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

Year of publication: Forthcoming
Link to published version: http://journals.lww.com/jrnldbp/pages/default.aspx
Publisher statement: 'This is not the original published version'

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

Running head: Crying and Feeding Problems in Infancy and Cognitive Outcome

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No financial relationships relevant to disclose, no conflict of interest.

ABSTRACT

Objective: To investigate whether regulatory problems, i.e., crying and feeding problems in infants > 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 four assessment points (neonatal, 5, 20, and 56 months of age). Excessive crying and feeding problems were measured at 5 months. Mental development was assessed 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 five 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 low 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: Regulatory problems in infancy have a small but significant adverse effect on cognitive development.

Index terms: infant crying and feeding problems, preschool cognition, prospective population study, predictors

There is increased recognition for the need of epidemiological studies of infant and toddler behavioral problems and their consequences.[1] However, a lack of consistent or standardized definition for disorders in the infancy and toddler years has hampered progress.[2,3] Current diagnostic classification schemes such as the ICD-10 and the DSM-IV only cover selected symptoms or problems of infants and toddlers, e.g., 'feeding disorder' (F98.2) in the ICD-10 or 'disorder of rumination' (307.53) and 'feeding disorder during infancy and toddlerhood' (307.59) in the DSM-IV, whereas other difficulties leading to frequent consultations with health professionals[4,5] such as persistent crying are not included or specified at all.[6-8]

One area of behavioral problems in infancy that has received increased attention are regulatory problems. These describe infants and toddlers with difficulties in regulating behavior in diverse areas such as sleeping, feeding, state control, self-calming, and mood regulation.[9] The Zero to Three organization (DC 0-3R) suggests three subtypes of regulatory problems, namely hypersensitive, hyposensitive, and sensory-stimulating/impulsive type.[10] However, a recent evaluation found that children diagnosed with the DC 0-3 classification for regulatory problems fell in a range of categories of other diagnostic schemes, indicating that it may be too wide ranging.[2] The German Child and Adolescent Psychiatric Association proposed in their diagnostic guidelines that excessive crying, feeding, and sleeping problems are the core symptoms of regulatory problems in the first year of life.[11,12]

The prevalence rates for regulatory problems during infancy and early childhood vary and are partly dependent on the underlying definition.[13,14] Persistent excessive crying (i.e., beyond the colic period or > 3 months of age) has been reported in 5-10% of infants,[15-17] while the prevalence of sleeping problems in the first years of life varies between 10% and 46%.[18-26] Feeding and eating difficulties are found in 3-10% when strict clinical criteria are applied and up to 41% in parent report studies.[2,27-34] The prevalence of multiple regulatory problems, i.e., two or three single regulatory problems occurring together, has been found in the range of 2-7% in the general population of infants and toddlers.[2,18,35,36]

While crying/fussing and/or sleeping problems are usually transient in early infancy,[18,37] there is increasing evidence that persistent excessive crying beyond the colic period (i.e., > 3 months of age) is predictive of increased attention-hyperactivity problems, lower fine motor function, and poorer educational, language, or cognitive outcome.[35,38] Up to 80% of children with persistent crying problems referred for treatment had also either sleeping or feeding problems or both.[39,40] Thus, the presence of multiple regulatory problems rather than the individual regulation difficulties may increase the risk for delays in motor, language, and cognitive development.[41]

Previous studies of the long-term outcome of regulatory problems have limitations. They were either based on referred samples,[38] were small in sample size,[35,42] or included only a limited range of possible confounder variables.[41] Furthermore, there is a continuous debate whether regulatory problems in infancy are causal precursors of adverse outcomes, an indicator of delayed maturation, or the result of neurodevelopmental problems,[35] an indicator of general family adversity or of poor parenting,[2,42] or due to the accumulation of risk.

A conceptual model concerning regulatory problems and cognitive development would have to consider a range of factors. In terms of regulatory problems and subsequent adverse cognitive outcome, there are mostly preliminary results as already mentioned above. In addition, neonatal neurological problems, shortened gestational age, and a poor parent-infant relationship may be predictors of infant regulatory problems.[38,43,44] Furthermore, gender differences have been found with respect to self-regulatory competencies in newborns,[45,46] and infant regulatory problems.[9,26,30,47,48] One study could show, that male newborns had significantly lower levels of self-regulation compared to female, and low levels of infant self-regulation were correlated with lower mental development at 2 years of age.[45] In contrast, concerning the cognitive development, some factors have repeatedly shown as predictors. The socioeconomic status is the most frequently reported major influence.[49,50-53] Additionally, there is evidence that breastfeeding, gestational age, neonatal neurological problems, growth of head circumference, and the parent-infant relationship are associated with the cognitive development in childhood.[49,54-61]

The present prospective study investigated a whole geographically defined population sample of neonatal at risk infants. We addressed the question whether infant regulatory problems, i.e., persistent excessive crying and/or feeding problems are predictive of cognitive outcome in preschool children[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 (BLS)[62,63] and consists of all infants born at risk in a geographically defined area in Southern Bavaria (Germany) during a 15-month period in 1985-1986 who were admitted to one of 16 children's hospitals within 10 days after birth (n = 7505 out of N = 70 600 life births, 10.6% of all life births, see Figure 1). No outpatients were included in the study. The overall aim of the BLS was to make a contribution to the prevention of developmental disorders, e.g., cerebral palsy, epilepsy, visual and hearing defects, mental retardation, and behavior problems. 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 to 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. Ethical approval was obtained from the University of Munich Children's Hospital. Figure A1 (Appendix) shows further details of the study protocol.

This report includes all children who had participated at all four 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.

Insert Figure 1 about here.

Those with missing data (dropouts) came more often from single parent families, were of lower socioeconomic status (SES), or were not born to German parents compared to 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 (INTI score), and their head circumference (HC) was smaller compared to dropouts. There were no differences between participants and dropouts in the prevalence of regulatory problems at 5 months (see Table 1).

Insert Table 1 about here.

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 one of the four criteria was fulfilled. For feeding problems at least one of the three symptoms had to be present.

Sleeping problems at 5 months of age were assessed[36] but not considered for the regulatory problem score as sleeping problems should not be diagnosed in infants younger than 6 months of age.[11]

Insert Table 2 about here.

Outcome Measures (20 and 56 Months)

At 20 months of age the mental development was evaluated using the *Griffiths Scale*[64,65] which assesses the following five dimensions: locomotor development, personal-social development, hearing and speech, hand and eye coordination, and performance. A total developmental quotient (DQ) across the five domains was computed according to the German norms:[64] DQ = (developmental age score / age at assessment) × 100. The Griffiths Scale is widely used in Europe,[66] and both reliability and validity have been demonstrated.[67-69]

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 *Columbia Mental Maturity Scale (CMMS)* assesses the general reasoning ability of children between the ages of 3 and 10 years.[70,71] The CMMS consists of eight age-specific levels, each contains between 51 and 65 pictorial and figural classification items. The child has to select from a series of drawings the 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,[62] and it has been shown to be a valid assessment of non-verbal IQ.[72-74]

The *Active Vocabulary Test (AWST)* evaluates the expressive vocabulary of preschool children.[75] It was developed for German-speaking countries and is similar to the widely used and valid Peabody Picture Vocabulary Test.[73,76-78] 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.[79]

The Beery-Buktenica Developmental Test of *Visual-Motor Integration (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.[80,81] 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 visual-motor integration.[81-85]

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 two methods differed by more than two weeks, Dubowitz examination result was used.[86]

Neonatal neurological problems were assessed by the method of Casaer and Eggermont.[87-89] Daily assessments of (1) care level, (2) respiratory support, (3) feeding dependency, and neurological status, i.e., (4) mobility, (5) muscle tone, and (6) neurological excitability, were carried out from day one after birth. Each of the six variables was scored daily on a 4-point rating scale (0 = normal/good state to 3 = worst state). The intensity of neonatal treatment index (*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* (*SES*) 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.[90] The SES scores were recoded into the following three categories:[91] 1 = lower class, 2 = middle class, and 3 = upper class.

The *Parent-Infant Relationship Index (PIRI)* was evaluated both by a standard interview with the parents and by study nurses' observations. It consisted of eight items, covering attachment-related parental concerns and feelings, and current or anticipated relationship problems (see Appendix, Table A1).[62] Seven of the eight items were assessed neonatally, and one item at 5 months of age (Table A1). Items were rated on 3- to 5-point rating scales and dichotomised 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 (*HC*) at 5 months of age was measured by research nurses during follow-up visits using a predefined protocol and standard tapes for head circumference measurement.[92] HC was measured twice, and the mean score was recorded (in cm).

Statistical Analyses

Statistical analyses were conducted with SPSS 11.0[93] and AMOS 5.0.[94] The criteria of normal distribution[95] 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).[96] High values in the transformed PIRI indicate poor parent-infant relationship, and high values in the transformed Griffiths Scale indicate low mental development.

Nonparametric chi-square tests (χ^2) and parametric *t* tests for independent samples were conducted to check for differences between participants and dropouts (see Table 1). In addition, nonparametric chi-square tests (χ^2) were conducted to evaluate gender differences concerning the prevalence of regulatory problems. Frequencies, degrees of freedom (*df*), and significance levels (*p*) are reported.

Bivariate correlation analyses (Pearson's) were conducted to evaluate associations between number of regulatory problems and outcome measures at 20 and 56 months of age, respectively. Correlation coefficients (*r*), significance levels (*p*) (two-tailed), and effect sizes according to Cohen[97] (small effect if $|r| \geq 0.10$; medium effect if $|r| \geq 0.30$; large effect if $|r| \geq 0.50$) are reported for the whole sample and separately for boys and girls (see Appendix, Table A2).

According to the findings in literature (see introduction) a structural equation model (SEM) was constructed and tested using the maximum likelihood estimation method (see Figure 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 (CFI) and the Bentler-Bonett Normed Fit Index (NFI) were ≥. 90, and the Root-Mean-Square Error of Approximation (RMSEA) ≤ .08. In addition, unstandardized path coefficients (*B*), standard errors (SE), critical ratios (CR), standardized path coefficients (β), and significance levels (p) are reported (Figure 2, Table 3).[98,99] The effect sizes of the standardized path coefficients can be classified as follows:[97,100] small effect if $|\beta| \geq 0.10$, medium if $|\beta| \geq 0.30$, and large if $|\beta| \geq 0.50$. 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 to more restricted models, i.e., models with constant parameters for boys and girls (see Appendix, Table A3).[101,102]

Using analyses of variance (ANOVAs), the main effect of regulatory problems (RP: 0 = no regulatory problems 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 $\times$ infant's gender on mental (Griffiths Scale at 20 months) and cognitive development (CMMS, AWST, and VMI at 56 months) were evaluated. All ANOVAs were adjusted for confounders (gestational age, INTI score, PIRI, SES, HC, and breastfeeding). For the main and interaction effects F values, degrees of freedom (*df*), and significance levels (p) are reported (see Table 4). If the main effect of regulatory problems was significant, post hoc tests (Bonferroni, adjusted for confounders) were conducted, and if the interaction term (RP $\times$ 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.[97]

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 at 5 months of age, namely 6.5% from single crying problems, 12.3% from single feeding problems, and 2.0% from multiple regulatory problems, i.e., both crying and feeding problems.

Boys had more often single crying problems compared to 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 regulatory problems (boys: 2.1%; girls: 1.8%; $\chi^2 = 1.51$; $df = 1$; $p = .22$).

Correlation Analyses

Table A2 shows that the number of regulatory problems 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 (see Appendix, Table A2).

Structural Equation Model (SEM)

The fit indices of the conceptual model were acceptable both for the whole sample (n = 4427) (RMSEA: 0.061; CFI: 0.94; NFI: 0.93) and for the subgroups of boys (n = 2397) and girls (n = 2030) (RMSEA: boys: 0.063 / girls: 0.060; CFI: 0.93 / 0.94; NFI: 0.93 / 0.93), respectively. For the whole sample 46% of the variance in cognition at 56 months were explained by the model, for the boys 47%, and 45% for the girls. In the multigroup analysis the χ^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) (see Appendix, 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 CFI and NFI > 0.90 and RMSEA < 0.08 (Table A3). Thus, model 1 (constant measurement weights) was adopted.

The estimated model including standardized path coefficients (*β*) is shown in Figure 2. In Table 3, unstandardized path coefficients (*B*), standard errors (SE), critical ratios (CR), and significance levels (*p*) are reported. In girls, the number of regulatory problems 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 ($\beta = -0.01$; $p = .57$). Nevertheless, both in boys and in girls, regulatory problems were predictive of low mental development at 20 months (boys: $\beta = 0.10$; $p < .001$; small effect; girls: $\beta = 0.05$; $p = .02$; very small effect), and in turn, mental development at 20 months was predictive of cognition at 56 months (for boys and girls: $\beta = -0.50$; $p < .001$; large effect). Thus, in boys, the indirect effect of regulatory problems on cognition via mental development at 20 months ($0.10 \times (-0.50) = -0.05$) was similar compared to the direct effect of regulatory problems on cognition in girls (-0.05). The indirect effect in girls was -0.03 ($0.05 \times (-0.50)$).[103]

Both in boys and girls, neonatal problems (i.e., neurological problems and short gestational age) and a poor parent-infant relationship were predictive of regulatory problems (see Figure 2 and Table 3).

Insert Figure 2 about here.

Insert Table 3 about here.

Effects of Regulatory Problems (RP) on Mental and Cognitive Development (ANOVA)

Table 4 shows that there were significant main effects and an interaction effect (RP × gender) on the Griffiths Scale (20 months). Thus, the post hoc tests for the Griffiths Scale were conducted separately for boys and girls. In girls, the three groups of regulatory problems did not differ significantly (Griffiths Scale: Group 0: 1.36 ± 0.15; Group 1: 1.38 ± 0.16; Group 2: 1.36 ± 0.17), whereas in boys, those with no regulatory problems at 5 months had lower scores on the Griffiths Scale (i.e., higher mental development at 20 months; 1.39 ± 0.16) compared to boys with single (1.41 ± 0.16; p = .013; |d| = 0.16, very small effect) or multiple (1.50 ± 0.16; p < .001; |d| = 0.68, medium effect) regulatory problems at 5 months, and male infants with multiple regulatory problems had higher scores on the Griffiths Scale (i.e., lower mental development) than those with single regulatory problems at 5 months (p = .004; |d| = 0.52, medium effect).

Furthermore, there was an interaction effect (RP × gender) on the nonverbal IQ score (CMMS, 56 months). Again, the post hoc tests were conducted separately for boys and girls. In girls, there were no significant differences between the three groups of regulatory problems (Group 0: 98.15 ± 18.25; Group 1: 95.88 ± 18.35; Group 2: 98.54 ± 18.17). In boys, infants with multiple regulatory problems had significantly lower CMMS scores (84.85 ± 19.84) compared to those with no regulatory problems (93.47 ± 19.82; p = .012; |d| = 0.44, small effect) or with single regulatory problems (94.65 ± 19.88; p = .005; |d| = 0.49, small effect), respectively.

Finally, concerning the AWST and the VMI, there were main effects of regulatory problems and of gender. The post hoc tests for the three groups of regulatory problems showed that infants with no regulatory problems had higher AWST and VMI scores compared to those suffering from single (AWST: p = .022; |d| = 0.11, very small effect / VMI: p = .008; |d| = 0.13, very small effect) or multiple (AWST: p = .017; |d| = 0.32, small effect / VMI: p = .087 (only significant trend); |d| = 0.25, small effect) regulatory problems at 5 months (means ± SD are reported in Table 4). Infants with single regulatory problems did not differ significantly from those with multiple regulatory problems (AWST: p = .25; |d| = 0.20, small effect / VMI: p = .87; |d| = 0.13, very small effect).

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

Insert Table 4 about here.

DISCUSSION

In this prospective whole population study with a sample born at risk, we found nearly one in five infants to suffer from a single regulatory problem, and 2% to suffer from combined crying and feeding problems at 5 months. These rates are consistent with those of other studies (e.g.,[15,33,35]). Most notably, our results indicate that regulatory problems 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: Regulatory problems make a small but significant contribution to the prediction of cognitive development.[35,38]

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 (IQ).[104] The unadjusted correlations of regulatory problems with the mental and cognitive measures at 20 or 56 months of age (.08 to .14, see Table A2) were small but similar to those found between early infancy developmental tests and childhood IQ. A recent evaluation of a new generation infant cognitive measure assessing efficiency of habituation also found no direct prediction of four-year IQ, but indirect effects on cognitive status.[56] Viewed in this context, it is notable that regulatory problems assessed at 5 months of age were found to relate to mental (20 months) and cognitive development (56 months), even after controlled for a range of potential confounders. We found that neonatal problems as measured by gestational age and the intensity of neurological complications were predictive both of regulatory problems 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.[105,106] Furthermore, shortened gestational age is often associated with maternal stress or anxiety during pregnancy.[107,108] Stress leads to a dysregulation of the HPA axis, and stress hormones adversely affect the development of the fetal brain and its plasticity,[109] inhibit neural genesis in the hippocampus,[110] and thus impact cognition. In addition, stress might change the distribution of dopamine levels in the prefrontal cortex,[111] and both dopamine and the prefrontal cortex are involved in cognitive and self-regulation processes.[112,113] 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.[114,115] However, we did not assess maternal stress during pregnancy, and thus could not replicate theses findings. Additionally, the quality of the parent-infant relationship may moderate the adverse effects of prenatal stress on subsequent adverse outcome.[116]

In our study, poor parent-infant relationship was also predictive both of lower cognition[49, 54-57] and of infant regulatory problems.[54] Papousek and Papousek[117] 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, and transition to sleep. If these intuitive skills are inhibited (i.e., by poor parent-infant relationship),[118] 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.[118,119] Problems occurring in the feeding interaction may affect social processing, and poor parent-infant relationship may have an adverse impact on cognitive development.[49, 54-57] However, the effect of the parent-infant relationship on cognition was smaller compared to the effects of mental development, socioeconomic status, head circumference, and neonatal problems, which might indicate that the PIRI is less important than the other variables.

As shown in previous studies,[49,50-53] the socioeconomic status had a major influence on the cognitive development. The mental development at 20 months had the largest effect on cognition at 56 months compared to all other variables in the model implicating that mental development as measured by the Griffiths Scale is a good predictor of preschool cognition.

Comparison of path models indicated significant gender differences. In girls, regulatory problems 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 which influence the rate of maturation of specific brain regions[120] or different brain activation and cognitive strategies.[121] Moreover, in boys, multiple regulatory problems had a larger adverse impact on the mental development and on the nonverbal IQ than single regulatory problems (small to medium effect sizes), whereas in girls, there were no significant differences between the impact of single and multiple regulatory problems. This effect might be due to the presence of a certain allele of the dopamine receptor gene (DRD4-7r$^+$): Becker et al. found that only in boys, the presence of this allele was associated with the occurrence of multiple regulatory problems.[122] Additionally, this allele seems to be correlated with the prevalence of attention-deficit/hyperactivity disorder in boys during childhood.[123] However, genes can be influenced by experiences, e.g., the DRD4-7r$^+$ interacts with the quality of parenting concerning the child's impulsivity.[113] As we did not assess the genetic profiles these associations could not be replicated in this study.

Finally, we found that girls had higher scores of mental and cognitive development than boys. This is in line with previous results.[124,45, 125, 126] Preschool boys might be less mature in social interactions, whereas girls might be more readily and willing to do a test.[127]

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 four measurement points in time. The study included both social and neurological measures. This allowed testing whether parenting or neurodevelopmental factors rather than regulatory problems are related to later cognitive development. Both were related to regulatory problems, but there were also unique effects of regulatory problems on cognition. By 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, regulatory problems were mainly assessed by maternal responses to a structured interview. The completion of structured diaries[128] would have been preferred but not realistic in a general population due to the often observed high subject loss in diary studies.[129]

This study could show associations between infant regulatory problems, preschool cognition, and possible underlying mechanisms, but could not investigate etiological factors which might lead to regulatory problems and subsequent adverse outcome. The etiology of regulatory problems such as the role of genetic factors or maternal stress during pregnancy (e.g., measured by cortisol level or stressful life events) should be focused in future prospective studies.[114,122] In addition, the role of moderating and mediating factors, e.g., family adversity,[42] concerning adverse outcome should be investigated.

Previous and the current findings indicate that there is an association between regulatory disorders and adverse cognitive development. The effects shown here are generally small.[97] Nevertheless, pediatricians should be aware of the stress caused by early regulatory problems and the longer term implications for the parent-child relationship and cognitive development.[5,35] Furthermore, infants born at risk, i.e., shortened gestational age with neonatal neurological problems or in socially deprived circumstances, may benefit from early interventions.[130,131]

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.

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Figure Legends

FIGURE 1. Flow-chart – Participants and Dropouts.

FIGURE 2. Estimated Model for Boys (n = 2397) / Girls (n = 2030) with Standardized Path Coefficients (Boys / Girls); Measurement Weights Assumed as Constant Across Groups.

ACKNOWLEDGMENTS

We thank Dr Marc Bornstein for his feedback on an earlier draft. The Bavarian Longitudinal Study was supported by grants PKE24 and JUG14 (01EP9504) from the German Ministry of Education and Science (BMBF). This specific work is part of the National Centre of Competence in Research (NCCR) Swiss Etiological Study of Adjustment and Mental Health (sesam). The Swiss National Science Foundation (SNF) (project no. 51A240-104890), the University of Basel, the F. Hoffmann-La Roche Corp. and the Freie Akademische Gesellschaft provide core support for the NCCR sesam.