeding</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Neonatal problems</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>Regulatory problems</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>5 months</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>20 months</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
<tr>
<td>56 months</td>
<td>0.10***</td>
<td>0.10***</td>
</tr>
</tbody>
</table>

**PIRI, Parent–Infant Relationship Index; VMI, Visual-Motor Integration; AWST, Active Vocabulary Test; CCMS, Columbia Mental Maturity Scale.**
effect in girls was the effect of RP on cognition in girls ([0.05 - 0.50] was similar compared with the direct effects in boys and girls (Griffiths Scale: Group 0: 1.36 ± 0.16; Group 2: 1.36 ± 0.17), whereas in boys, those with no RP at 5 months had lower scores on the Griffiths Scale (20 months). Thus, the post hoc tests for the Griffiths Scale were conducted separately for boys and girls.

### Table 3. Estimated Model With Measurement Weights Assumed as Constant Across Groups—Unstandardized Path Coefficients (B), SE, Critical Ratios, and Significance Levels (p)

<table>
<thead>
<tr>
<th></th>
<th>Boys (n = 2397)</th>
<th></th>
<th></th>
<th>Girls (n = 2030)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE (B)</td>
<td>CR</td>
<td>p</td>
<td>B</td>
<td>SE (B)</td>
</tr>
<tr>
<td>Neonatal problems</td>
<td>0.018</td>
<td>0.003</td>
<td>5.26</td>
<td>&lt; .001</td>
<td>0.018</td>
<td>0.003</td>
</tr>
<tr>
<td>Regulatory problems</td>
<td>0.126</td>
<td>0.048</td>
<td>2.60</td>
<td>.009</td>
<td>0.142</td>
<td>0.049</td>
</tr>
<tr>
<td>Head circumference</td>
<td>-0.049</td>
<td>0.010</td>
<td>-4.99</td>
<td>&lt; .001</td>
<td>-0.049</td>
<td>0.010</td>
</tr>
<tr>
<td>Head circumference</td>
<td>0.037</td>
<td>0.007</td>
<td>5.20</td>
<td>&lt; .001</td>
<td>0.020</td>
<td>0.008</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>-0.389</td>
<td>0.083</td>
<td>-4.69</td>
<td>&lt; .001</td>
<td>-0.321</td>
<td>0.084</td>
</tr>
<tr>
<td>Mentality development</td>
<td>-0.021</td>
<td>0.003</td>
<td>-8.27</td>
<td>&lt; .001</td>
<td>-0.019</td>
<td>0.003</td>
</tr>
<tr>
<td>Mental development</td>
<td>0.017</td>
<td>0.001</td>
<td>12.56</td>
<td>&lt; .001</td>
<td>0.017</td>
<td>0.001</td>
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<tr>
<td>Neonatal problems</td>
<td>-0.093</td>
<td>0.006</td>
<td>-14.38</td>
<td>&lt; .001</td>
<td>-0.093</td>
<td>0.006</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>0.359</td>
<td>0.022</td>
<td>16.39</td>
<td>&lt; .001</td>
<td>0.322</td>
<td>0.023</td>
</tr>
<tr>
<td>Regulatory problems</td>
<td>1.071</td>
<td>0.409</td>
<td>2.62</td>
<td>.009</td>
<td>0.228</td>
<td>0.432</td>
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<tr>
<td>Mental development</td>
<td>-0.376</td>
<td>0.663</td>
<td>-0.57</td>
<td>.57</td>
<td>-1.531</td>
<td>0.703</td>
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<tr>
<td>Head circumference</td>
<td>-48.918</td>
<td>1.987</td>
<td>-24.61</td>
<td>&lt; .001</td>
<td>-43.663</td>
<td>1.939</td>
</tr>
<tr>
<td>Head circumference</td>
<td>-1.195</td>
<td>0.170</td>
<td>-7.02</td>
<td>&lt; .001</td>
<td>-1.167</td>
<td>0.182</td>
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<tr>
<td>Breastfeeding</td>
<td>2.118</td>
<td>0.239</td>
<td>8.88</td>
<td>&lt; .001</td>
<td>1.941</td>
<td>0.258</td>
</tr>
<tr>
<td>Parent-Infant relationship</td>
<td>-6.198</td>
<td>1.560</td>
<td>-3.97</td>
<td>&lt; .001</td>
<td>-8.356</td>
<td>1.540</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>5.002</td>
<td>0.438</td>
<td>11.43</td>
<td>&lt; .001</td>
<td>4.455</td>
<td>0.450</td>
</tr>
</tbody>
</table>

CR, critical ratios; PIRI, Parent–Infant Relationship Index.

aCR = B/SE (CR > 1.96 indicates that the path coefficient is significant at the .05 level). bPIRI: high values indicate poor relationship. cMental development: high values indicate low mental development.

### Table 4. Effects of RP at 5 mo, Infant’s Gender, and RP × Infant’s Gender on Mental and Cognitive Development at 20 and 56 mos

<table>
<thead>
<tr>
<th></th>
<th>Number of RPa</th>
<th></th>
<th></th>
<th>Main Effects</th>
<th></th>
<th></th>
<th></th>
<th>Interaction Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 3501)</td>
<td>1 (n = 829)</td>
<td>2 (n = 88)</td>
<td>Gender</td>
<td>RP</td>
<td>Gender</td>
<td>RP × Gender</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>Mean</td>
<td>F; df</td>
<td>p</td>
<td>F; df</td>
<td>p</td>
</tr>
<tr>
<td>Griffiths Scale</td>
<td>1.37</td>
<td>0.17</td>
<td>1.40</td>
<td>0.16</td>
<td>1.43</td>
<td>0.17</td>
<td>9.49; 2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CMMS</td>
<td>95.94</td>
<td>19.12</td>
<td>95.38</td>
<td>19.31</td>
<td>91.84</td>
<td>19.33</td>
<td>41.25; 1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>AWST</td>
<td>94.08</td>
<td>18.65</td>
<td>91.98</td>
<td>18.80</td>
<td>88.12</td>
<td>18.87</td>
<td>4.11; 1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>VMI†</td>
<td>6.50</td>
<td>2.47</td>
<td>6.19</td>
<td>2.47</td>
<td>5.88</td>
<td>2.48</td>
<td>3.22; 1</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

RP, Regulatory Problems; INTI, intensity of neonatal treatment index; PIRI, Parent–Infant Relationship Index; SES, socioeconomic status; HC, head circumference; CMMS, Columbia Mental Maturity Scale; AWST, Active Vocabulary Test; VMI, Visual-Motor Integration.

aNumber of RP at 5 mo: 0 = no regulatory problems; 1 = single (crying or feeding problem); 2 = multiple (crying and feeding problems). bGriffiths Scale (20 mos): reflected and log-transformed; high values indicate low mental development. cCognitive development at 56 mos. Analyses adjusted for gestational age, INTI score, PIRI, SES, HC, and breastfeeding; significant effects (p < .05) are in bold.
Griffiths Scale (i.e., higher mental development at 20 months; 1.39 ± 0.16) compared with boys with single (1.41 ± 0.16; \( p = 0.013; d = 0.16 \), very small effect) or multiple (1.50 ± 0.16; \( p < 0.001; d = 0.68 \), medium effect) RP at 5 months, and male infants with multiple RP had higher scores on the Griffiths Scale (i.e., lower mental development) than those with single RP at 5 months (\( p = 0.004; d = 0.52 \), medium effect).

Furthermore, there was an interaction effect (RP × gender) on the nonverbal intelligence quotient score (Columbia Mental Maturity Scale, 56 months). Again, the post hoc tests were conducted separately for boys and girls. In girls, there were no significant differences among the 3 groups of RP (Group 0: 98.15 ± 18.25; Group 1: 95.88 ± 18.35; Group 2: 98.54 ± 18.17). In boys, infants with multiple RP had significantly lower Columbia Mental Maturity Scale scores (84.85 ± 19.84) compared with those with no RP (93.47 ± 19.82; \( p = 0.012; d = 0.44 \), small effect) or with single RP (94.65 ± 19.88; \( p = 0.005; d = 0.49 \), small effect), respectively.

Finally, concerning the Active Vocabulary Test (AWST) and the Visual-Motor Integration (VMI), there were main effects of RP and of gender. The post hoc tests for the 3 groups of RP showed that infants with no RP had higher AWST and VMI scores compared with those suffering from single (AWST: \( p = 0.22; d = 0.11 \), very small effect/VMI: \( p = 0.008; d = 0.13 \), very small effect) or multiple (AWST: \( p = 0.17; d = 0.32 \), small effect/VMI: \( p = 0.087 \) [only significant trend]; \( d = 0.25 \), small effect) RP at 5 months (means ± SD are reported in Table 4). Infants with single RP did not differ significantly from those with multiple RP (AWST: \( p = 0.25; d = 0.20 \), small effect/VMI: \( p = 0.87; d = 0.13 \), very small effect).

Besides, the main effects of gender on the Griffiths Scale, the Columbia Mental Maturity Scale, the AWST, and the VMI indicated that boys had significantly lower mental and cognitive development scores than girls (more detailed results available on request).

**DISCUSSION**

In this prospective whole population study with a sample born at risk, we found nearly 1 in 5 infants to suffer from a single regulatory problem (RP), and 2% to suffer from combined crying and feeding problems at 5 months. These rates are consistent with those of other studies (e.g., Refs. 15,33,35). Most notably, our results indicate that RP maintained weak but significant effects on mental and cognitive development at 20 and 56 months, even when controlled for gestational age, neurological problems, parent-infant relationship, socioeconomic status, head circumference, and breastfeeding. This large prospective study supports findings of previous smaller studies: RP make a small but significant contribution to the prediction of cognitive development. 55,58

Cognitive development from early infancy into childhood is unstable, thus individuals have been found to change unpredictably in their abilities with traditional developmental tests in the first 6 months of life showing little or no prediction to later intelligence quotient. 106 The unadjusted correlations of RP with the mental and cognitive measures at 20 or 56 months of age (0.08 to 0.14, Table A2) were small but similar to those found between early infancy developmental tests and childhood intelligence quotient. A recent evaluation of a new generation infant cognitive measure assessing efficiency of habituation also found no direct prediction of 4-year intelligence quotient, but indirect effects on cognitive status. 55 Viewed in this context, it is notable that RP assessed at 5 months of age were found to relate to mental (20 months) and cognitive development (56 months), even after controlling for a range of potential confounders. In contrast, mental development assessed at 20 months made the largest contribution to the prediction of cognition at 56 months compared with all other variables. Thus, mental development assessed in the second year of life is a fairly good predictor of preschool cognition.

We found that neonatal problems as measured by gestational age and the intensity of neurological complications were predictive both of RP and of mental and cognitive development suggesting that early neurological difficulties influence infant behavior regulation and cognition. As shown in previous studies, shortened gestational age and neonatal complications can have adverse impact on brain development. 107,108 Furthermore, shortened gestational age is often associated with maternal stress or anxiety during pregnancy. 109,110 Stress leads to a dysregulation of the HPA (hypothalamic-pituitary-adrenal) axis, and stress hormones adversely affect the development of the fetal brain and its plasticity. 111 inhibit neural genesis in the hippocampus, 112 and may thus impact cognition. In addition, stress might change the distribution of dopamine levels in the prefrontal cortex, 113 and both dopamine and the prefrontal cortex are involved in cognitive and self-regulation processes. 114,115 It has been shown that women who experienced stress and emotional problems during pregnancy were at increased risk for having an excessively crying infant at 3 to 6 months of age. 44,116 However, we did not assess maternal stress during pregnancy, and we can thus only speculate that stress and minor neurological damage may be mechanisms linking neonatal complications with both RP and cognition. Additionally, the quality of the parent-infant relationship may moderate the adverse effects of prenatal stress on subsequent adverse outcome. 117

In our study, poor parent-infant relationship made a small prediction of infant RP 59,118 and of lower cognition, 46,47 after controlling for the major impact of socioeconomic status of the family. 50-55 Papousek and Papousek 49 proposed that parents use intuitive parenting skills to support the infant’s regulation of affective arousal and attention, quality of alert waking states, self-soothing, transition to sleep, or feeding. If these intuitive
skills are inhibited (i.e., by poor parent–infant relationship), parents are less able to compensate for the infant’s limited initial self-regulatory competencies. For example, feeding problems reflect relational problems in the social-engagement process. Problems occurring in the feeding interaction may affect social processing, and poor parent–infant relationship may have an adverse impact on cognitive development.

Comparison of path models indicated significant gender differences. In girls, RP were directly predictive of lower cognition at 56 months, whereas in boys, the influence on cognition at 56 months was mediated by low mental development at 20 months. Our results suggest that sensor-motor experiences are more important for boys than girls. This finding might be explained by differences in androgens that influence the rate of maturation of specific brain regions or different brain activation and cognitive strategies. Moreover, in boys, multiple RP had a larger adverse impact on the mental development and on the nonverbal intelligence quotient than single RP (small to medium effect sizes), whereas in girls, there were no significant differences between the impact of single and multiple RP. Although we did not assess genetic profiles, recent reports suggest that only in boys, the presence of a certain allele of the dopamine receptor gene (DRD4-7r) is associated with the occurrence of multiple RP. Additionally, this allele seems to be correlated with the prevalence of attention-deficit/hyperactivity disorder in boys during childhood. However, small genetic effects may be moderated by experience, e.g., the DRD4-7r interacts with the quality of parenting concerning the child’s impulsivity.

Finally, we found that girls had higher scores of mental and cognitive development than boys. This is in line with previous results. Preschool boys might be less mature in social interactions, whereas girls might be more ready and willing to do a test.

Overall, there are a number of strengths to this study. The dropout rate in our sample was low; 66% of the eligible survivors participated at all 4 measurement points in time. The study included both social and neurological measures. This allowed testing whether parenting or neurodevelopmental factors rather than RP are related to later cognitive development. Both were related to RP, but there were also unique effects of RP on cognition. In contrast, all infants were admitted to a children’s hospital after birth and were thus at increased risk for potential developmental problems. The results might not be generalizable to all infants requiring normal postnatal care. Furthermore, RP were mainly assessed by maternal responses to a structured interview. The completion of structured diaries would have been preferred but not realistic in a general population due to the often observed high subject loss in diary studies.

This study could show that infant RP make a small but independent prediction of preschool cognition in line with previous small scale studies. Furthermore, multiple RP have a more adverse effect on cognitive development than single crying or feeding problems. However, this was only found for boys. Finally, both neonatal complications and neonatal parent–infant relationship are associated with the development of RP at 5 months of age. To better understand whether RP in early infancy are the result or indicative of underlying neuronal mechanisms, genetic susceptibility, early parenting, or alterations of the brain due to maternal stress during pregnancy (e.g., measured by cortisol level or stressful life events) future prospective studies starting in pregnancy are required. Nevertheless, pediatricians should be aware of the stress caused by early RP to the parents and the longer term implications for the parent–child relationship and cognitive development. Furthermore, infants born at either biological risk, i.e., shortened gestational age with neonatal neurological problems, or in socially deprived circumstances may benefit from early interventions.

CONCLUSION

Regulatory problems may contribute to later problems in cognitive development, i.e., they may make it more difficult for infants to accommodate cognitive information, possibly because similar brain regions are involved in self-regulation and cognitive processes. Pediatricians should be aware that regulatory problems may have small adverse effects on cognitive development.

ACKNOWLEDGMENTS

We thank Dr. Marc Bornstein for his feedback on an earlier draft.

REFERENCES


Crying and Feeding Problems in Infancy and Cognitive Outcome


### Table A1. PIRI—Items, Informants, and Measurement Points

<table>
<thead>
<tr>
<th>Item</th>
<th>Informant</th>
<th>Measurement Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Mother has not yet established a relationship to the infant</td>
<td>Mother</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(2) Mother visits the infant one time per week/less on the neonatal ward</td>
<td>Mother</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(3) Father visits the infant one time per week/not at all on the neonatal ward</td>
<td>Mother or father</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(4) Mother feels very insecure with the infant’s care at home</td>
<td>Mother</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(5) Mother shows (very) little pleasure when interacting with the infant</td>
<td>Study nurse</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(6) Father shows (very) little pleasure when interacting with the infant</td>
<td>Study nurse</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(7) The probability of subsequent parent-infant care problems is rated high</td>
<td>Study nurse</td>
<td>Neonatal</td>
</tr>
<tr>
<td>(8) Mother had difficulties in establishing a relationship to the infant</td>
<td>Mother</td>
<td>At 5 mos of age</td>
</tr>
</tbody>
</table>

PIRI, Parent–Infant Relationship Index.

### Table A2. Bivariate Correlation Analyses (Pearson’s) Between Number of Regulatory Problems at 5 mos and Outcome Measures at 20 and 56 mos

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>All (n = 4427)</th>
<th>Boys (n = 2397)</th>
<th>Girls (n = 2030)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Griffiths (20 mos)</td>
<td>.12</td>
<td>&lt;.001</td>
<td>.14</td>
</tr>
<tr>
<td>CMMS (56 mos)</td>
<td>−0.08</td>
<td>&lt;.001</td>
<td>−0.08</td>
</tr>
<tr>
<td>AWST (56 mos)</td>
<td>−0.12</td>
<td>&lt;.001</td>
<td>−0.12</td>
</tr>
<tr>
<td>VMI (56 mos)</td>
<td>−0.11</td>
<td>&lt;.001</td>
<td>−0.11</td>
</tr>
</tbody>
</table>

CMMS, Columbia Mental Maturity Scale; AWST, Active Vocabulary Test; VMI, Visual-Motor Integration.

*Griffiths Scale: reflected and logarithmically transformed; high scores indicate low mental development

Effect sizes according to Cohen(99): small effects (r ≥ .10) are in bold.

### Table A3. Multigroup Analysis to Check for Differences Between Boys/Girls: Fit Indices, $\chi^2$ Statistics, and $\chi^2$ Difference Test

<table>
<thead>
<tr>
<th>Model</th>
<th>Fit Indices</th>
<th>$\chi^2$ Statistics</th>
<th>$\chi^2$ Difference Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RMSEA</td>
<td>CFI</td>
<td>NFI</td>
</tr>
<tr>
<td>Unconstrained</td>
<td>0.043</td>
<td>0.936</td>
<td>0.930</td>
</tr>
<tr>
<td>1a</td>
<td>0.042</td>
<td>0.936</td>
<td>0.929</td>
</tr>
<tr>
<td>2b</td>
<td>0.063</td>
<td>0.837</td>
<td>0.830</td>
</tr>
<tr>
<td>3c</td>
<td>0.062</td>
<td>0.818</td>
<td>0.810</td>
</tr>
<tr>
<td>4d</td>
<td>0.061</td>
<td>0.818</td>
<td>0.810</td>
</tr>
<tr>
<td>5e</td>
<td>0.060</td>
<td>0.818</td>
<td>0.809</td>
</tr>
<tr>
<td>6f</td>
<td>0.058</td>
<td>0.815</td>
<td>0.806</td>
</tr>
</tbody>
</table>

RMSEA, Root-Mean-Square Error of Approximation; CFI, Comparative Fit Index; NFI, Normed Fit Index.

*Model 1: measurement weights (factor loadings) are constant across groups.
*Model 2: Model 1 and additionally, measurement intercepts are constant across groups.
*Model 3: Model 1, 2, and additionally, structural weights (path coefficients) are constant across groups.
*Model 4: Model 1–3, and additionally, structural intercepts are constant across groups.
*Model 5: Model 1–4, and additionally, structural residuals are constant across groups.
*Model 6: all parameters are constant across groups.

NPAR = number of parameters.

The unconstrained model (=model in which the coefficients are allowed to differ between boys and girls) was compared to a nested hierarchy of 6 models (see footnotes*). Using the $\chi^2$ difference test the difference between the unconstrained model and the more restricted models was tested [$\Delta\chi^2 = \chi^2_{\text{restricted}} - \chi^2_{\text{unconstrained}}$]. If the $\chi^2$ difference test is significant the less restricted model should be retained as the null hypothesis of equal fit for both models is rejected. If the $\chi^2$ difference test is not significant which means that the fit of the restricted model is not significantly worse than the fit of the unrestricted model the restricted model should be favored. As the $\chi^2$ statistic is affected by sample size, the fit indices (RMSEA, CFI, NFI) of the models were considered, too.