

RAPID COMMUNICATION

MR-Determined Hippocampal Asymmetry in Full-Term and Preterm Neonates

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ABSTRACT: Hippocampi are asymmetrical in children and adults, where the right hippocampus is larger. To date, no literature has confirmed that hippocampal asymmetry is evident at birth. Furthermore, gender differences have been observed in normal hippocampal asymmetry, but this has not been examined in neonates. Stress, injury, and lower IQ have been associated with alterations to hippocampal asymmetry. These same factors often accompany preterm birth. Therefore, prematurity is possibly associated with altered hippocampal asymmetry. There were three aims of this study: First, we assessed whether hippocampi were asymmetrical at birth, second whether there was a gender effect on hippocampal asymmetry, and third whether the stress of preterm birth altered hippocampal asymmetry. This study utilized volumetric magnetic resonance imaging to compare left and right hippocampal volumes in 32 full-term and 184 preterm infants at term. Full-term infants demonstrated rightward hippocampal asymmetry, as did preterm infants. In the case of preterm infants, hippocampal asymmetry was proportional to total hemispheric asymmetry. This study is the first to demonstrate that the normal pattern of hippocampal asymmetry is present this early in development. We did not find gender differences in hippocampal asymmetry at term. Preterm infants tended to have less asymmetrical hippocampi than full-term infants, a difference which became significant after correcting for hemispheric brain tissue volumes. This study may suggest that hippocampal asymmetry develops in utero and is maintained into adulthood in infants with a normal neurological course. © 2008 Wiley-Liss, Inc.

KEY WORDS: infant; premature; magnetic resonance imaging (MRI); volumetry; hippocampus

INTRODUCTION

The main role of the hippocampus is in learning and memory (Burgess et al., 1999). It is also implicated in neuropsychiatric disorders (Geuze et al., 2005), and memory impairments such as Alzheimer's disease and amnesia (Jack et al., 2000). Hemispheric changes in the hippocampus may differentially affect function. Surgical damage to the left hippocampus reveals deficits in memory for verbal material (i.e., words), whereas damage to the right reveals deficits in nonverbal memory (i.e., faces or nonsense figures) (Zaidel, 1995).

Neurologically normal adults (Weis et al., 1989; Watson et al., 1992; Jack et al., 2000) and children (Giedd et al., 1996; Pfluger et al., 1999; Utsunomiya et al., 1999) have significantly larger right hippocampi. However, there is no literature confirming the presence or absence of hippocampal asymmetry at earlier stages in brain development. Hence, it is uncertain how early in brain development asymmetry is acquired: in utero, during infancy or childhood. We therefore utilized quantitative MR Imaging technologies to determine whether hippocampal asymmetry was present in infants at term.

Gender differences have been associated with hippocampal asymmetry in older neurologically normal populations (Giedd et al., 1996; Pfluger et al., 1999). To determine if gender effects are evident at term, we compared hippocampal asymmetry between newborn males and females.

The hippocampus is vulnerable to stress (Perlman, 2001) and a wide variety of neurological insults including hypoxic-ischemic injury and metabolic insults (Schmidt-Kastner and Freund, 1991). Abnormal hippocampal asymmetry is associated with lower IQ (Abernethy et al., 2002) and temporal lobe epilepsy (Cook et al., 1992). The vulnerabilities and impairments associated with the hippocampus are

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TABLE 1.

Perinatal and Demographic Characteristics of the Cohorts

| Characteristic | Full-term, <i>n</i> = 32 | Preterm, <i>n</i> = 184 |
|--|--------------------------|-------------------------|
| Gestational age at birth (wk)—mean (SD) | 39.0 (1.2) | 27.6 (1.9) |
| Gestational age at MRI—mean (SD) | 40.5 (1.0) | 40.1 (1.1) |
| Birthweight (g)—mean (SD) | 3,289 (504) | 964 (219) |
| Weight at MRI (g)—mean (SD) | 3,484 (490) | 2,971 (531) |
| Male— <i>n</i> (%) | 18 (56) | 93 (51) |
| Multiple births— <i>n</i> (%) | 1 (3) | 79 (43) |
| Bronchopulmonary dysplasia ^a — <i>n</i> (%) | 0 (0) | 68 (35) |
| Inotropic support— <i>n</i> (%) | 0 (0) | 71 (39) |
| Postnatal corticosteroids ^b — <i>n</i> (%) | 0 (0) | 14 (8) |
| Intrauterine growth restriction ^c — <i>n</i> (%) | 2 (6) | 22 (12) |
| Necrotizing enterocolitis— <i>n</i> (%) | 0 (0) | 19 (10) |
| Proven sepsis— <i>n</i> (%) | 1 (3) | 80 (44) |
| Antenatal corticosteroids— <i>n</i> (%) | 0 (0) | 164 (89) |
| Positive pressure ventilation (hr)—mean (SD) | 0.59 (3.4) | 223 (365) |
| Parenteral nutrition (days)—mean (SD) | 0.19 (1.1) | 14 (17) |
| Patent ductus arteriosus (indomethacin administered), <i>n</i> (%) | 0 (0) | 63 (34) |
| WM injury (any grade), <i>n</i> (%) | 1 (3) | 118 (64) |
| WM injury (Grade III/IV), <i>n</i> (%) | 0 (0) | 31 (17) |
| Intraventricular hemorrhage, <i>n</i> (%) | 0 (0) | 24 (13) |

^aRequired oxygen at 36 weeks gestational age.

^bPostnatal dexamethasone, 0.15 mg/kg per day, reducing over 10 days.

^cZ score > 2 SD below mean weight for gestational age.

reminiscent of the difficulties faced by preterm infants. Specifically, preterm infants often experience stressors such as hypoxic-ischemic injury and metabolic disorders (Fuller et al., 1983). They often have cognitive and learning deficits (Hack and Fanaroff, 1999), memory impairments (Briscoe et al., 1998), and increased risk of neuropsychological disorders such as attention deficit hyperactivity disorder (Warner-Rogers, 2002). These impairments may be related, at least in part, to hippocampal changes, and specifically hippocampal asymmetry. Our group has previously shown that the hippocampi of preterm infants are not disproportionately smaller than full-term infants' relative to overall brain size (Thompson et al., 2008). However, uncorrected preterm hippocampal volumes were significantly smaller for the right hemisphere only (Thompson et al., 2008). Preterm birth is a stressful experience, and its effect on hippocampal asymmetry has never been specifically investigated. Therefore, we compared preterm and full-term hippocampal asymmetry at term.

Two hundred thirty three preterm infants (birth weight < 1,250 g or gestational age < 30 weeks) from the Royal Women's Hospital in Melbourne and 51 healthy full-term controls were recruited between July 2001 and December 2003. This study population has been previously described (Thompson et al., 2008).

All infants were scanned at term equivalent age (TEA: 38–42 weeks' postmenstrual age) without sedation. Images were acquired with a 1.5 Tesla General Electric Signa magnetic resonance imaging (MRI) scanner (Milwaukee, WI). T2 dual echo

fast spin echo sequences were performed with interleaved acquisition (1.7–3.0 mm coronal slice thickness; in-plane resolution 0.35–0.43 mm²; repetition time 4,000 ms; echo time 60/160 ms; field of view 22 × 16 cm; matrix 256 × 192, interpolated 512 × 512). One hundred eighty four preterm and 32 full-term MRI scans (76% of those recruited) were able to be analyzed. The remaining scans were not performed within the TEA range (9%), or experienced movement or imaging artifacts (15%). Images were considered inappropriate for volumetric analysis if the brain tissue contrast was too poor for tissues to be classified by automated segmentation (Warfield et al., 2000). The perinatal and demographic characteristics of the cohort are described in Table 1. Preterm infant gestational age ranged from 22 to 32 weeks, and birth weight ranged from 414 to 1,395 g. There were no significant differences between the preterm and full-term infants for either the gestational age at the time of MRI ($P = 0.7$) or the male:female ratio ($P = 0.6$) (Table 1).

Volumetric MRI analyses were undertaken on Sun Microsystems workstations (Palo Alto, CA). The hippocampus was manually outlined as previously described (Thompson et al., 2008) by a single operator blinded to all perinatal data. The hippocampus was outlined on the coronal view of a combined raw T2-weighted and proton density weighted image volume with "3D slicer 2.5" software (<http://slicer.org/>). Combining these two images improved tissue contrast for optimized visualization of the hippocampal boundaries. Considering the neonatal brain is largely unmyelinated, T2 images display improved gray-white matter contrast over the T1 images routinely used

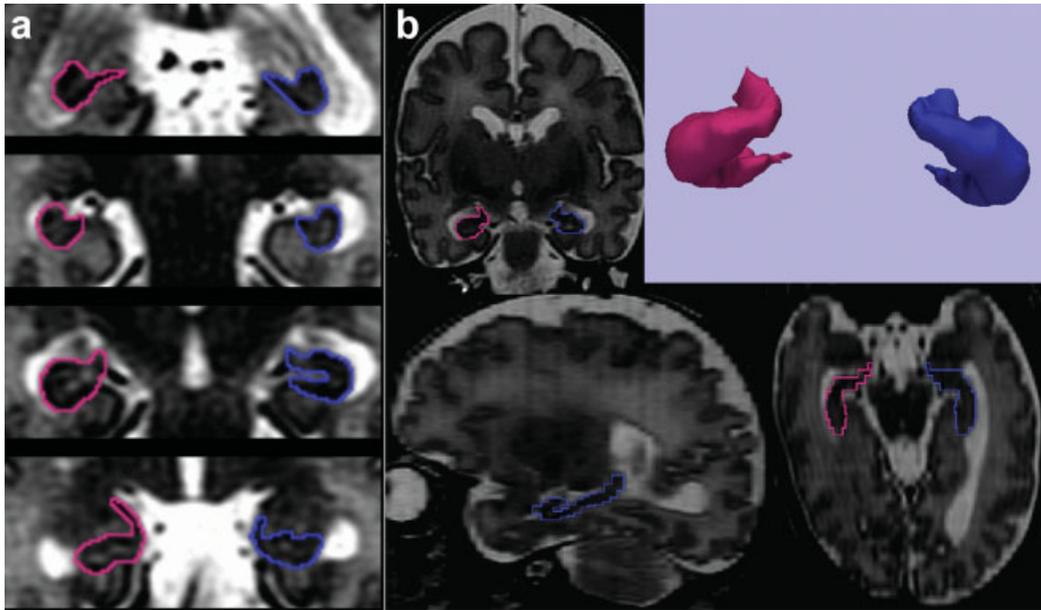


FIGURE 1. (a) Segmentation boundaries of four coronal sections through the hippocampal tail, body, and head. (b) The hippocampal segmentation boundaries shown in all three orthogonal

views: axial, sagittal, and coronal, as well as a three-dimensional representation of the left (blue) and right (pink) hippocampal volumes.

in children and adults (Bernasconi et al., 2003; Abernethy et al., 2004). Generally, anatomical boundaries followed the approach of Watson et al. (1992). First, the posterior boundary at the hippocampal tail was defined as the most anterior slice where the fornix was seen in its entirety. The inferior boundary of the hippocampal tail consisted of the white matter of the parahippocampal gyrus (excluded). The fimbria, subiculum, and alveus were included in the measurement. In-plane boundaries were traced sequentially on each slice. The uncus was included once it appeared fused to the hippocampal body. The anterior boundary at the head of the hippocampus was defined as the most anterior slice, where cerebrospinal fluid was still seen temporally to the hippocampus. The head of the hippocampus was distinguished from the overlying amygdala by following the path of the top of the temporal horn of the lateral ventricles, where a line of intermingling CSF and white matter was often visible. This resulted in a 3D hippocampal volume for both the right and left hippocampi (Fig. 1). The average (standard deviation) number of slices from which the full-term hippocampi were obtained was 10.4 (2.0) for a total hippocampal length (measured between the first and last slice) of 21.4 (3.0) mm. Intraclass correlation coefficients for intraobserver reliability were 0.97 for the right and 0.96 for the left hippocampi.

Each image was segmented twice, once in original orientation and again after being flipped in the left/right direction. This minimized possible hemispheric bias by the operator. Tracing mirrored and nonmirrored scans were alternated and always traced at least 1-day apart. There were no significant differences between the hippocampal volumes traced in the original space and those that had been flipped, for either the right

[Original: 1.14 (0.17) cm³; Flipped: 1.14 (0.17) cm³, $P = 0.8$], or the left hippocampi [Original: 1.11 (0.18) cm³; Flipped: 1.13 (0.18) cm³, $P = 0.2$]. These results suggest that there was no hemispheric bias in the operator. The two volumes (original and flipped) were averaged for each hemisphere.

Statistical analyses were performed using SPSS version 15.0. To assess hippocampal asymmetry, the left and right hippocampal volumes were compared by paired samples t -tests. The paired variables were the left and right hippocampal volume. The entire cohort was analyzed as well as preterm and full-term infants separately. Differences in asymmetry based on gender were examined by repeated measures analysis of variance (ANOVA), with hemisphere as the within-subjects variable, and gender as the between-subject factor. Differences in asymmetry based on group were also examined by repeated measures ANOVA, again with hemisphere as the within-subject variable, but group as the between-subject factor. Correction for total head size (intracranial volume) was performed as previously described (Thompson et al., 2008). Results did not differ, and therefore these analyses are not included. The same method was used to correct hippocampal volumes for the total brain tissue of each hemisphere, including cortical and deep nuclear gray matter, myelinated and unmyelinated white matter (excluding cerebrospinal fluid). The hemispheres were divided along the midsagittal plane after aligning the brain image along the anterior and posterior commissure line (Thompson et al., 2007). Correcting for each hemisphere ensured that hippocampal asymmetry was not simply a reflection of whole brain laterality differences.

Hippocampal asymmetry at term: Newborn infant's hippocampi were asymmetrical at term. The right (R) was 0.019 cm³

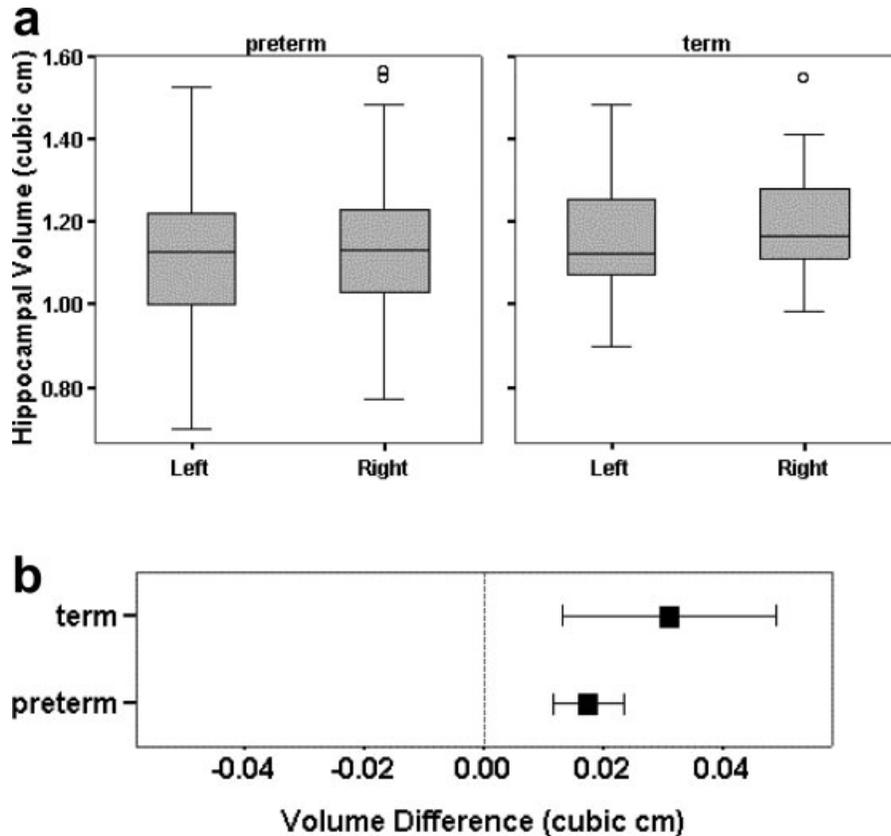


FIGURE 2. (a) Right and left hippocampal volumes for preterm and full-term infants. Box plots display the median, 25th and 75th centiles, range of the data and outliers. (b) Estimated differ-

ences in mean hippocampal volumes (corrected for asymmetry in total brain tissue) between right and left hemispheres (Right minus Left, 95% CI), for both preterm and full-term infants.

larger than the left (L) hemisphere [R 1.14 (0.156) cm³, L 1.12 (0.160) cm³; 95% Confidence Interval (CI) 0.014, 0.025; $P < 0.001$]. This was significant for both the full-term infants, with 0.031 cm³ larger right hippocampi [R 1.19 (0.121) cm³, L 1.16 (0.132) cm³; 95% CI 0.013, 0.049; $P = 0.001$], and the preterm infants with 0.017 cm³ larger right hippocampi [R 1.13 (0.160) cm³, L 1.12 (0.164) cm³; 95% CI 0.012, 0.023; $P < 0.001$] (Fig. 2a). Hippocampal asymmetry was significant only for the full-term infants after correcting for total brain tissue of the hemisphere. The difference between left and right hippocampi was no longer significant for preterm infants after correcting for total hemispheric asymmetry [All infants: R 1.17 (0.127), L 1.16 (0.128), $P = 0.2$; FT: R 1.19 (0.104), L 1.16 (0.112), $P = 0.01$; PT: R 1.16 (0.130), L 1.16 (0.131), $P = 0.9$].

Gender effect on hippocampal asymmetry: Gender did not substantially affect hippocampal asymmetry in neonates ($F_{1,214} = 0.32$, $P = 0.6$), either full-term ($F_{1,30} = 0.10$, $P = 0.8$) or preterm ($F_{1,182} = 0.77$, $P = 0.4$), even after correction for total hemispheric tissue (All infants: $P = 0.2$, FT: $P = 0.1$, PT: $P = 0.6$).

Effect of preterm birth on hippocampal asymmetry: Preterm infants tended to have reduced hippocampal asymmetry when

compared with full-term infants, although this did not reach statistical significance ($F_{1,214} = 2.7$, $P = 0.09$). However after correction for total brain tissue within the hemisphere, the difference in asymmetry between preterm and full-term infants was significant ($F_{1,214} = 7.4$, $P = 0.007$) (Fig. 2b).

Hippocampal asymmetry is present at term. Furthermore, at term males and females do not differ in their pattern of asymmetry. Preterm hippocampi tend to be less asymmetrical than full-term infants'.

The maximum growth rate of the hippocampus occurs between the first and second month after birth (Kretschmann et al., 1986; Utsunomiya et al., 1999), and continues up to 2 yr (Utsunomiya et al., 1999). Although the hippocampus is still at an early stage of development, this study confirmed that hippocampal asymmetry is present at birth. The right hippocampus was significantly larger than the left for both full-term and preterm infants. In contrast, during adolescence, left and right hippocampi do not appear to be different in either preterm or full-term subjects (Isaacs et al., 2000). The current study extends previous volumetric findings that have shown that the cortical and deep nuclear gray matter, as well as total brain tissue volume (excluding cerebrospinal fluid) demonstrate "rightward" asymmetry in neonates (Thompson et al., 2007).

When taking into account the asymmetry of the total brain, preterm right and left hippocampi were no longer different; suggesting that hippocampal asymmetry in the preterm infants is proportional to total brain asymmetry. In contrast, full-term infant hippocampi were more asymmetrical than the rest of the brain. This suggests that under normal circumstances, rightward hippocampal asymmetry is greater than total brain asymmetry. This disproportionate growth of the right hippocampus may prime the infant for greater visuospatial (right brain) as opposed to linguistic ability (left brain).

The underlying mechanisms for the right-larger-than-left asymmetry in the hippocampus are largely unknown. Originally it was thought that asymmetry was functionally based (Geschwind and Levitsky, 1968). However, the fact that asymmetry is present at birth may suggest otherwise. Twin studies suggest moderate heritability of hippocampal volumes in healthy subjects (Peper et al., 2007). However, hippocampal volume loss in psychiatric conditions appears to be influenced by environmental factors (van Erp et al., 2004; de Geus et al., 2007) such as pregnancy and birth complications (Stefanis et al., 1999) or stress (Sapolsky, 2000). We have previously shown that white matter injury, postnatal steroid exposure, and indomethacin treatment negatively influence hippocampal growth in preterm infants (Thompson et al., 2008). Environmental influences may affect the hippocampus asymmetrically (Stefanis et al., 1999; Vythilingam et al., 2002).

This study could not detect a gender difference in hippocampal asymmetry for either the full-term or preterm infants, contrary to the findings of Pfluger et al., who determined that male children had greater asymmetry (Pfluger et al., 1999). Giedd et al. suggested that sex-specific maturational changes in the hippocampus of healthy children were potentially due to hormonal responsivity (Giedd et al., 1996). Other studies have been unable to find a gender effect on hippocampal asymmetry (Jack et al., 1989; Szabo et al., 2001). Gender differences may become apparent later in development. Therefore, hormonal influences on hippocampal development are worthy of further investigation, particularly longitudinally through adolescence.

Raw hippocampal volumes showed a tendency to be more symmetrical in preterm infants compared to full-term infants, but this was not statistically significant. Similarly, a previous study examining adolescents born preterm did not find asymmetrical differences between preterm and full-term hippocampi (Isaacs et al., 2000). One interpretation of these results is that preterm hippocampal asymmetry develops similarly to that of the full-term infant, and is therefore “normal.” It should be noted, however, that our relatively small sample of full-term infants may have contributed to this nonsignificant finding in both the current study and our previous study (Thompson et al., 2008). Furthermore, correction for total brain volume within each hemisphere revealed that preterm hippocampal asymmetry was significantly smaller than for full-terms. Therefore, an alternative interpretation is that preterm hippocampal asymmetry is not developing normally. Overall, these results suggest that hippocampal asymmetry normally develops in utero, but in preterm infants born at least 10 weeks early, this

disproportionate growth of the right hippocampus may not proceed normally.

The hippocampi were manually segmented based on solid neuroanatomical landmarks, ensuring a representative and reproducible measurement. The same landmarks were used in each hemisphere, and hippocampal segmentation was performed in both original and flipped orientation. This should have precluded hemispheric bias of the segmentation method or operator. Hippocampal volumetry is subject to artifacts arising from MRI acquisition and postprocessing. Nonetheless, the high intraobserver reliability estimates (>0.95) indicate that acquisition and processing were adequate to obtain reliable hippocampal volume measurements. The in-plane resolution was high for these scans. However, 46% of infant images (86 preterm and 13 full-term) were acquired with large slice thicknesses (3.0 mm) relative to their hippocampal size. This may generate partial volume error, particularly at the borders of the hippocampal tail and head. Cook et al. suggested that slices of 3 mm or thinner allow accuracy within 5% for adult hippocampal volumes (Cook et al., 1992). Presumably, this level of accuracy would require thinner slices for smaller neonatal hippocampi. We recognize that it would have been desirable to obtain more slices of reduced thickness. However, this would require an increased imaging time, which was impractical for infants of this age.

This study is the first to demonstrate that healthy newborn infants have “rightward” hippocampal asymmetry. This normal pattern of asymmetry is similar for both male and female full-term infants. There is evidence to suggest that preterm infant hippocampal asymmetry is altered. The implications of these findings in regards to future neurological health of these infants require further investigation. Consequently, neurodevelopmental follow-up of this cohort is planned.

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