Hippocampal shape variations in very preterm infants

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Introduction: The hippocampus is important for learning and memory, which are two cognitive functions often reportedly altered by prematurity[1]. The hippocampus undergoes its most rapid growth and development in the perinatal months, and there is recent evidence to suggest that hippocampal inversion may not be complete until up to 25 weeks' of gestation[2]. Thus, the hippocampus is particularly vulnerable during the preterm period, making infants born very preterm (VPT) at <30 weeks' gestational age, or <1250g at birth especially susceptible to hippocampal alterations. Previous research has shown that VPT infants with an abnormal neurological course have reduced hippocampal volumes[3]. Hippocampal shape changes related to prematurity, however, have not been investigated. Studies based on a range of other neurological diseases have shown that altered hippocampal shape may have developmental origins and functional consequences.

Aims: The aims of this study were to determine: 1) shape changes to the hippocampus in very VPT compared to full-term (FT) neonates, 2) the effect of various perinatal factors on hippocampal shape within VPT infants, and 3) whether particular morphological characteristics of the hippocampus are associated with delayed working memory function in VPT infants.

Methods: MRI was performed for 184 VPT infants and 32 FT neonates on a 1.5 T General Electric scanner at term equivalent (38 - 42 weeks) without sedation. T2 and proton density (PD) weighted dual echo fast recovery fast spin echo sequences with interleaved acquisition (1.7 mm coronal; TR 4000 ms; TE 60 / 160 ms; flip angle 90°; FOV 180 × 135 mm^2; matrix 256 × 224). T2 and PD image volumes were combined by image addition to enhance contrast to noise ratio, and hippocampi were manually delineated on the resulting images. The spherical harmonics-point distribution model (SPHARM-PDM) shape analysis pipeline was applied to the binary hippocampal masks, to obtain a measure of global and local changes. Semi-automatic preprocessing was performed in order to enforce spherical topology on the segmentation masks. The SPHARM-PDM tools were then applied to generate smoothed PDM shape representations of the segmentation boundaries that were subsequently registered to enforce correspondence. Massively univariate statistical testing was then carried out on the corresponding boundary points across all subjects. Permutation testing was used to correct for multiple comparisons, thus controlling the family-wise error rate. Shape comparisons were made for the VPT vs FT group. Hippocampal volume was included in the analysis as a scaling factor, to correct for the effect of size differences. Perinatal data were collected by chart review, and hippocampal shape comparisons were made for male vs female, gestational age ≤ 26 weeks vs > 26 weeks, oxygen required at 36 weeks gestational age (bronchopulmonary dysplasia) vs not required, postnatal glucocorticoid exposure vs no exposure, moderate / severe white matter injury vs no or mild injury, intraventricular haemorrhage vs no haemorrhage. Several neurobehavioural assessments were carried out at 5 years corrected age to test approaches to learning, and in particular working memory skills. Delayed functioning (standard score < 85) vs normal functioning was compared for hippocampal shape changes on the digit recall, backward digit recall, and non-word recall assessments.

Results: Significant hippocampal shape differences were evident between VPT and FT neonates, in a variety of regions within the hippocampal head, body and tail of both the left and right hippocampus (Fig. 1). Within the VPT infants, bronchopulmonary dysplasia was associated with shape change in several focal regions of the posterior body and tail of both hippocampi (Fig. 2a). There was a region of shape difference within the head (right and left) and tail (left) associated with white matter injury (Fig. 2b), a region of difference within the body of the left hippocampus associated with gestational age (Fig. 2c), and a very small, but significant shape change in the body of the right hippocampus of VPT infants exposed to postnatal glucocorticoids (Fig. 2d). There was no significant hippocampal shape change associated with gender or intraventricular haemorrhage. Neither were there any significant hippocampal shape changes in VPT infants with working memory delay when compared with those who had normal memory functioning.

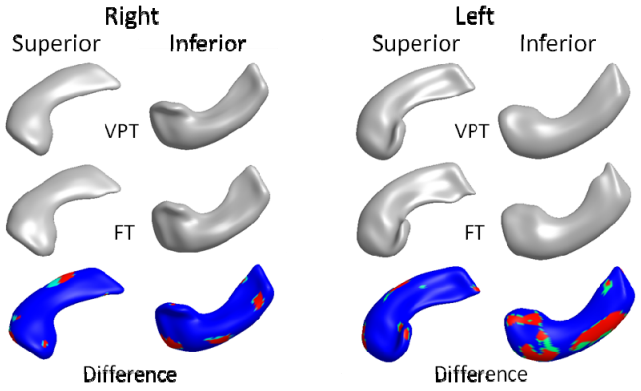

Figure 1. *Shape representation of the VPT group, FT group, and statistical map of shape difference. Right and left hippocampi, superior and inferior views are displayed. Red = significant clusters of shape change.*

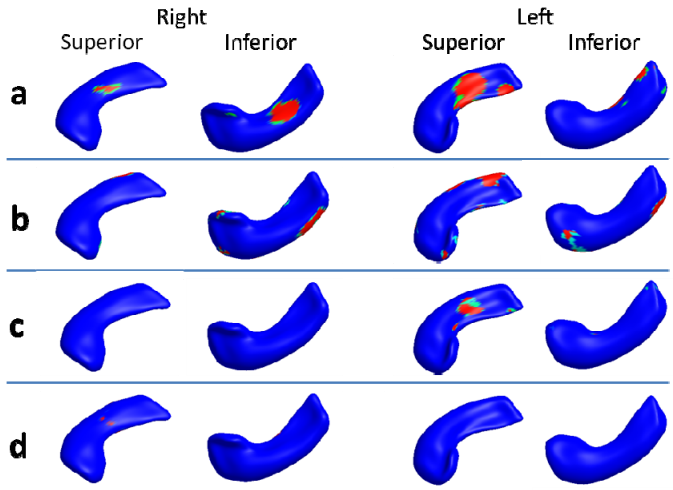

Figure 2. *Statistical maps of shape differences between VPT infants with or without (a) bronchopulmonary dysplasia, (b) moderate to severe white matter injury, (c) gestational age ≤ 26wks , or (d) postnatal glucocorticoid exposure.*

Conclusions: Hippocampal shape is altered in VPT neonates, in a range of diffuse regions throughout both the right and left hippocampi. This suggests that there may not be specific regional vulnerabilities in hippocampal structure as a result of prematurity. On the other hand, certain perinatal exposures may have specific morphological effects on the hippocampus, particularly bronchopulmonary dysplasia and white matter injury. There did not appear to be characteristic shape differences between those VPT children with delayed working memory compared to those with intact working memory. This study provides further insight into the nature of hippocampal abnormalities associated with prematurity.

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[1] Bohbot VD et. al. *Ann NY Acad Sci.* 2000;911:355-368 [2] Bajic D et. al. *Neuroradiology*. 2010;52:489-494 [3] Thompson DK et. al. *Ann Neurol*. 2008;63 :642-651