Infant Neuromotor Development and Childhood Problem Behavior

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abstract

BACKGROUND: Research of adults and school-aged children suggest a neurodevelopmental basis for psychiatric disorders. We examined whether infant neuromotor development predicted internalizing and externalizing problems in young children.

METHODS: In Generation R, a population-based cohort in the Netherlands (2002–2006), trained research assistants evaluated the neuromotor development of 4006 infants aged 2 to 5 months by using an adapted version of Touwen's Neurodevelopmental Examination (tone, responses, and senses and other observations). We defined nonoptimal neuromotor development as scores in the highest tertile. Mothers and fathers rated their children's behavior at ages 1.5, 3, 6, and 10 years with the Child Behavior Checklist (n = 3474, response: 86.7%). The associations were tested with generalized linear mixed models.

RESULTS: Overall, neuromotor development predicted internalizing scores, but no association was observed with externalizing scores. Nonoptimal muscle tone was associated with higher internalizing scores (mothers' report: β = .07; 95% confidence interval [CI]: 0.01 to 0.13; fathers' report: β = .09, 95% CI: 0.00 to 0.16). In particular, nonoptimal low muscle tone was associated with higher internalizing scores (mothers' report: β = .11; 95% CI: 0.05 to 0.18; fathers' report: β = .13; 95% CI: 0.04 to 0.22). We also observed an association between senses and other observations with internalizing scores. There was no relationship between high muscle tone or reflexes and internalizing scores.

CONCLUSIONS: Common emotional problems in childhood have a neurodevelopmental basis in infancy. Neuromotor assessment in infancy may help identify vulnerability to early internalizing symptoms and offer the opportunity for targeted interventions.

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WHAT'S KNOWN ON THIS SUBJECT: Researchers who conducted studies with adults and school-aged children suggest that an association exists between early developmental problems and later diagnosis of psychiatric disorders; however, the prospective association with problem behavior in children, in particular emotional problems, is less understood.

WHAT THIS STUDY ADDS: In 3474 children from the general population, infant neuromotor development predicted internalizing problems but not externalizing problems through age 10 years. These findings reveal that internalizing problems in childhood may have a neurodevelopmental basis that is evident early in life.

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Childhood psychiatric problems are common and are associated with adverse mental health outcomes, poor school achievements, and delinquent behavior in later ages.[1–3] Problem behavior in children often coincides with early developmental problems. In a community-based sample of twins, a modest association was reported between problem behavior and cognitive problems.[4] Similarly, in a population-based follow-up study, delays in motor function and deviant language development predicted later psychiatric disorders.[5] These observations are in accordance with the notion that an association exists between early developmental problems and later problem behavior. A possible explanation for this link comes from research on developmental disorders.[6] For example, children with autism are shown to have problems with muscle tone in infancy.[7] Other abnormalities, such as difficulties in motor coordination, were also observed in children at risk for autism.[8] Neuromotor abnormalities, including abnormal movement and motor coordination problems, can also be a precursor of schizophrenia.[9] Overall, with this line of research, it is suggested that early motor impairment, reflecting diffuse neural dysfunction, represents a vulnerability marker for psychopathology.[10,11] Nonetheless, the association with later problem behavior in young children and in particular emotional problems is poorly understood. The association between neuromotor development and later psychopathology could be a potential treatment target for early detection and prevention. If early neuromotor impairment can predict specific patterns of behavioral traits in the general population, we may be able to better influence disease development with early interventions.

In registry studies, researchers using routine assessment of motor milestone have unveiled important findings in psychopathological research, but they have several limitations (eg, appropriate adjustment for confounders).[11,12] Also, researchers who conducted studies that assess motor functioning and psychiatric disorders in large samples have relied on parents to report on the age of achieving a motor milestone.[10] In contrast, the studies based on full neurologic examinations conducted by professionals to assess neuromotor development as a precursor of psychopathology are typically administered in small or clinical samples.[10]

Thus, our goal was to study the prospective association between objective measures of neuromotor development conducted in infancy with repeated measures of children's internalizing and externalizing problems through age 10 years. On the basis of our previous work, which demonstrated the importance of later executive functioning in infants with suboptimal motor development, we tested children's shifting and planning as the underlying mechanisms of any potential association.[13] Although child behavior was measured by using parental rating, the infant neuromotor development was assessed by research nurses, eliminating common method bias.[14] We hypothesized that infants with nonoptimal neuromotor development had an increased risk of internalizing and externalizing problems.

METHODS

Participants

Participants were from the Generation R Study, a population-based cohort in the Netherlands, which follows children and their parents from fetal life onwards.[15,16] Pregnant women with an expected delivery date between 2002 and 2006 in Rotterdam were invited to participate in the study.

A flowchart of the study population is shown in Supplemental Fig 3. A total of 4006 infants underwent a neuromotor assessment at corrected ages between 2 and 5 months of age during a home visit. Information on 1 or more assessments of child behavior up to age 10 years was available for 3474 children (86.7% of 4006). Because the random exclusion of siblings did not change our results, they were included in the analyses. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center. Written informed consent was obtained from adult participants.

Neuromotor Development

We performed a full neurologic age-adequate examination, encompassing assessment of tone, elicited responses, and senses and other observations (such as spontaneous movements) at age 2 to 5 months. There were 2 versions of the neuromotor assessment instrument (for 9–15 weeks and for 15–20 weeks) adapted from Touwen's Neurodevelopmental Examination.[17] All measured items were categorized in the following 3 groups: tone, responses, and senses and other observations. Tone items were scored as normal, low, or high tone; most responses and senses and other observations were scored as present, absent, or excessive. An age-appropriate response was labeled "normal"; a response that indicated delayed development was labeled "not normal." Senses and other observations comprise strabism, fixation eyes, following movement eyes, hearing, sweating, and startled reactions. Within the subscale measuring tone, a further distinction was made between low tone and high tone, resulting in 2 additional scales for tone: "low tone symptoms" and

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"high tone symptoms." As we studied a nonclinical population, the outcome measures were skewed; thus, we categorized the sum scores of the total and the subscales into tertiles, subsequently classifying the lowest and the middle tertiles as optimal neuromotor development and the highest as nonoptimal.[18]

We examined the short-interval test-retest intraobserver reliability and the interobserver reliability of the assessment (n = 76). The intraclass correlation coefficient for the interobserver reliability was 0.64.[13]

Child Behavior

Two versions of the Child Behavior Checklist (CBCL) were used to obtain standardized parent reports of children's problem behavior: the preschool version (CBCL/$1_{1/2}$–5) and the school-aged version (CBCL/6–18). By summing the scores of specific questions from the CBCL/$1_{1/2}$–5, the following syndrome scales were obtained: emotionally reactive, anxious and/or depressed, somatic complaints, withdrawn, sleep problems, attention scores, and aggressive behavior. The CBCL/6–18 includes similar scales as the CBCL/$1_{1/2}$–5, with the exception of the emotionally reactive and sleep problems scores. There are 2 broadband scales: internalizing comprises the anxious and/or depressed, withdrawn-depressed, and somatic complaints scales, whereas externalizing comprises attention problems and aggressive behavior. According to the taxonomy of the CBCL, internalizing behaviors comprise problems that manifest mainly within the self, such as sad mood or anxiety, somatic complaints without known medical cause, and withdrawal from social contacts. These problems that pertain to emotions are often more difficult to detect than overt behavioral problems. Externalizing problems that are outer-directed generate discomfort and conflict.[19,20] Good reliability and validity have been reported for both versions of the CBCL.[21] Scale values were used continuously after a square root transformation to approximate normality. Because the CBCL/6–18 scores had different scales compared to the version for younger ages, we standardized all CBCL scale scores by dividing them by the corresponding SD. This method enabled us to compare 2 scores that are from different distributions.

Covariates

Questionnaires were used to obtain information on parents' highest level of education completed, age, antenatal psychiatric symptoms, child ethnicity, history of smoking during pregnancy, and household income. Maternal smoking was assessed by using questionnaires at enrollment, in midpregnancy, and in late pregnancy. Family income was defined by the total net monthly income of the household. The Brief Symptom Inventory was used to assess parents' antenatal psychiatric symptoms.[22] Child ethnicity was based on the parents' countries of birth. Fetal ultrasound examinations were used to establish gestational age at birth. Midwife and hospital registries provided information on the infant's date of birth, birth weight, and sex. Parents reported on their children's autistic-like behaviors at age 6 years by using a short form of the Social Responsiveness Scale.[21] Parents also rated their children's executive functioning at age 4 years in domains of shifting and planning by using the Behavior Rating Inventory of Executive Function-Preschool version.[23]

Statistical Analyses

Differences in characteristics between children with and without data on problem behavior were compared by χ^2 tests and independent samples t tests. We observed that mothers of infants with missing data were lower educated and suffered from more antenatal psychological symptoms compared with those included; this has been observed previously.[18,24] There were no differences in other characteristics between the 2 groups. In Table 1, we provide the percentage missing for the covariates.

TABLE 1 Participants' Characteristics (N = 3474)

Characteristics	
Maternal	
Age at enrollment, y	30.9 (5.0)
Missing data	0
Education, n (%)	
Primary	630 (18.1)
Secondary	945 (27.2)
High	1674 (48.2)
Missing data	225 (6.5)
Antenatal psychiatric symptoms	0.15 (0.06 to 0.31)
Missing data	
Smoking during pregnancy, n (%)	672 (20.8)
Missing data	250 (7.2)
Household income, n (%)	
Poor	168 (4.8)
Low	389 (11.2)
Modal and above	2098 (60.4)
Missing data	819 (23.6)
Partner	
Age at enrollment, y	33.5 (5.4)
Missing data	977
Education %	
Primary	395 (11.4)
Secondary	594 (17.1)
High	1239 (35.7)
Missing data	1246 (35.9)
Child	
Age at neuromotor assessment, wk	12.6 (2.0)
Missing data	0
Sex, boy (%)	1702 (49.0)
Missing data	0
Ethnic background, n (%)	
Dutch	1858 (53.5)
Other Western	388 (11.2)
Non-Western	1167 (33.6)
Missing data	61 (1.8)
Gestational age at birth, wk	39.9 (1.7)
Missing data	5
Instrument (9–15 wk), %	2802 (80.7)
Instrument (15–20 wk), %	672 (19.3)
Missing data	0

Numbers are mean (SD) for variables with normal distribution, median (quartile range) for not-normally distributed variables, and percentages for categorical variables.

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We used generalized linear mixed models (GLMMs) to estimate the standardized coefficients (β) and 95% confidence intervals (CIs) of the association between neuromotor development measured in infancy and internalizing and externalizing scores up to age 10 years. Subsequently, we examined the associations with the different CBCL syndrome scales. All models included a child-level random intercept and slope to account for repeated measures of child behavior and to model the child-specific variable effect. In these models, we used children's repeated CBCL scores from age 1.5 years to age 10 years. GLMMs are robust to loss to follow-up under the missing at random assumption.[25,26] Testing for missing assumptions[27] confirmed that the missingness in externalizing scores but not internalizing was completely at random. All models were rerun with neuromotor development as a continuous variable.

Models were adjusted for confounders, selected on the basis of the change-in-estimate method or the theoretical framework of the study question. We also adjusted the models for the version of the instrument used. In an additional step, we adjusted the models for a child's autistic-like behaviors to assess whether our results were independent of autistic traits.[28] Interaction terms of neuromotor development with the age of each CBCL assessment, sex, ethnicity, and educational level were tested. Because the likelihood ratio tests did not reveal significant differences between nested models, except for the model for low muscle tone and age in relation to externalizing problems, the interaction terms were not included in other final models.

We ran mediation models with 99% bias-corrected bootstrap CIs, applying 5000 bootstrap samples by using an SPSS macro (IBM SPSS Statistics, IBM Corporation, Armonk, NY).[29] We explored the indirect effects of infant neuromotor development on child's internalizing behavior through shifting and planning (scores square-root transformed).

To handle the missing values on covariates, we used multiple imputations. Imputations were based on information on the infant neuromotor development and all covariates measured. Five independent data sets were generated and pooled estimates for those data sets were calculated. Multiple imputations were performed by using SPSS version 22.0. All other analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) and R 3.4.0.[30]

RESULTS

Participants' characteristics are presented in Table 1. Neuromotor development was assessed at an average age of 12.6 weeks (SD = 2 weeks). In Table 2, we show the relationship between infant neuromotor development and internalizing scores through age 10 years. Nonoptimal overall neuromotor development predicted internalizing scores across childhood. Low muscle tone in infancy was associated with higher internalizing scores (mothers' report: adjusted β = .11; 95% CI: 0.05 to 0.18; fathers' report: adjusted β = .13; 95% CI: 0.04 to 0.22). In Supplemental Fig 4, we show associations between low muscle tone and internalizing scores at each assessment (adjusted for covariates and also additionally for previous observations). There was also an association between senses and other observations in infancy and internalizing scores (Table 2) but not between high muscle tone or reflexes and internalizing scores.

There was no association between nonoptimal overall neuromotor development in infancy and externalizing scores. Neither low nor high muscle tone was associated with externalizing scores (Table 3). We depict how infants' low muscle tone relates to internalizing and externalizing scores over time in Figs 1 and 2. When we repeated the analysis with continuous neuromotor variables, the results remained essentially unchanged (Supplemental Table 3).

When the interaction of motor development with age at CBCL assessment was tested, we observed that for externalizing scores, the likelihood ratio test revealed model fit improvement compared to the model with no interaction term. There was no constant overall association between infant low muscle tone and externalizing scores through age 10 (Fig 2).

We examined the association between infant neuromotor development and internalizing subscales (mother and father report) and found that children with nonoptimal neuromotor development were more likely to have higher withdrawn, emotionally reactive, and anxious and/or depressed scores (the latter with the father's report only) (Supplemental Tables 5 and 6). In particular, a low muscle tone was consistently associated with higher withdrawn scores (mothers' report: adjusted β = .09; 95% CI: 0.05 to 0.14; fathers' report: adjusted β = .09; 95% CI: 0.03 to 0.16). No association was observed with high muscle tone.

Using a bootstrapping technique, we observed a significant indirect effect of low muscle tone on internalizing and, in particular, withdrawn problems explained by shifting problems (adjusted β = .03; 95% CI for internalizing: 0.00 to 0.06; adjusted β = .02; 95% CI: 0.00 to 0.04 for withdrawn). We did not observe any mediation by planning.

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TABLE 2 Infant Neuromotor Development and Internalizing Scores Across Childhood Within the Generation R Study

Nonoptimal Neuromotor Development	Internalizing Scores					
	Mother Report[a] (1.5, 3, 6, and 10 y)			Father Report[b] (3 and 10 y)		
	N	β (95% CI)	*P*	*N*	β (95% CI)	*P*
Overall neuromotor development						
Unadjusted	3402	.12 (0.06 to 0.18)	<.001	3023	.11 (0.03 to 0.19)	.009
Adjusted	3402	.08 (0.02 to 0.14)	.008	3023	.10 (0.02 to 0.18)	.022
Muscle tone						
Unadjusted	3321	.09 (0.03 to 0.15)	.003	2954	.09 (0.01 to 0.17)	.031
Adjusted	3321	.07 (0.01 to 0.13)	.028	2954	.09 (0.00 to 0.16)	.041
Low tone symptoms						
Unadjusted	3327	.13 (0.07 to 0.20)	<.001	2959	.14 (0.05 to 0.22)	.003
Adjusted	3327	.11 (0.05 to 0.18)	<.001	2959	.13 (0.04 to 0.22)	.004
High tone symptoms						
Unadjusted	3441	.06 (0.00 to 0.12)	.048	3056	.09 (−0.01 to 0.20)	.091
Adjusted	3441	.06 (−0.02 to 0.14)	.114	3056	.07 (−0.04 to 0.18)	.211
Responses						
Unadjusted	3267	.03 (−0.03 to 0.09)	.271	2901	.05 (−0.03 to 0.14)	.195
Adjusted	3267	.00 (−0.06 to 0.06)	.923	2901	.05 (−0.03 to 0.13)	.258
Senses						
Unadjusted senses	3452	.12 (0.06 to 0.18)	<.001	3068	.13 (0.04 to 0.22)	.003
Adjusted senses	3452	.06 (0.00 to 0.12)	.040	3068	.10 (0.02 to 0.19)	.019

The association between nonoptimal neuromotor development and internalizing through age 10 y were estimated with GLMMs to account for repeatedly assessed outcome. All models adjusted for a child's age, sex and ethnicity, gestational age at birth, antenatal maternal psychiatric symptoms, household income, maternal history of smoking in pregnancy, and the version of neuromotor instrument.

[a] In addition, all models are adjusted for age of the mother and education level of the mother.

[b] In addition, all models are adjusted for age of the father and educational level of the father.

TABLE 3 Infant Neuromotor Development and Externalizing Scores Across Childhood Within Generation R Study

Nonoptimal Neuromotor Development	Externalizing Scores					
	Mother Report[a] (1.5, 3, 6, and 10 y)			Father Report[b] (3 and 10 y)		
	N	β (95% CI)	*P*	*N*	β (95% CI)	*P*
Overall neuromotor development						
Unadjusted	3402	.02 (−0.03 to 0.08)	.381	3023	.04 (−0.04 to 0.11)	.353
Adjusted	3402	−.01 (−0.07 to 0.04)	.617	3023	.03 (−0.05 to 0.10)	.520
Muscle tone						
Unadjusted	3321	.01 (−0.05 to 0.06)	.832	2954	.01 (−0.08 to 0.10)	.704
Adjusted	3321	−.02 (−0.08 to 0.03)	.466	2954	.02 (−0.06 to 0.09)	.737
Low tone symptoms						
Unadjusted	3327	—[c]	—	2959	.04 (−0.04 to 0.12)	.386
Adjusted	3327	—[c]	—	2959	.03 (−0.05 to 0.11)	.446
High tone symptoms						
Unadjusted	3441	.04 (−0.01 to 0.10)	.136	3056	.02 (−0.10 to 0.15)	.764
Adjusted	3441	.01 (−0.06 to 0.09)	.686	3056	−.02 (−0.12 to 0.09)	.765
Responses						
Unadjusted	3267	.01 (−0.04 to 0.07)	.692	2901	.04 (−0.03 to 0.12)	.276
Adjusted	3267	−.01 (−0.06 to 0.05)	.785	2901	.04 (−0.03 to 0.11)	.299
Senses						
Unadjusted senses	3452	.03 (−0.02 to 0.09)	.242	3068	.03 (−0.05 to 0.11)	.445
Adjusted senses	3452	−.02 (−0.07 to 0.04)	.556	3068	.01 (−0.07 to 0.08)	.807

The association between nonoptimal neuromotor development and externalizing through age 10 y were estimated with GLMMs to account for repeatedly assessed outcome. All models adjusted for a child's age, sex and ethnicity, gestational age at birth, antenatal maternal psychiatric symptoms, household income, maternal history of smoking in pregnancy, and the version of neuromotor instrument. —, not applicable.

[a] In addition, all models are adjusted for age of the mother and education level of the mother.

[b] In addition, all models are adjusted for age of the father and educational level of the father.

[c] Because of the interaction effect of low muscle tone with age, results cannot be presented here. See Fig 2.

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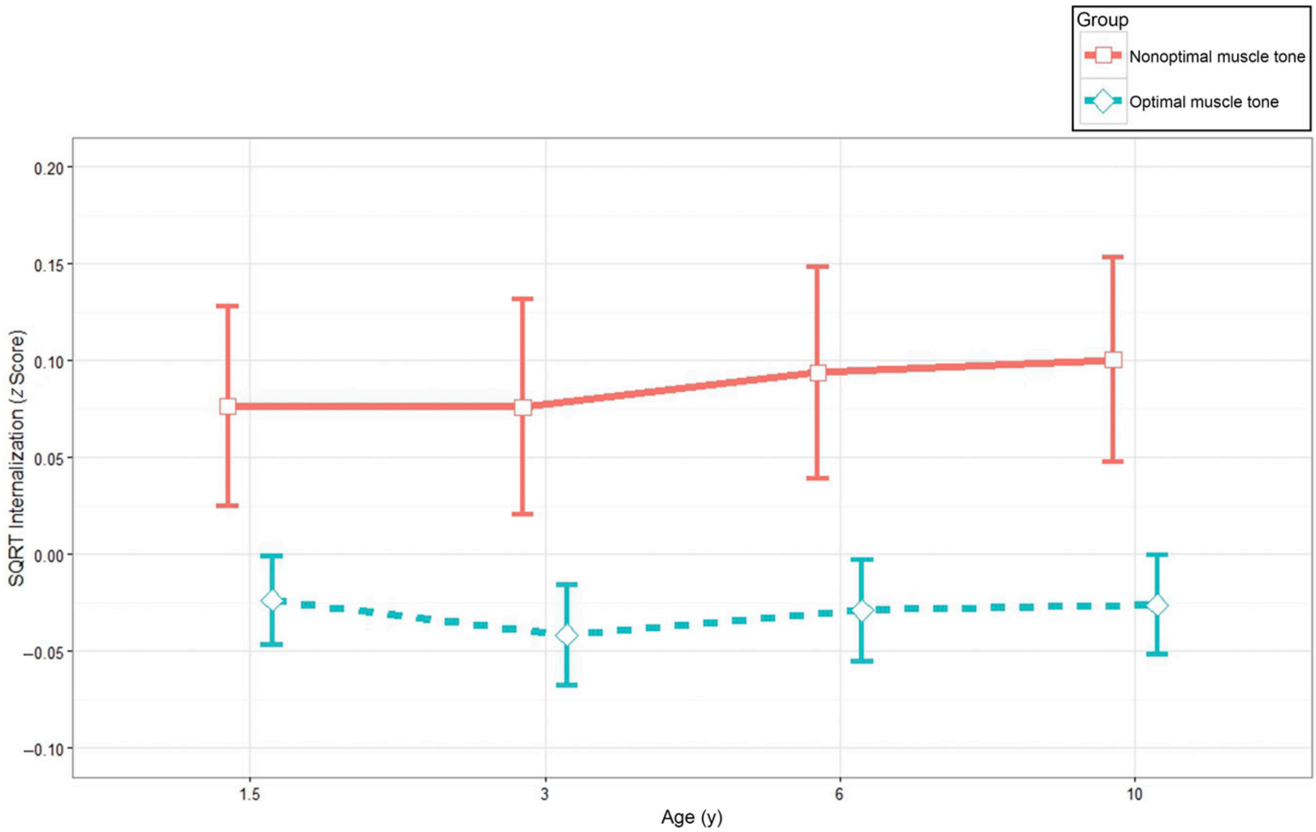

FIGURE 1

Internalizing *z* scores in children with optimal and nonoptimal neuromotor development in infancy (fitted values from the linear mixed model) with bootstrap CIs from 1000 runs. The mean of the fitted values from the multivariate model on association between infant neuromotor development and mother report of internalizing scores through age 10 years in children with optimal and nonoptimal low muscle tone are shown in the graph. The association was estimated with GLMMs to account for repeatedly assessed internalizing problems. The model is adjusted for a child's age, sex and ethnicity, gestational age at birth, antenatal maternal psychiatric symptoms, household income, maternal history of smoking in pregnancy, maternal age, maternal education level, and the version of neuromotor instrument. CIs were calculated from 1000 bootstrap runs. SQRT, square root.

In all analyses, adjustment for autistic traits did not change the results. With exclusion of 21 children with physical impairments, the results remained unchanged. There was no difference in sex in the relation between infant neuromotor development and child behavior (data not shown).

DISCUSSION

We found that nonoptimal infant neuromotor development and, in particular, low muscle tone and nonoptimal senses were consistently associated with internalizing scores, as repeatedly reported by mothers and fathers through age 10 years. This association was mainly accounted for by withdrawn problems and was partly mediated by problems in the shifting domain. We observed no association between nonoptimal neuromotor development and externalizing scores.

Common genetic and environmental factors might underlie both nonoptimal neurodevelopment and child problem behavior. Subtle genetic variations, represented by single nucleotide polymorphisms or copy number variation, have been associated with subtle abnormalities of brain development.[31] In recent genome wide meta-analysis, researchers have shown that internalizing problems are heritable and moderately genetically stable from childhood to adulthood.[32] At the same time, teratogens may cause brain abnormalities during prenatal development,[33] which in turn lead to neurodevelopmental problems during the course of life. Examples of these adverse influences are nicotine and alcohol exposure during gestation,[34,35] viral infections,[36,37] as well as maternal stress, nutrition, and age.[38,39] In our analysis, we controlled for several environmental factors. We observed that gestational age and birth weight as indicators of insults during pregnancy did not substantially affect the associations under study. Likewise, parental psychiatric symptoms, possible indicators of stress, did not explain our observations.[40,41] With

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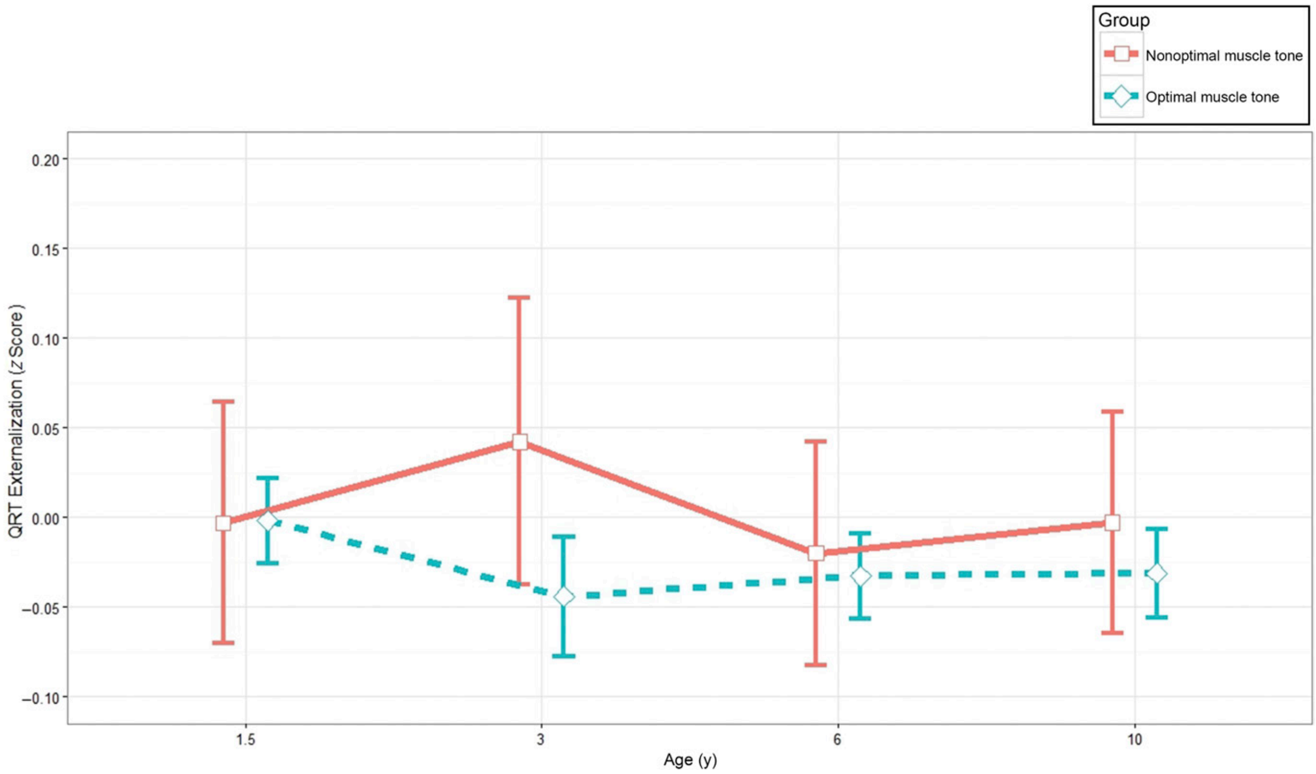

FIGURE 2
Externalizing *z* scores in children with optimal and nonoptimal neuromotor development in infancy (fitted values from the linear mixed model) with bootstrap CIs from 1000 runs. The mean of the fitted values from the multivariate model on association between infant neuromotor development and mother report of externalizing scores through age 10 years in children with optimal and nonoptimal low muscle tone are shown in the graph. The association was estimated with GLMMs to account for repeatedly assessed externalizing problems. The model is adjusted for a child's age, sex and ethnicity, gestational age at birth, antenatal maternal psychiatric symptoms, household income, maternal history of smoking in pregnancy, maternal age, maternal education level, and the version of neuromotor instrument. CIs were calculated from 1000 bootstrap runs. SQRT, square root.

adjustment, the relationship between early neuromotor development and problem behavior was attenuated for parental psychopathology but remained. Postnatal factors (eg, a child's physical health) may also underlie the association between infant neuromotor development and internalizing problems in children.[42,43] Although we cannot completely rule out potential influences by a third factor (that underlies both nonoptimal neuromotor and child psychopathology) based on our results, we can conclude that motor skills are at the core of infants' and children's everyday actions and interactions and consequently affect perceptual, cognitive, and social development.[44,45] Therefore, motor skills may initiate a cascade of events, influencing subsequent development. Since Piaget's original observations that infants own sensorimotor experiences are critical for their learning about the environment, researchers in several studies have reported evidence for relations between motor skills and development in seemingly unrelated domains, such as object perception, face processing, and language skills.[46] For example, early experiences of successful reaching at 3 months have been found to be associated with infants' attention to faces over objects.[47] Similarly, in another study, the onset of sitting independently at 3 to 5 months predicted language development at 10 and 14 months.[48] Low muscle tone affects how infants move and develop and may mean that the infants achieve the major developmental milestones late. These infants get upset when confronting new situations on motor tasks and therefore spend less time exploring objects and different ways to do things. This cautious and fearful infant behavior style may have long-term consequences for communications and emotional and cognitive development. As a consequence, infants can become more reactive.

We showed an association between low muscle tone and internalizing and, in particular, withdrawn problems, which was independent of autistic traits. This finding is compatible with Touwen's theory that describes infants with suboptimal neuromotor development (ie, mild neurologic

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signs) as typically displaying "clumsy behavior" that worsens between 4 and 9 years.[49] Infants with low muscle tone might have difficulties in initiating movement and interacting with the environment and therefore show symptoms of withdrawal behavior during toddlerhood and school age. With our results, we suggest that low muscle tone in infancy might be an independent precursor of withdrawal behavior in these children. It is unclear if children withdraw because they lack the drive for social interaction or because of fear and anxiety. Whatever the origins of minor and mild neurologic signs, their presence plays a role in the development of behavioral and learning problems, most likely in combination with other factors.

To our knowledge, this study is the first to investigate whether executive functioning underlies the path from low muscle tone to internalizing problems. We found that a higher-order cognitive process, such as shifting, is an important factor in children's vulnerability to psychopathology. Shifting presents a separate domain from other executive function domains.[13,50,51] Children with shifting problems are often described as rigid, inflexible, not creative in problem solving, or upset with changes in routines. The specific neurobiological characteristics of shifting, described as the ability to make transition and to change the focus from 1 mindset to another, are less known than those of other aspects of executive function.[52] Shifting aspect of executive function builds on other domains of executive function such as inhibition and develops later through development.[53] Infants with low muscle tone face more problems when adapting to new circumstances during childhood. These more "rigid" children are at a higher risk of developing internalizing and, in particular, withdrawn behavior.[54] The combined cognitive and motor problems may be the result of underlying inhibition problems or a general automation deficit. Researchers suggested that motor development predicts shifting and inhibition.[13,55] Shifting particularly addresses the ability to automate behavior.[56] Based on our findings, we postulate that the children with low muscle tone are less likely to learn to shift their focus of attention and therefore will experience more difficulties in adapting to changes in the environment.

We did not find an association between infant neuromotor development and externalizing scores. Externalizing problems, like aggression, are highly prevalent in young children[57] and probably often reflect a normal developmental stage of children as evident by the decline in externalizing symptoms seen in both the children with optimal and nonoptimal motor development. Developing a sense of autonomy and determination to become independent of caregivers typically involve conflicts with parents and other caregivers. This could explain why in young children, scores in the borderline range of externalizing behavior are less likely to have origins in deviant neuromotor development. In twin studies, researchers have shown that although externalizing behaviors have unique genetic and a shared environmental basis, internalizing behaviors are associated with unique genetic influences only.[58] Our findings are compatible with the notion that externalizing behaviors are sensitive to environmental influence as indicated by an early nonnormative development in children with more hypotonus at baseline; although, in theory, such an age-limited difference could also be of genetic origin.

This study has several strengths, including a large sample, considering many potential confounders, and objective assessments of neuromotor development independently of the mother. This is important, as relying on parents' report for both neurodevelopment and the child's behavior may introduce shared method bias.[14] Also, we used the mother's and father's reports of child behavior to test consistency and obtain a more accurate description of the children's problems.[59] But we faced limitations. First, we experienced a loss to follow-up. However, we used GLMMs that are robust to loss to follow-up if the assumption holds that missing outcome happened at random. Second, we had only parental rating data on child behavior. Parents who are aware of their infant's delay in neuromotor development could have been more attentive to their child's problem behavior. In addition, parents were blinded to delayed neuromotor development and, therefore, their report was independent of neuromotor development in infancy. We considered many confounders; however, we cannot rule out residual confounding. We performed several rounds of tests. Therefore, chance finding should be considered when interpreting data. Also, the observed betas indicate small effects as expected in the general population.

CONCLUSIONS

In a prospective population-based study, we found that infants with nonoptimal neuromotor development and, in particular, low muscle tone, have higher

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internalizing scores during childhood. With our findings, we suggest that internalizing problems in childhood might have origins in early neurodevelopment. Future studies are needed to examine whether evaluation of early neuromotor development might help in identifying vulnerability to internalizing symptoms and can be used for targeted interventions in young children. For example, scaffolded reaching experiences have been shown to improve developmental parameters in 3-month-old infants at risk for motor delay.[60]

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ABBREVIATIONS

CBCL: Child Behavior Checklist
CBCL/$1_{1/2}$–5: Child Behavior Checklist preschool version
CBCL/6–18: Child Behavior Checklist school-aged version
CI: confidence interval
GLMM: generalized linear mixed model

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