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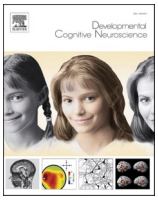

Neonatal hippocampal volume moderates the effects of early postnatal enrichment on cognitive development

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ABSTRACT

Environmental enrichment, particularly during the early life phases of enhanced neuroplasticity, can stimulate cognitive development. However, individuals exhibit considerable variation in their response to environmental enrichment. Recent evidence suggests that certain neurophenotypes such as hippocampal size may index inter-individual differences in sensitivity to environmental conditions. We conducted a prospective, longitudinal investigation in a cohort of 75 mother-child dyads to investigate whether neonatal hippocampal volume moderates the effects of the postnatal environment on cognitive development. Newborn hippocampal volume was quantified shortly after birth (26.2 ± 12.5 days) by structural MRI. Measures of infant environmental enrichment (assessed by the IT-HOME) and cognitive state (assessed by the Bayley-III) were obtained at 6 months of age (6.09 ± 1.43 months). The interaction between neonatal hippocampal volume and enrichment predicted infant cognitive development ($b = 0.01$, 95 % CI [0.00, 0.02], $t = 2.08$, $p = .04$), suggesting that exposure to a stimulating environment had a larger beneficial effect on cognitive outcomes among infants with a larger hippocampus as neonates. Our findings suggest that the effects of the postnatal environment on infant cognitive development are conditioned, in part, upon characteristics of the newborn brain, and that newborn hippocampal volume is a candidate neurophenotype in this context.

1. Introduction

Environmental conditions are known to play a crucial role in shaping brain development and cognitive functioning, particularly during sensitive developmental windows (Di Segni et al., 2017). Early postnatal life is among the most sensitive of these windows because this is a period of high brain plasticity (Lupien et al., 2009; Tottenham, 2014). During this period exposure to unfavorable and favorable conditions, such as a deprived or enriched, more stimulating environment, may produce detrimental or salutary effects, respectively, on cognitive development and its underlying neurobiological systems (Batty and Deary, 2004; Calvin et al., 2011). Of note, poorer cognitive performance in childhood accompanies the majority of psychiatric symptoms in childhood and has also been proposed as an antecedent of later adverse mental health outcomes (Gunnell et al., 2002, 2005; Koenen et al., 2009; Mortensen et al., 2005; van Os et al., 1997). Good cognitive abilities in the contrary have been demonstrated to function as a protective factor in terms of later psychopathology.

Experimental findings in animals on early environmental conditions and cognitive development have demonstrated a causal role for experience-induced modifications within the cortex and hippocampus, with consequences for cognitive functions such as memory and learning (for review see van Praag et al., 2000). Correlational studies in humans have also documented a link between key early environmental conditions and later cognitive outcomes. For example, a series of findings in children raised in deprived institutional settings suggest a variety of neurobiological and behavioral sequalae, such as deviations or delays in cognitive development, which, in turn, were positively affected by

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enhanced early caregiving through foster care (Nelson et al., 2007). Moreover, socioeconomic status (SES), which is often associated with the quality of the rearing environment, such as environmental stimulation, parenting styles, and chronic stress has been linked to various child cognitive outcomes, including IQ and school achievement (Bradley et al., 2001; Evans, 2004).

Although there is extensive empirical support from both animal and human studies that the early environment plays a role in shaping infants' cognitive development, there is also growing evidence that suggests individuals differ in the degree to which they are amenable to the modulating role of environmental conditions (Belsky and Pluess, 2009a, 2013; Ellis et al., 2011; Obradovic and Boyce, 2009). This assertion has mostly been embedded within a diathesis-stress model with a focus on individual differences in vulnerability in the context of adversity. This classic vulnerability model has been extended by several theoretical frameworks, according to which individuals differ not only in terms of their vulnerability but more generally in terms of their sensitivity to environmental influences, in a for-better-and-for-worse manner. For example, the frameworks of *Sensory-Processing Sensitivity* (Aron and Aron, 1997; Aron et al., 2012), *Differential Sensitivity Theory* (Belsky, 1997; Belsky et al., 2007; Belsky and Pluess, 2009a, 2013), and *Biological Sensitivity to Context* (Boyce and Ellis, 2005; Ellis and Boyce, 2008) propose that individuals with higher sensitivity are not just more reactive to negative experience but also more sensitive to positive environmental influences. Within these frameworks the specific notion that individuals benefit more from positive features of the environment has been conceptualized in the framework of *Vantage Sensitivity* (Pluess, 2017; Pluess and Belsky, 2013). Recently, these different concepts have been integrated into an overarching framework, according to which individuals differ in their "ability to perceive and process environmental stimuli" defined as *Environmental Sensitivity* (Pluess, 2015). Environmental sensitivity, which comprises accurate perception and interpretation of environmental cues, is a necessary condition enabling adaptation to environmental conditions.

The identification of individual characteristics that underlie differences in environmental sensitivity is an area of active investigation. To date, determinants of inter-individual differences in sensitivity to environmental conditions identified in the literature range from behavioral predispositions (e.g. temperament), to biological characteristics such as physiological reactivity, as well as allelic variation within the human genome (Kim and Kochanska, 2012; Obradovic et al., 2010). Based on the assumption that heightened sensitivity reflects a more sensitive central nervous system, Pluess (2015) has suggested that those empirically-established factors of environmental sensitivity (e.g. behavioral predispositions, biological characteristics, allelic variation) can be integrated. Specific gene variants may contribute to certain neurophenotypes of increased sensitivity in certain brain regions, which, in turn, manifests in physiological reactivity and personality traits with consequences for inter-individual variability in the sensitivity to the caregiving environment. Therefore, properties of the brain (e.g. structure, function) may constitute promising phenotypes indexing environmental sensitivity. Identification of such neurophenotypes may advance our understanding of the mechanisms that underlie interindividual differences in the capacity to register and process external stimuli.

In this context, the question of the relationship between hippocampal volume and sensitivity to environmental contingencies is of particular interest for the following reasons. First, the hippocampus plays a major role in consolidation and representation of contexts and events regardless of valence (Ostby et al., 2012; Redondo et al., 2014). Second, the hippocampus (size and function) is linked to well-established determinants of environmental sensitivity such as stress reactivity (Pruessner et al., 2007), genetic variants (e.g., polymorphism of the dopamine 4-receptor gene; Strange et al., 2014), and personality traits (e.g., negative affectivity; Whittle et al., 2006). Third, the hippocampus itself exhibits developmental plasticity. In neonates there is substantial inter-individual variability in hippocampal size, as a consequence of the interactive effects of genetic factors and prenatal environmental conditions (Qiu et al., 2017; Wang et al., 2018).

The objective of the current study was to prospectively investigate whether infants differ in the degree to which their cognitive development benefits from an enriched rearing environment, and to specify the role of neonatal hippocampal size in this context. Enrichment was based on home observation and semi-structured interview with mothers and captures the extent to which the caregiving environment is stimulating and supportive of learning experiences. We hypothesized that neonatal hippocampal size moderates the association between variations in environmental enrichment and infant cognitive development at 6 months of age.

2. Materials and methods

2.1. Participants and study design

The study was part of an on-going longitudinal study conducted at the University of California, Irvine, Development, Health and Disease Research Program in a clinical convenience cohort of 131 pregnant women, which is described in detail elsewhere (Moog et al., 2018). Mothers were recruited during pregnancy and had singleton, intrauterine pregnancies, with no cord, placental or uterine anomalies or fetal congenital malformations. Upon birth, the newborn children of those women who consented to an MRI scan of their children were included in the study. Exclusionary criteria for infants were as follows: birth before 34 weeks gestation and evidence of a congenital, genetic or neurological disorder.

The complete MRI sequence was obtained in 94 newborns. These MRI scans were then independently screened for quality control and excluded if they had excessive motion ($n = 6$) and/or significant abnormalities as reviewed by a clinical neuroradiologist ($n = 2$) resulting in 86 high-quality structural MRI scans. Of those newborns with high-quality MRI scans, 11 had missing 6 months behavioral measurements, resulting in a final sample size of 75. Mother-child dyads that could not be included in the analyses because no MRI scan was obtained or because of insufficient quality of the MRI scan or missing behavioral data ($n = 56$) did not differ from the group with high-quality structural MRI scans and behavioral data ($n = 75$) with respect to SES, maternal age, maternal ethnicity, gestational age at birth, or infant sex (p's $> .05$).

All study procedures were approved by the university's Institutional Review Board, and all participants (pregnant women and parents on behalf of their infants) provided written informed consent.

2.2. Procedure

The study employed a prospective, longitudinal design. MRI of the child's brain was performed shortly after birth (26.2 ± 12.5 (mean $\pm$ SD) days). At the time of the behavioral assessment infants were approximately 6 months of age (6.09 ± 1.43 (mean $\pm$ SD) months). Detailed demographic information is presented in Table 1.

2.3. Infant cognitive development

Infant cognitive development at 6 months age was assessed using the Cognitive Scale composite score from the Bayley Scales of Infant and Toddler Development, Third Edition Bayley (2006). This widely-used standardized measure of infant development includes developmentally appropriate measures of emerging attention, memory skills, and understanding of the environment. The Cognitive Scale composite score does not allow for the identification of specific cognitive skills, but instead provides an index of overall cognitive development relative to a normative sample. This measure is suitable for this age group, in which reliable measurement of specific subdomains of cognitive functioning is difficult (Posner et al., 2012). Assessment involves tasks that measure

Table 1
Characteristics of the Study Population.

Infants ($N = 75$)	
Gestational Age at Birth (weeks)	38.77 ± 1.48
Age at MRI Scan (days)	26.91 ± 12.52
Age at Behavioral Assessment (months)	6.09 ± 1.43
Total Hippocampal Volume (mm^3)[1]	2983.89 ± 170.71
Enrichment[2]	14.47 ± 2.8
Cognitive Development[3]	103.6 ± 9.36
Female Infant Sex	32 (42,7)
Mothers ($N = 75$)	Age (Years)
Age (Years)	28.4 ± 6.16
SES[4]	3.16 ± 0.9
Highest Maternal Educational Level	
Less than High School	2 (2.7)
High School	12 (16)
Vocational Training or Some College without Degree	35 (46.7)
Associates or Bachelor's Degree	19 (25.3)
Advanced Degree (Master's / Doctorate)	7 (9.3)
Household Income Last Year (in $)	
Below 15 000	*7 (9,3)*
15 000–29 999	*13 (17,3)*
30 000–49 999	*18 (24)*
50 000–100 000	*27 (36)*
Over 100 000	*6 (8)*
Race/Ethnicity	
Non-Hispanic White	*30 (40)*
Non-Hispanic Other	*10 (13.3)*
Non-Hispanic Asian	*6 (8)*
Hispanic White	*24 (32)*
Hispanic Other	*5 (6.6)*
Maternal Intellectual Ability[5]	95.35 ± 11.87
Maternal Sensitivity[6]	10.29 ± 2.9

Values are mean ± SD or *n* (%).

[1] Adjusted for intracranial volume, gestational age at birth and age at MRI scan.

[2] Combination of access to variety in daily stimulation, provision of appropriate play material and involvement in activities that afford learning assessed by Infant-Toddler Home Observation for Measurement of the Environment (IT-HOME).

[3] Cognitive Scale composite score from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006).

[4] Maternal socioeconomic status (SES) was defined as a combination of maternal educational level (originally assessed in categories from less than high school to advanced degree and then recoded into values from 1 to 5) and household income (originally assessed in categories from $15,000 to $100,000 and then recoded into values from 1 to 5; $n = 4$ missing values replaced by mean substitution).

[5] Perceptual reasoning subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS; Wechsler, 1955).

[6] Sum score of sensitivity to non-distress, positive regard and intrusiveness based on coders rating of a semi-structured play situation (Jaeger, 1999).

attention to familiar and unfamiliar objects, interest in novel things and interaction with different toys. Infant cognitive development was assessed at 6 months to minimize potential confounding influences of the postnatal environment beyond influences of the early caregiving environment assessed in our study.

2.4. Early postnatal enrichment

The Infant-Toddler Home Observation for Measurement of the Environment (IT-HOME) Inventory (Caldwell and Bradley, 2003) was used to index the quality of the family environment. The IT-HOME consists of a home observation and semi-structured interviews with the mothers, which were conducted during a 1 -h home visit when the child was 6 months old. Data collectors were trained and achieved reliability with a certified administrator of this inventory (95 % agreement on two consecutive videos). A composite score was constructed based on the following scales: exposure to variety in daily stimulation, the provision of appropriate play materials, and parental involvement in activities that afford learning scales, thus capturing the extent to which the physical environment is stimulating and supportive of learning experiences. Henceforth, the term *enrichment* will be used for this composite representing child exposure to stimulating and supportive environmental conditions. This composite was entered as a predictor of cognitive development in all analyses reported below.

2.5. Magnetic resonance image acquisition and analysis

MRI was performed in unsedated newborns during natural sleep using a Siemens 3 T scanner (TIM Trio, Siemens Medical System Inc., Erlangen, Germany). T1-weighted images were obtained using a three-dimensional magnetization-prepared rapid gradient echo sequence (repetition time = 2400 ms; echo time = 3.16 ms; inversion time = 1200 ms; flip angle 8°; 6 min 18 s) and T2-weighted images were obtained with a turbo spin echo sequence (repetition time 3200 ms; echo time 1 = 13 ms; echo time 2 = 135 ms; flip angle 180°; 4 min 18 s). The spatial resolution was a 1 × 1 × 1 mm voxel for T1-weighted images and 1 mm × 1 mm × 1 mm voxel with 0.5 mm interslice gap for T2-weighted images.

Hippocampi were individually segmented via a multitemplate-based automatic method combining T1 and T2-weighted high-resolution images (J. Wang et al., 2014). Manual correction was performed in ITK-Snap (Yushkevich et al., 2006) with data realigned such that the anterior-posterior direction was positioned along the hippocampal long axis. Scan/rescan stability tests for the automatic segmentation procedure have been conducted in a separate sample set. Reliability for manual correction was established for raters on this dataset via a standard reliability study, in which 5 datasets were triplicated and randomized. These 15 datasets were then segmented automatically, and manually corrected by two raters. For manual correction of these 15 datasets, agreement between the two raters (inter-rater correlation coefficient) and agreement within the same rater across the same dataset (intra-rater correlation coefficient) were both above 0.98.

Hippocampal volumes were adjusted for intracranial volume, gestational age at birth, and postnatal age at scan. Gestational age at birth was confirmed by obstetric ultrasonographic biometry performed before 15 weeks' gestation using standard clinical criteria (O'Brien et al., 1981).

Adjusted total neonatal hippocampal volume was included as the moderator of the association between enrichment and cognitive development in the main analyses.

2.6. Covariates

Maternal sensitivity and maternal intellectual ability as well as maternal educational level are known to influence infant cognitive development (Donovan & Leavitt, 1978; Cabrera et al., 2011; Tong et al., 2007), and were therefore considered as covariates in the analyses.

Maternal sensitivity was assessed at 6-mo age with a semi-structured play situation in the infant's natural home environment that was video recorded (Jaeger, 1999). Two trained and reliable coders rated maternal sensitivity to non-distress, positive regard and intrusiveness (inter-rater reliability (ICC): 0.97 – 1). The scores were summed up (intrusiveness was inverted) to a total sensitivity score (range: 3–15), which was then used as a covariate in the analyses.

Maternal intellectual ability was measured with perceptual reasoning subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS; (Wechsler, 2008). The perceptional reasoning index is designed to measure nonverbal reasoning and perceptual organization abilities. Only this subtest was administered in the study because it represents a language-free component of general intelligence. Each of the above-mentioned covariates were entered into all analyses reported below. Furthermore, hippocampal volumes were adjusted for

intracranial volume, gestational age at birth, and postnatal age at scan. Gestational age at birth was confirmed by obstetric ultrasonographic biometry performed before 15 weeks' gestation using standard clinical criteria (O'Brien et al., 1981).

Maternal educational level was originally assessed in categories from less than high school to advanced degree (master/doctorate) and then recoded into values from1 to 5.

2.7. Statistical analysis

All data analyses were performed in SPSS 23.0. In a first step prior to our main moderation analyses, we conducted a linear regression model to test for main effects of total hippocampal volume and environmental enrichment on cognitive development. To then test our key hypothesis that hippocampal volume moderated the effects of environmental enrichment on cognitive development, we utilized the PROCESS macro for SPSS to analyze regression models (Hayes, 2013). Cognitive development at 6 months was the dependent variable. The PROCESS macro yields coefficient and standard error estimates for the predictor, moderator, and interaction term and is intended for use in moderation analyses that can be represented by a single regression coefficient. The interaction term between neonatal hippocampal volume and postnatal enrichment was computed after centering the continuous variables to avoid multicollinearity.

3. Results

Table 1 shows key infant and mother characteristics. Bivariate correlation coefficients for continuous predictor, outcome, moderating and confounding variables are provided in Table 2. Table 3 reports the main findings from the regression models testing moderation effects.

Enrichment ranged from 7 to 20 (M = 14.47, SD = 2.80). Enrichment was non-normally distributed, with skewness of -0.48 (SE = 0.28) and kurtosis of -0.03 (SE = 0.548). The negative skewness value indicates that fewer infants were exposed to low levels of environmental enrichment.

In the regression model that did not include the interaction term between newborn hippocampal volume and environmental enrichment, there was no statistically significant main effect of environmental stimulation on infant cognition ($\beta = 0.18$, $p = .83$). However, and in accordance with our hypothesis, the interaction of total hippocampal volume and environmental enrichment significantly predicted infant cognitive development at 6 months ($b = 0.01$, 95 % CI [0.00, 0.02], $t = 2.08$, $p = .04$) suggesting that the relationship between early postnatal enrichment and cognitive development differs based on neonatal hippocampal volume. The interaction term remained significant after including infant sex as a covariate. As depicted in Fig. 1, environmental enrichment was positively associated with cognitive development at 6 months only in infants with a larger neonatal hippocampal volume.

Table 2
Bivariate Correlations among Study Variables.

	1	2	3	4	5	6	7
1. Gestational Age at Birth		.046	−.238 *	.08	.02	.036	−.088
2. Enrichment[1]			−.011	.238 *	.299 **	.104	.025
3. Maternal Intellectual Ability[2]				.093	.133	−.009	.076
4. Maternal Sensitivity[3]					.323 **	.027	.076
5. Maternal Educational Level[4]						−.089	.084
6. Total Hippocampal Volume[5]							.159
7. Cognitive Performance[6]							

[1] Combination of access to variety in daily stimulation, provision of appropriate play material and involvement in activities that afford learning assessed by Infant-Toddler Home Observation for Measurement of the Environment (IT-HOME).
[2] Perceptual reasoning subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS; Wechsler, 1955).
[3] Sum score of sensitivity to non-distress, positive regard and intrusiveness based on coders rating of a semi-structured play situation (Jaeger, 1999).
[4] Maternal educational level was originally assessed in categories from less than high school to advanced degree (master/doctorate) and then recoded into values from1 to 5.
[5] Adjusted for intracranial volume and age at MRI scan.
[6] Cognitive Scale composite score (percentile rank) from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006).
* Significant correlation ($p < 0.05$).
** Significant correlation ($p < 0.01$).

Table 3
Model testing the effects of neonatal hippocampal volume[1] and environmental enrichment[2] on cognitive function[3].

	b	*SE B*	*t*	*p*
Total Hippocampal Volume[1]	0.02 [-0.01, 0.05]	0.01	1.18	0.24
Environmental Enrichment[2]	0.15 [-1.72, 2.02]	0.94	0.16	0.87
Interaction term	0.01 [0.00, 0.02]	0.01	2.08	0.04*

Model includes the covariates maternal sensitivity, maternal intellectual ability, maternal education.
[1] Adjusted for intracranial volume, gestational age at birth and age at MRI scan.
[2] Combination of access to variety in daily stimulation, provision of appropriate play material and involvement in activities that afford learning assessed by Infant-Toddler Home Observation for Measurement of the Environment (IT-HOME).
[3] Cognitive Scale composite score (percentile rank) from the Bayley Scales of Infant and toddler Development, Third Edition (Bayley-III; Bayley, 2006).
* Significant correlation ($p < 0.05$).

4. Discussion

To the best of our knowledge, this study is the first to prospectively examine the effect of the early postnatal environment on infant cognitive development conditioned upon newborn brain structure. We found that the effect of an enriched postnatal environment on infant cognitive outcome at 6 months of age varied as a function of neonatal

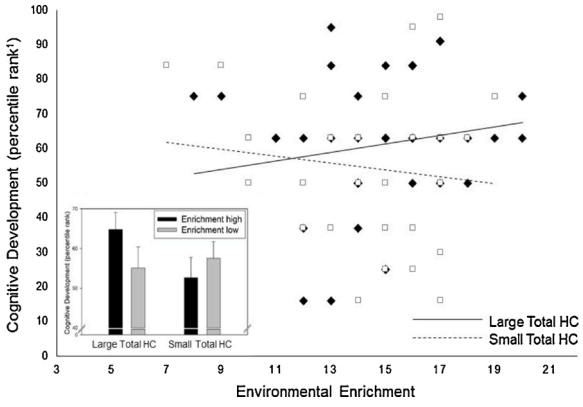

Fig. 1. Scatterplot and bar chart depicting the interaction total neonatal hippocampal volume with environmental enrichment in the prediction of cognitive development at 6 months age.
[1]Cognitive Scale composite score (percentile rank) from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006).
Note: Environmental enrichment in the bar chart and hippocampal volume were dichotomized by the median value.

hippocampal volume. Specifically, we found that environmental enrichment was more strongly associated with more advanced infant cognitive development in infants who had a larger hippocampus at birth. Thus, our results suggest that infants are differentially sensitive to the beneficial effects of an enriched environment, and that this differential sensitivity is influenced, in part, by neonatal hippocampal size.

The present findings support the model of *Vantage Sensitivity* (Pluess, 2017; Pluess and Belsky, 2013), which reflects the proclivity of an individual to benefit from positive competence-promoting features of the environment, describing the positive end within the more general framework of *Environmental Sensitivity* (Pluess, 2015). Within the framework of *Environmental Sensitivity,* Pluess (2015) has postulated that individuals generally differ in their sensitivity to environmental influences, with some being more susceptible and some being more resistant to the beneficial and detrimental effects of favorable or adverse environments, respectively. The limited number of children exposed to low enrichment in the present study did not enable us to test the hypothesis that hippocampal volume may be an indicator of general environmental sensitivity rather than vantage sensitivity. However, based on other empirical evidence, one could suggest that larger hippocampal size is not exclusively associated with positive outcomes, as shown in our work. It may rather be associated with general sensitivity to environmental features, and may also constitute a vulnerability factor in the context of adverse environmental circumstances. For instance, a rodent study found that adolescent mice with a larger hippocampal volume manifested greater social withdrawal and avoidance tendencies after exposure to social defeat (Tse et al., 2014). Whittle et al. (2011) demonstrated that adolescents with larger hippocampal volumes appeared to be more sensitive to both harmful effects of maternal aggressiveness on exacerbation in depressive symptoms as well as to protective effects of low levels of maternal aggressiveness. Likewise, a recent study on the manifestation of depressive symptoms found that adolescents with larger versus smaller hippocampal volumes showed heightened sensitivity to the protective effects of family connectedness as well as to the risk factor of community crime (Schriber et al., 2017). Future studies may need to further examine the role of the hippocampus as a potential sensitivity factor across both negative, development-undermining and supportive, development-enhancing contexts. Contextual influences reflecting the continuum of environmental conditions from unfavorable settings on its one end, to enriched settings on the other end, would help to elucidate whether hippocampal structure promotes vulnerability, vantage sensitivity, or general environmental sensitivity.

The elucidation of precise mechanisms that underlie the varying degree to which individuals are amenable to environmental conditions is an area of current, active investigation. Thus far, the majority of studies propose that susceptible individuals are more sensitive to the environment due to genetic (Bakermans-Kranenburg and van Ijzendoorn, 2011; Van Ijzendoorn and Bakermans-Kranenburg, 2006; van Ijzendoorn et al., 2012), temperamental (Kim and Kochanska, 2012; Pitzer et al., 2011) and physiological characteristics (Obradovic et al., 2010). Our findings suggest that hippocampal volume may constitute yet another marker of susceptibility. Hippocampal integrity (e.g., volume and function) has been associated with these established individual characteristics of environmental sensitivity, (Carver and White, 1994; Cherbuin et al., 2008; Hooker et al., 2008; Pitzer et al., 2011; Pruessner et al., 2007; Strange et al., 2014; Sutin et al., 2010; van Ijzendoorn et al., 2012; Whittle et al., 2011), suggesting it may integrate these different susceptibility characteristics. This is consistent with the assumption by Pluess (2015), according to which specific gene variants contribute to certain neurophenotypes of increased sensitivity in specific brain regions (e.g. hippocampus), which, in turn, manifest in physiological reactivity and personality traits, and thereby confer sensitivity to the environment. Regional brain volume, such as hippocampal size, could be considered a function of the number of neurons and their interconnections, as well as an indicator of its processing capacity (Barton, 1998). Consequently, larger hippocampal volume has been linked in several studies to a greater capacity to process contextual environmental elements (Ashtari et al., 2011; Maguire et al., 2000). It is possible that a larger hippocampal volume may enable deeper processing of environmental stimuli, with greater beneficial effects of enrichment on cognitive development.

At first glance, a larger hippocampus representing increased environmental sensitivity may contradict the notion of a smaller hippocampus constituting a well-established risk factor for both cognitive deficits and psychopathology. Studies investigating effects of early life stress (ELS) on brain development have commonly identified smaller hippocampal volume to reflect a vulnerability factor (Buss et al., 2007; Frodl and O'Keane, 2013; Vythilingam et al., 2002). The application of a developmental perspective may facilitate an integration of these observations with the observations of our study. It is possible that reduced hippocampal size, that has been established as a consequence of ELS in a number of retrospective studies (i.e. hippocampal size was measured several years after stress exposure), may be the result of a disrupted developmental trajectory of hippocampal growth (reflecting diminished rates of neurogenesis and dendritic atrophy; (Leuner and Gould, 2010). Applying the environmental sensitivity framework and assuming hippocampal size affects environmental sensitivity, the consequences of ELS in children with a larger hippocampus prior to exposure to adversity may be more pronounced and may eventually result in smaller hippocampal volume. Interestingly, observations in rodents by Tse et al. (2014) confirm this hypothesis, in that they show that a larger hippocampal volume before stress exposure was found to confer sensitivity to stress-induced disruption of normal hippocampal growth and vulnerability to psychopathology (Tse et al., 2014). Prospective, longitudinal studies with baseline (before stress exposure) and serial follow-up assessments (after stress exposure) will be necessary to unravel the precise role of the hippocampus in terms of susceptibility, conditional brain development, and cognitive and mental health outcomes.

Studies on differential environmental focusing on cognitive development as an outcome are sparse, with most of these studies testing the role of difficult temperament (e.g. negative emotionality) as a sensitivity factor. Blair (2002) demonstrated that children scoring high on negative emotionality benefitted more from an early educational intervention program in terms of their later cognitive development. In consistency, it has been shown, that parenting and child care quality predicted cognitive functioning and achievement more strongly in children who manifested difficult temperaments as infants (Pluess and Belsky, 2010). No study so far has tested, whether brain structure functions as a sensitivity factor moderating the effect of environmental experiences on cognitive development.

Research on brain structure as a sensitivity factor has so far exclusively focused on psychopathology as a developmental outcome (Schriber et al., 2017; Whittle et al., 2011; Yap et al., 2008), which often is accompanied or predicted by poorer early cognitive abilities (Gale et al., 2012; Kilpatrick et al., 2007). In consistency with our results, those existing studies have identified brain structure (i.e., hippocampal size, amygdala) as a moderator of environmental influences on development (Schriber et al., 2017; Whittle et al., 2011; Yap et al., 2008).

Importantly, studies on brain structure relevant to differential sensitivity assessed variability in brain structure in older infants or adolescents, thus treating individual differences in hippocampal volume as a relatively stable factor of environmental sensitivity (Schriber et al., 2017; Whittle et al., 2011; Yap et al., 2008). But the hippocampus is known to be a plastic brain structure and is therefore likely shaped by early prenatal and postnatal influences (Luby et al., 2012, 2016). By assessing hippocampal volume soon after birth, the present study was, to the best of our knowledge, the first to examine the function of hippocampal integrity as a neurophenotype of environmental sensitivity. Our findings support the suggestion that inter-individual differences in environmental sensitivity may already be apparent at birth, raising questions regarding the genetic and intrauterine determinants of

environmental sensitivity in general and in particular to hippocampal volume. Despite a substantial body of work demonstrating that genetic variation may account for differences in environmental sensitivity (for review see Belsky, 2016; Belsky et al., 2009; Belsky and Pluess, 2009a), growing evidence indicates that sensitivity itself can be shaped by developmental experiences (Boyce and Ellis, 2005). In this context Pluess and Belsky hypothesized that postnatal sensitivity might, to a certain degree, be shaped by the intrauterine environment (Pluess and Belsky, 2011). This suggests that at any given time, a phenotype and its response to contemporaneous conditions is the result of a chain of prior conditional probabilities. Indeed, evidence from animal and human studies suggests that exposure to prenatal stress and anxiety affects hippocampal development (Jia et al., 2010; Qiu et al., 2013). Maternal stress hormone levels during gestation also have been linked to amygdala volume in children (Buss et al., 2012), which itself has been shown to represent yet another neurophenotype moderating the effects of parenting behavior on depressive symptoms in adolescents (Yap et al., 2008). Moreover, the prenatal environment has been linked to other established markers of environmental sensitivity. For example, maternal prenatal stress predicted infant cortisol reactivity (Gutteling et al., 2005) or negative emotionality (de Weerth et al., 2003). Taken together, it is reasonable to assume that early postnatal environmental sensitivity, reflected by inter-individual variability in hippocampal size, may be shaped by the intrauterine environment and most likely also moderated by genetic makeup (Qiu et al., 2017; Wang et al., 2018). This would be in accordance with genotype-dependent consequences of the prenatal environment on programming sensitivity (Belsky and Pluess, 2009b; Pluess et al., 2011).

Our study has some limitations. The main limitations likely are the relatively small sample size as well as lack of variation in the early rearing environment towards lower and higher ends of environmental enrichment. The latter may have accounted for the fact that no main effect of environmental enrichment on cognitive development was observed (as reported in previous studies (Espy et al., 2001; Gottfried and Gottfried, 1984)). Third, due to relatively small sample size, we were not able to test effect modification by infant sex, which should be addressed in future studies because sex has been shown in previous studies to be a determinant of environmental sensitivity (Whittle et al., 2011; Yap et al., 2008). We note that the observed interaction effect in our study remained significant after including infant sex as a covariate. Fourth, since we focused on global volume of the hippocampus, we cannot speak to whether specific subregions of the hippocampus did moderate the effect of an enriched environment on cognitive development. The acquisition of high-resolution MRI scans of the hippocampus in future studies will permit such characterization and shed further light on the potential mechanisms that may underlie higher environmental sensitivity in individuals with a larger hippocampus. Finally, we did not assess whether the mother was the infant's primary care giver and how much time the infants spent away from their mothers with another care giver or in a different setting (e.g., daycare). This should be controlled for in future studies testing the effect of the home environment on developmental outcomes.

Despite these limitations, the current findings provide the first evidence to date suggesting individual variation in neonatal hippocampal size may reflect environmental sensitivity, whereby individuals with larger hippocampal size may benefit more from enriched environments in terms of cognitive development. These results may shed light on the neural determinants underlying environmental sensitivity and may help to better understand the complex role of biological and environmental factors in cognitive development.

Declaration of Competing Interest

The authors declare no conflict of interest.

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