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Maternal sensitivity predicts anterior hippocampal functional networks in early childhood

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Abstract

Maternal care influences child hippocampal development. The hippocampus is functionally organized along an anterior–posterior axis. Little is known with regards to the extent maternal care shapes offspring anterior and posterior hippocampal (aHPC, pHPC) functional networks. This study examined maternal behavior, especially maternal sensitivity, at 6 months postpartum in relation to aHPC and pHPC functional networks of children at age 4 and 6 years. Maternal sensitivity was assessed at 6 months via the "Maternal Behavior Q Sort (MBQS) mini for video". Subsequently, 61 and 76 children underwent resting-state functional magnetic resonance imaging (rs-fMRI), respectively, at 4 and 6 years of age. We found that maternal sensitivity assessed at 6 months postpartum was associated with the right aHPC functional networks in children at both 4 and 6 years of age. At age 4 years, maternal sensitivity was associated positively with the right aHPC's functional connectivity with the sensorimotor network and negatively with the aHPC's functional connectivity with the top–down cognitive control network. At 6 years of age, maternal sensitivity was linked positively with the right aHPC's functional connectivity with the visual-processing network. Our findings suggested that maternal sensitivity in infancy has a long-term impact on the anterior hippocampal functional network in preschool children, implicating a potential role of maternal care in shaping child brain development in early life.

Keywords Resting-state fMRI · Maternal sensitivity · Anterior hippocampus · Posterior hippocampus · Functional networks

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Introduction

Maternal sensitivity has been defined as the ability to recognize and respond both effectively and promptly to the distress and needs of one's child (Ainsworth et al. 1978). It is widely associated with infant's early linguistic (Paavola et al. 2006), cognitive (Frick et al. 2018), and self-regulation development (Ispa et al. 2017; Frick et al. 2018), as well as school-age performance (Treyvaud et al. 2016). Maternal sensitivity is also considered protective, buffering influences of early adversity on child behavioral and cognitive development (Faure et al. 2017; Drury 2012). Currently, much attention has been devoted to the relationships between maternal sensitivity and child cognition and behavior. Only a few studies (Rifkin-Graboi et al. 2015a; Wen et al. 2017b) have begun to explore maternal sensitivity's influence upon functional brain networks in early childhood, which may, perhaps in turn, bias subsequent offspring sensory information and cognitive processing.

Converging evidence has documented that the broader concept of maternal care impacts hippocampal glucocorticoid receptors (Liu et al. 1997), hippocampal transcriptome (Weaver et al. 2006), hippocampal plasticity (Champagne et al. 2008) and function (Bagot et al. 2012; Nguyen et al. 2015) in animal models. In line with these findings, human-imaging studies have found that maternal care associates with a larger hippocampal volume in the preschool period (Luby et al. 2016b). Also, past work with 6-month-old infants demonstrates the relationship of maternal sensitivity with the hippocampal volume, as well as hippocampal functional connectivity with brain regions involved in cognitive flexibility, such as the dorsolateral prefrontal cortex (dlPFC), and autobiographical memory, such as the lingual gyrus (Rifkin-Graboi et al. 2015a). Nevertheless, some imaging studies revealed negative association or no association between the aspect of positive parenting (Rao et al. 2010; Bernier et al. 2019) and the hippocampal volume in early childhood (Whittle et al. 2014). The specificity of relations between the caregiving environment and brain development may be influenced by the timing of exposure and the age of MRI assessment.

One proposed mechanism influencing such neural changes involves the hypothalamic–pituitary–adrenal (HPA) axis and stress responsiveness. That is, low maternal sensitivity may be a salient source of stress in offspring during early development, and as such may alter HPA reactivity and eventually children's emotional experience and neurocognitive development (Blair et al. 2006). Importantly, the hippocampus is one of the core brain regions involved in stress responsiveness and regulation (Herman et al. 2005). It is also essential for autobiographical memory and thinking about the future—two processes critical to the building of cognitive-emotional schemas that may guide daily life and social relationships (Cabeza and St Jacques 2007; Hassabis et al. 2007).

The hippocampus is thought to be functionally organized along an anterior–posterior axis (Poppenk et al. 2013). A few studies suggested that the anterior hippocampus is involved in the non-emotional processes such as spatial memory (Strange et al. 2014; Zeidman and Maguire 2016; Sapolsky et al. 1985). Moreover, the posterior hippocampus is engaged to the stress-related traits such as anxiety and depression (Satpute et al. 2012) and chronic stress (Sapolsky et al. 1985), as well as is associated with risk of anxiety and depression (de Geus et al. 2007). Nevertheless, there is a consensus that the anterior portion of the hippocampus is thought to reflect motivational processing and information encoding in episodic memory, whereas the posterior portion of the hippocampus is responsible for retrieval processing in episodic memory and spatial cognition (Poppenk et al. 2013; Nadel et al. 2012). In addition, animal and human studies show a specific role of the anterior hippocampus in anxiety-related behaviors (Bannerman et al. 2004; Satpute et al. 2012) and stress-related processing via its close connections with other subcortical structures relevant to the HPA axis (Bannerman et al. 2004; Fanselow and Dong 2010; Mahar et al. 2014). This may suggest that stress related to the caregiving environment has a larger impact upon the anterior, rather than the posterior hippocampus. Moreover, young adults with a history of caregiving deprivation and emotional neglect were found to exhibit greater anterior, but not posterior, hippocampal activation during processing of threatening information such as fearful faces (Maheu et al. 2010). In line with these findings, Fanselow and Dong have reviewed research indicating that the anterior hippocampus and its neural connectivity are involved in stress, emotion, and affect from the behavioral, anatomical, and genetic perspectives. Hence, we hypothesized that the anterior hippocampal circuitry might be predominantly influenced by maternal care in early childhood. However, it is unclear which specific anterior hippocampal circuitry could be influenced by maternal care. Given the previous findings on the emphasis of hippocampal-sensory and cognitive networks in relation to maternal sensitivity in infants (Rifkin-Graboi et al. 2015a), we would expect that these networks may continue being influenced by maternal sensitivity in early childhood.

In this study, we investigated the above hypothesis and examined the extent to which maternal sensitivity is associated with anterior and posterior hippocampal functional networks in preschool children at 4 and 6 years of age using resting-state functional magnetic resonance imaging (rs-fMRI). We studied preschool children partly because of the rapid development of the brain during this period and the feasibility of imaging children at this young age. Moreover,

a previous study also suggested that preschool is a sensitive period for the influence of maternal support on hippocampal development (Luby et al. 2016a). Moreover, the associations of maternal behaviors/adversity with child behaviors and neurodevelopment are sex dependent. Maternal cortisol during pregnancy was associated with affective problems and a larger amygdala volume in girls but not in boys (Buss et al. 2012). Maternal depressive symptoms were linked with more internalizing behavioral problems in girls than in boys (Essex et al. 2003) and were associated with the amygdala structural and functional development in 4-year-old girls but not boys (Wen et al. 2017a; Soe et al. 2016). Hence, we examined the interactive effect of sex-by-maternal sensitivity on the anterior and posterior hippocampal functional networks. We then utilized a reduced model to independently estimate maternal sensitivity's influence upon anterior and posterior hippocampal functional connectivity when no interaction effects were observed. We expected that the association of maternal sensitivity with the hippocampal functional networks might be sex dependent.

Materials and methods

Participants

This study was approved by the National Healthcare Group Domain Specific Review Board (NHGDSRB) and the Sing Health Centralized Institutional Review Board (CIRB). Written informed consent was obtained from mothers and the oral informed consent was obtained from children prior to participation.

Three hundred and forty-two and 398 mother–child dyads who participated in the prospective Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study were recruited for neuroimaging when children were 4 years and 6 years of age, respectively. The details of the GUSTO cohort can be found in our previous papers (Soh et al. 2012).

Maternal education level and maternal ethnicity were obtained from survey questionnaires conducted as part of a scheduled appointment during the 26th week of pregnancy. Birth outcomes (gestational age, birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score and sex) and pregnancy measures were obtained from hospital records. This study only included children with gestational age ≥ 34 weeks, birth weight ≥ 2 kg and a 5-min APGAR score ≥ 9 to avoid potential influences of pregnancy outcomes upon brain development. Our inclusion criteria were matched with previously reported criteria (Buss et al. 2012).

Of the 342 subjects who underwent MRI at 4 years of age, 78 subjects had unusable T1 data due to unsatisfactory image quality, 4 did not meet the inclusion criteria, 119 mothers did not have maternal sensitivity data, 10 mothers had unusable maternal sensitivity data (i.e., data lost ($n = 3$), faulty audio ($n = 5$), view issue ($n = 1$), and language issue ($n = 1$)), 30 mothers of infants did not complete depression questionnaires (i.e., EPDS), 2 mothers did not complete demographic information questionnaires (i.e., maternal education) and 38 subjects had large head motion of rs-fMRI (maximal framewise displacement, FD > 0.5 mm). Hence, the 4-year-old sample in this study included 61 subjects (33 girls and 28 boys).

Of the 398 subjects who underwent MRI at 6 years of age, 81 subjects had unusable T1 data due to unsatisfactory image quality, 7 did not meet the inclusion criteria, 149 mothers did not have maternal sensitivity data, 16 mothers had unusable maternal sensitivity data (i.e., data lost ($n = 3$), faulty audio ($n = 7$), view issue ($n = 3$), procedural inconsistency ($n = 2$), and father–child interaction ($n = 1$)), 28 mothers of infants did not complete depression questionnaires (i.e., EPDS), 2 mothers did not complete demographic information questionnaires (i.e., maternal education) and 39 subjects had large head motion of rs-fMRI (FD > 0.5 mm). Hence, the 6-year-old sample in this study included 76 subjects (46 girls and 30 boys). Table 1 lists the demographic information of the two samples that were used in this study.

Maternal sensitivity

A 15-min mother–child interaction was recorded as part of a 3-h laboratory visit when infants were 6 months of age (± 2 weeks). The mother was asked to "interact or play" with her 6-month-old infant "as she normally would at home". The room was equipped with a foldable chair, highchair, and a mat, but no toys for the first 5 min. After 5 min, a standard set of attractive toys and books was brought into the room. Maternal sensitivity was assessed using the Revised Mini-A short form of the Maternal Behavioral Q-Sort-V (Mini-MBQS-V) (Tarabulsy et al. 2009). The Mini-MBQS-V consists of 25 items, each representing different possible aspects of sensitive, and inversely, insensitive, maternal behavior during interaction with an infant. Coders sort the 25 items into piles of 5, ranging from 1 being "least like the mother", to 5 being "most like the mother." Ratings are then correlated with that of a theoretically constructed prototypical sensitive mother to derive the global sensitivity score, ranging from − 1 (very much unlike a prototypical sensitive mother) to 1 (very much similar to a prototypical sensitive mother). For example, if the mother's behavior is very similar to a "prototypically sensitive mother", coders might assign values of "5" to cards such as: "Mother builds on the focus of the baby's attention" and "Mother responds to the baby's distress and non-distress signals even when engaged in some other activity". Likewise, when viewing

Table 1 Demographics

Measure	4-year-old sample ($N=61$)	6-year-old sample ($N=76$)
APGAR score, mean $\pm$ SD (min–max)	9.02 ± 0.13 (9–10)	9.0 ± 0.0 (9–9)
Gestational age (week), mean $\pm$ SD (min–max)	38.76 ± 1.35 (34.8–40.6)	39.12 ± 1.11 (34.8–41.1)
Birth weight (g), mean $\pm$ SD (min–max)	3133.4 ± 434.8 (2265–4390)	3118.2 ± 447.2 (2265–4390)
Sex, male/female	33/28	46/30
Age (year), mean $\pm$ SD (min–max)	4.57 ± 0.08 (4.36–4.75)	6.03 ± 0.13 (5.83–6.61)
Maternal sensitivity score, mean $\pm$ SD (min–max)	0.25 ± 0.49 (-0.68–0.85)	0.21 ± 0.44 (-0.68–0.81)
3-month EPDS score, mean $\pm$ SD (min–max)	8.46 ± 8.56 (0–38)	7.53 ± 6.71 (0–32)
Maternal ethnicity, %		
Chinese	42.6	40.8
Malay	36.1	36.8
Indian	21.3	22.4
Maternal education, %		
Primary school	4.9	4.0
Secondary school	29.5	27.6
Pre-university, diploma or technical course	36.1	36.8
University undergraduate level	26.2	30.3
Above university undergraduate level	3.3	1.3

SD standard deviation, *EPDS* Edinburgh Postnatal Depression Scale, *APGAR* appearance, pulse, grimace, activity, and respiration

a mother who is very similar to a prototypically sensitive mother, coders might assign values of "1" to cards describing insensitive behavior such as, "Mother tends to tune out and not notice the infant's bids for attention" and "The content and pace of the interaction is set by the mother rather than the baby's response". Three Southeast Asian coders scored the larger GUSTO cohort cases, and the two of whom who scored the majority of cases were directly trained by the developers of the Mini-MQS-V coding system. Together, the local coders were fluent in both English and the predominant mother tongue languages of Singapore (i.e., Malay, Mandarin, and/or Tamil). Training included the scoring of Western and Singaporean tapes. Reliability for MBQS sensitivity was assessed between the first two coders across 59 cases (roughly 15% of the GUSTO sample), and between Coder Three and Coder One and Coder Two, respectively, across 35 and 31 tapes. The Absolute Intraclass Correlation Coefficient (ICC) Single Measures across all three coders for sensitivity equaled 0.720, and was 0.861 between Coders One and Two.

Maternal depression scales

We included the scale of maternal depressive symptoms as a confounding variable as it is negatively associated with maternal sensitivity (Crockenberg and Leerkes 2003). Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) at 3 months postpartum. The EPDS is a widely used 10-item self-report scale designed as a screening instrument for maternal

postnatal depression and valid for use in the prenatal and early postnatal time points (Bergink et al. 2011). Each EPDS item is scored on a four-point scale (0–3), and items three and five-through-ten are reverse scored. All item points are summed for a total score. Higher EPDS scores indicate higher levels of depressive symptomatology.

MRI acquisition and preprocessing

Children underwent MRI scans at age of 4.5 years ($\pm$ 1 months) and 6 years ($\pm$ 2 months) using a 3T Siemens Skyra scanner with a 32-channel head coil at KK Women's and Children's hospital. The image protocols were: (1) high-resolution isotropic T_1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE; 192 slices, 1 mm thickness, in-plane resolution 1 mm, sagittal acquisition, field of view 192×192 mm^2, matrix $= 192 \times 192$, repetition time $= 2000$ ms, echo time $= 2.08$ ms, inversion time $= 877$ ms, flip angle $= 9°$, scanning time $= 3.5$ min); (2) isotropic axial rs-fMRI protocol (single-shot echo-planar imaging; 48 slices with 3 mm slice thickness, no inter-slice gaps, matrix $= 64 \times 64$, field of view $= 192 \times 192$ mm^2, repetition time $= 2660$ ms, echo time $= 27$ ms, flip angle $= 90°$, scan time of the first run $= 5.27$ min, scan time of the second run $= 3.19$ min). The children were required to close their eyes during the rs-fMRI scan. The practical scanning procedure was detailed in the Supplementary of (Wen et al. 2017a). Only the first run of rs-fMRI was used in this study.

The image quality was verified immediately after the acquisition through visual inspection when children were

still in the scanner. A scan was repeated when the ring artifact on T_1-weighted images was large. The image was removed from the study if no acceptable image was acquired after three repetitions.

Structural MRI FreeSurfer was used to segment brain images into three tissue types, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Post-processing quality checks were conducted according to instructions on https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData. Non-linear image normalization was achieved by aligning individual T_1-weighted MRI images to the JHU atlas (Zhang et al. 2014; Mori et al. 2008) via large deformation diffeomorphic metric mapping (LDDMM) (Tan and Qiu 2016; Du et al. 2011; Zhong et al. 2010). Visual inspection was conducted to detect any obvious mapping errors.

Rs-fMRI Rs-fMRI data that had more than 10 volumes in a row with large motion or a checkered-board image appearance were discarded from any further analysis. FSL was used to process the rs-fMRI scan for slice time correction, motion correction, skull stripping, and intensity normalization. We computed framewise displacement (FD) of a time series based on the definition given in (Power et al. 2012) to quantify head motion. In brief, FD was defined as the sum of the absolute values of the derivatives of the six realignment parameters. Rotational displacements are converted from degrees to millimeters by calculating displacement on the surface of a sphere of radius 50 mm (Power et al. 2012). We excluded rs-fMRI data if one or multiple volumes had framewise displacement (FD) greater than 0.5 mm. The mean and standard deviation values of the maximal FD among the subjects included in this study were 0.181 mm and 0.136 mm in the 4-year-old sample and 0.198 mm and 0.134 mm in the 6-year-old sample; the range was from 0.033 mm to 0.496 mm in the 4-year-old sample and from 0.033 mm to 0.481 mm in the 6-year-old sample. Figure S1 in the Supplementary Material shows the distributions of max FD and FD of each rs-fMRI volume over all the subjects at 4 and 6 years, as well as FD across the time series in subjects with the lowest and highest motion at 4 and 6 years. Linear regression analysis was performed to partial out six motion parameters (three translations and three rotation parameters), global signal, WM and CSF signals. Global signal regression was carried out to eliminate artifactual variance due to head motion, known to be a problem in pediatric populations (Power et al. 2014). Band-pass filtering (0.01–0.08 Hz) was then applied. For each subject, the mean functional volume was aligned to the corresponding anatomical image via rigid body alignment. The functional data were finally transformed to the JHU atlas space via LDDMM obtained based on the T_1-weighted MRI.

Anterior and posterior hippocampal functional networks

The hippocampus was defined using the Harvard–Oxford subcortical atlas (Desikan et al. 2006) from the FSL Software Library (Smith et al. 2004). Next, the left and right hippocampi were vertically divided into the anterior (aHPC) and posterior (pHPC) segments at $Y = -21$ mm in the MNI space (Poppenk et al. 2013). As illustrated in Fig. 1, we discarded 2 coronal slices between the anterior and posterior segments along the anterior–posterior hippocampal axis to avoid signal mixture between the anterior and posterior hippocampus.

For each subject, the mean time courses of aHPC and pHPC were calculated and were correlated with the time courses of the whole brain to construct bilateral aHPC and pHPC functional connectivity maps. These maps were then converted to z value maps using Fisher's r-to-z transformation and smoothed with a Gaussian kernel with a full width half maximum of 6 mm.

Statistical analysis

We examined associations between maternal sensitivity and the aHPC and pHPC functional connectivity maps in children at both 4 and 6 years of age using a mixed-effects FLAME 1 model implemented in FSL. Maternal education and ethnicity, age at MRI scan, postnatal maternal depressive symptoms at 3 months postpartum, and FD were included as covariates. These factors were taken into account because maternal education and ethnicity have been shown
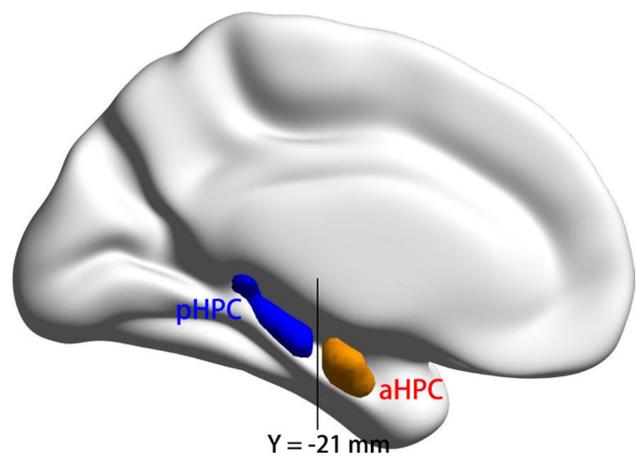

Fig. 1 Illustration of the anterior and posterior hippocampal seed regions. The whole hippocampus was divided into the anterior and posterior section based on the location of uncal apex in the MNI space (i.e., $Y = -21$ mm). To avoid contamination effects between the aHPC and pHPC, a 2-mm coronal slice from each of the two adjacent ends was removed. *L* left, *aHPC* anterior hippocampus, *pHPC* posterior hippocampus

to affect maternal mood (González et al. 2010), and age at MRI and FD can influence the functional network (Van Dijk et al. 2012).

In regression analysis, covariates were entered into the first block of equations. In the second block, mean-centered maternal sensitivity and sex were entered. The interaction term, the product of mean-centered maternal sensitivity and sex, was entered into the third block. When the interactive effect was not significant, a reduced model, controlling for the same covariates and sex, examined maternal sensitivity in relation to the same outcome measures. Statistical results were determined at a cluster level ($z > 3.1$, $p < 0.001$) and at a family-wise error rate of 0.05 for the correction for multiple comparisons (Eklund et al. 2016).

Results

Demographics

The 4- and 6-year-old samples did not differ in APGAR score ($t_{(135)} = 0.515$, $p = 0.608$), gestational age ($t_{(135)} = -1.657$, $p = 0.100$), birth weight ($t_{(135)} = 0.199$, $p = 0.842$), postnatal maternal depression ($t_{(135)} = 0.714$, $p = 0.477$), maternal sensitivity ($t_{(135)} = 0.482$, $p = 0.631$), sex ($\chi^2_{(1)} = 1.899$, $p = 0.168$), maternal ethnicity ($\chi^2_{(2)} = 0.794$, $p = 0.672$) and maternal education ($\chi^2_{(4)} = 4.058$, $p = 0.398$). The 4- and 6-year-old samples, respectively, had 4 and 2 subjects whose gestational age was less than 37 weeks. Only 35 subjects had maternal sensitivity as well as both 4-year and 6-year rs-fMRI data. Due to this small sample at both time points, we did not examine our results in a longitudinal manner.

Maternal sensitivity did not vary significantly as a function of postnatal maternal depressive symptoms ($r = -0.005$, $p = 0.970$), gestational age ($r = 0.029$, $p = 0.823$), sex ($t_{(59)} = -0.651$, $p = 0.517$), and birth weight ($r = -0.033$, $p = 0.802$) in the 4-year-old sample. Similarly, maternal sensitivity was not significantly associated with postnatal maternal depressive symptoms ($r = -0.142$, $p = 0.223$), gestational age ($r = 0.182$, $p = 0.115$), sex ($t_{(74)} = -0.901$, $p = 0.371$), and birth weight ($r = 0.071$, $p = 0.545$) in the 6-year-old sample.

Associations of maternal sensitivity with anterior and posterior hippocampal functional networks

The interaction between maternal sensitivity and sex did not predict the bilateral aHPC and pHPC functional networks at 4 or 6 years of age. Next, we report results from the reduced models.

Four year olds Maternal sensitivity during infancy was positively associated with 4-year-old's functional connectivity between the right aHPC and the right precentral

gyrus (corrected $p = 0.001$), the left postcentral gyrus (corrected $p < 0.001$) and the right postcentral gyrus (corrected $p < 0.001$). Maternal sensitivity was negatively associated with functional connectivity between the right aHPC and the left dorsolateral prefrontal cortex (dlPFC) (corrected $p = 0.016$) (Fig. 2). Table 2 lists the anatomical coordinates of these regions in the MNI space and the cluster size of these findings. These results remained significant even when the premature subjects (GA < 37 weeks, $n = 4$) were excluded (see Figure S2 in the Supplementary Material). In sum, these findings indicated that maternal sensitivity predominantly predicted aHPC's functional connectivity with sensorimotor and top–down cognitive control networks in 4-year-old children.

Six year olds Maternal sensitivity during infancy was positively associated with the right aHPC functional connectivity and aspects of the visual-processing network, including the left calcarine (corrected $p < 0.001$), right calcarine (corrected $p < 0.001$), right lingual (corrected $p < 0.001$), and left cuneus cortex (corrected $p < 0.001$) in 6 year olds (Fig. 3). The anatomical coordinates and cluster sizes of these findings are listed in Table 2. When the premature children (GA < 37 weeks, $n = 2$) were excluded, these results remained significant (see Figure S3 in the Supplementary Material). Together, these findings suggested that maternal sensitivity predicted the aHPC's functional connectivity with the visual-processing network in 6-year-old children.

No significant findings were observed with regards to the bilateral pHPC and left aHPC functional networks in 4- or 6-year-old children.
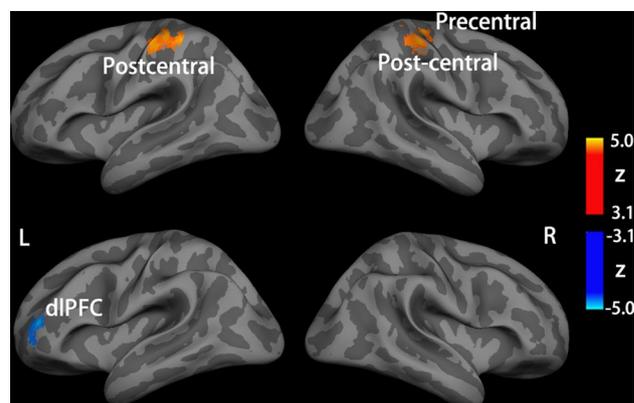

Fig. 2 Influences of maternal sensitivity on the right anterior hippocampal functional network in 4-year-old sample. *L* left, *R* right, *dlPFC* dorsolateral prefrontal cortex

Table 2 Statistical associations between maternal sensitivity (MS) and right anterior hippocampal functional networks

Sample	Effects	Anatomy	Peak MNI coordinate			Cluster size (voxels)
			X	Y	Z	
4 year olds	MS (positive)	R Precentral	20	−28	54	39
		L Postcentral	−36	−34	58	171
		R Postcentral	40	−30	58	95
	MS (negative)	L dlPFC	−34	52	14	79
6 year olds	MS (positive)	L Calcarine	−22	−64	6	79
		R Calcarine	12	−68	12	77
		R Lingual	20	−56	2	41
		L Cuneus	−8	−72	20	13

Below lists anatomical structures, their coordinates in the MNI space, and cluster size

Positive and negative, respectively, indicate positive and negative correlations between maternal sensitivity and the right anterior hippocampal functional network

MS maternal sensitivity, *dlPFC* dorsolateral prefrontal cortex, *L* left, *R* right
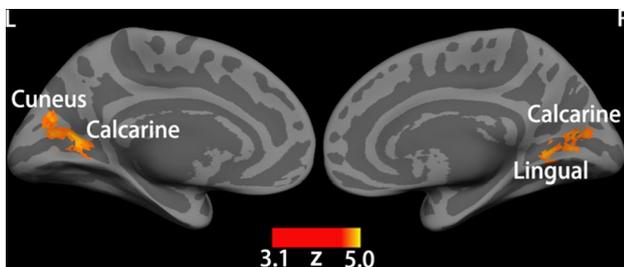

Fig. 3 Influences of maternal sensitivity on the right anterior hippocampal functional network in the 6-year-old sample. *L* left, *R* right

Discussion

Here, we observed that maternal sensitivity, assessed at 6 months postpartum, predicted the right aHPC functional networks in children at both 4 and 6 years of age. When children were 4 years of age, previously assessed levels of maternal sensitivity were positively related to the right aHPC's functional connectivity with the sensorimotor network and negatively to the right aHPC's functional connectivity with the top–down cognitive control network. When children were 6 years of age, previously assessed levels of maternal sensitivity were positively linked to the right aHPC's functional connectivity with the visual-processing network. Our findings suggested that maternal sensitivity in infancy has a long-term impact on the anterior hippocampal functional networks in preschool children.

The sensorimotor network is mainly composed of the precentral and postcentral cortex (Berman et al. 2016). Its developmental course starts early and peaks at 2–3 years of age (Casey et al. 2005). Around 4 years of age, its connections to the hippocampus are greater in the aHPC rather than pHPC regions (Riggins et al. 2016). The sensorimotor

development in early life is critical and vulnerable to exposure to psychological adversity, such as maternal anxiety and depression and maternal care (Sale et al. 2009). In the same GUSTO sample, we previously employed diffusion tensor imaging (DTI) and reported that antenatal maternal anxiety predicted variation in the microstructure of the precentral and postcentral cortex as well as the medial temporal lobe (Rifkin-Graboi et al. 2015b). Maternal anxiety at 19 weeks gestation was associated with gray matter volume reductions in the medial temporal lobe and the postcentral cortex in 6–9-year-old children (Buss et al. 2010). Moreover, a preliminary study with a small sample ($n = 20$) showed that maternal sensitivity influences the hippocampal volume and functional organization in 6-month-old infants (Rifkin-Graboi et al. 2015a, b). Furthermore, abnormalities in the sensorimotor functional network have been identified in children with withdrawn behavioral problems assessed using child behavior checklist (CBCL) at early childhood (Wee et al. 2018). These findings suggest that maternal psychological adversity and behavior might manipulate the development of the sensorimotor systems.

In contrast to the enhanced coupling between the aHPC and sensorimotor networks, we observed decoupling between the aHPC and the cognitive control network as a function of maternal sensitivity. Such aberrant aHPC-prefrontal functional connectivity has also been observed in studies focused upon the association between early adversity (e.g., childhood poverty and childhood maltreatment) and neurodevelopment in school-age (7–12) children (Barch et al. 2016; Birn et al. 2014). Our previous study with a limited sample ($n = 20$) from the same GUSTO cohort suggested that maternal sensitivity at 6 months postpartum was associated with increased coupling between the hippocampus and dlPFC in 6-month-old infants (Rifkin-Graboi et al. 2015a, b). Together, these findings suggest that directional

effects of the early caregiving environment upon the aHPC-prefrontal functional connectivity may be influenced by age at assessment. Indeed, our additional analysis (see Figure S4 in the Supplementary Material) showed that age does modulate the relationship of maternal sensitivity and the aHPC's functional network. Similarly, past research showed that the aHPC-prefrontal functional connectivity negatively predicts episodic memory in 4 year olds but positively predicts episodic memory in 6 year olds (Riggins et al. 2016). It is unclear why the relationship of the aHPC-prefrontal functional connectivity with maternal care or child cognition shifts from positive to negative association from younger to older age in early life. Nevertheless, this phenomenon is not unique to the hippocampus. In typical development, the amygdala-prefrontal functional organization also shifts from positive to negative connectivity from childhood to adolescence (Gee et al. 2013; Gabard-Durnam et al. 2014). It has been suggested that earlier amygdala development may drive heavier bottom–up signaling early in life, which accelerates the prefrontal development (Gee et al. 2013; Gabard-Durnam et al. 2014). As top–down signaling increasingly emerges over time, the prefrontal cortex plays a role in regulating signals from the amygdala (Gee et al. 2013; Gabard-Durnam et al. 2014). This intriguing model may be applied to the general development of regulatory connections between the amygdala-hippocampal complex and prefrontal cortex. In our study, this shift happened much earlier, suggesting that early childhood demarcates as a critical and malleable period in the hippocampal-cortical formation, along with increased vulnerability to environmental influences.

Finally, in the current study, higher levels of maternal sensitivity were associated with increased functional connectivity between the aHPC and the visual-processing network in 6 year olds. The visual-processing network identified in the present study consisted of the lingual, cuneus and calcarine cortex. Prior studies have indicated that the lingual cortex enhances activity during spatial and visual working memory (Migo et al. 2015), associates with chronic perceived stress (Veer et al. 2010), and is linked to resilience to childhood maltreatment (van der Werff et al. 2013). The calcarine cortex is thought to play a role in the perception of visual cues for saccades (Lalli et al. 2006) and visual-mental imagery (Klein et al. 2000), as well as positive affect processing (Malhi et al. 2007; Park et al. 2010; Killgore and Yurgelun-Todd 2007). In line with the findings in this study, our previous study on 6-month infants (n = 20) showed the positive associations of maternal sensitivity with the functional connectivity between the hippocampus and the visual-processing network (Rifkin-Graboi et al. 2015a). These findings suggest the long-term impact of maternal care on the hippocampal and visual-processing network. However, further investigation is needed to find out the relationships among maternal care, hippocampal and visual-processing functional organization, and child cognitive and behavioral outcomes.

In our study, we showed that maternal sensitivity selectively affected the anterior but not the posterior hippocampal functional networks at both 4 and 6 years of age. A substantial body of literature supports the associations of maternal psychological factors and care with children's socioemotional behavior (Leerkes et al. 2009; Palmer et al. 2018). And a consensus from the literature suggests the aPHC is involved in stress regulation, emotion, and affect (Fanselow and Dong 2010). This evidence together with our findings may potentially suggest that the aPHC functional organization might be vulnerable to maternal care and play a crucial role in early socioemotional development.

Our study highlighted the importance of the right but not left aHPC functional organization in relation to maternal sensitivity. Our previous study with a small sample (n = 35) also showed the growth of the right hippocampal volume in the first 6 months of life in association with maternal anxiety (Qiu et al. 2013). The right hippocampal volume was selectively associated with chronic perceived stress (Gianaros et al. 2007). It is unclear what are underlying mechanisms for this specific laterality of the hippocampus sensitive to stress and maternal psychological factors and care. One suggested explanation was that an asymmetric concentration of stress-related neurotransmitters, such as serotonin, may play a role in manipulating right-lateralized hippocampal functions (Bremner et al. 1995).

There were several limitations of this study. Head motion of rs-fMRI is considered a major factor that influences the rs-fMRI signal. Nevertheless, there is no gold standard to characterize the potential effects of head motion on the rs-fMRI signal. This study utilized a global signal regression to remove micro-motion that cannot be characterized using motion parameters (e.g., rotation and translation) (Power et al. 2014). Even though there is a debate that a global signal regression could induce spurious negative correlation, we performed additional analysis and demonstrated that the global signal regression at least did not influence our findings (see Figure S5 in the Supplementary Material). Moreover, the sample size of this study was relatively large for a pediatric imaging study at 4 and 6 year olds. Nevertheless, the overlap between 4- and 6-year-old samples was small, limiting our ability to capture longitudinal trajectories. This research, then, calls for further studies of the relation between maternal sensitivity and the developmental trajectory of hippocampal functional networks.

In summary, our findings suggest a long-term impact of maternal sensitivity during infancy upon anterior hippocampal functional networks in early childhood. Our findings suggest a potential role of maternal care in shaping early-life child brain development and underscore the importance

of public health efforts to enhance maternal care during infancy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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