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Brainstem shape is affected by clinical course in the neonatal intensive care unit

Marcus Lo[a,*], Leire Zubiaurre-Elorza[a,b], Conor Wild[a], Annika C. Linke[a], David S.C. Lee[c], Victor K. Han[c], Rhodri Cusack[a,c]

[a] Brain and Mind Institute, Western University, London, Canada
[b] Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain
[c] Children's Health Research Institute, London, Canada

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ABSTRACT

The brainstem, critical for motor function, autonomic regulation, and many neurocognitive functions, undergoes rapid development from the third trimester. Accordingly, we hypothesized it would be vulnerable to insult during this period, and that a difficult clinical course in the neonatal intensive care unit (NICU) would affect development, and be reflected through atypical shape. Our study population consisted of 66 neonates – all inpatients from the NICU at Victoria Hospital, London Health Sciences Centre, ON, Canada, of which 45 entered the final analysis. The cohort varied in gestational age (GA) and ranged from neurologically healthy to severely brain-injured. Structural MRI was used to quantify brainstem shape at term-equivalent age. From these images, brainstems were semi-automatically segmented and co-registered across subjects. The anterior-posterior dimensions on a sagittal maximum intensity projection were used as the basis for shape comparison. Factor analysis was used to summarize variation in shape and in clinical course to determine three shape factors and three clinical factors, and their relationship assessed using correlation. A factor driven by low GA and associated complications correlated with alterations in the posterior medulla, while a factor driven by complications independent of GA correlated with alterations in the midbrain. Additionally, single clinical measures most representative of their respective clinical factor (days in NICU; days on ventilation) predicted the changes. Thus, different clinical courses in the NICU may have different effects on the shape of the brainstem, and may mediate some of the distinct neurodevelopmental profiles observed in premature and brain-injured neonates.

1. Introduction

The brainstem plays a pivotal role in brain function and is critical for survival, regulating processes including rhythmic breathing, blood pressure, and sleep cycles (Cohen 1979; Guertzenstein and Silver 1974; Hobson et al. 1975). Stimulation to the brainstem has also been shown to elicit complex goal-oriented behavior, and has been further implicated in controlling locomotion associated with behavioral responses to rewarding or aversive stimuli (Berntson and Micco 1976; Drew et al. 2004). It also serves as an important relay station for cortical signals, and is innervated by the auditory, visual, and motor networks. Improper regulation or interruption of any of these functions can result in severe consequences.

Indeed, adverse neurodevelopmental outcomes are an established risk of perinatal insult (Jiang et al. 2009; Nosarti et al. 2014, 2008; Payne et al. 2013; Vohr et al., 2000; White et al. 2014). In response, there is strong interest in understanding the consequences that arise from premature birth and perinatal brain injury. Better measurement of the anatomical alterations that result from these insults might provide improved diagnostic markers, and elucidate the mechanisms through which brain function is affected – guiding intervention and reducing future cognitive and behavioral impairments.

During gestation, the third trimester is particularly important for brainstem development, and it undergoes rapid developmental changes during this period (Darnall et al. 2006; Geva and Feldman 2008; Hüppi et al. 1998). As such, the brainstem may be particularly vulnerable to insult at this time.

Past studies concerning the negative effects of prematurity and brain injury on brainstem structure have primarily discussed structural alterations in terms of visible size differences and volumetric alterations (Barkovich and Sargent 1995; Messerschmidt et al. 2008; Mewes et al., 2006; Padilla et al. 2015). Shape changes resulting from these insults

Abbreviations: FA, Flip angle; GA, Gestational age; NICU, Neonatal intensive care unit

* Corresponding author at: Brain and Mind Institute, Western University, London, ON N6A 5B7, Canada.
E-mail address: mlo53@uwo.ca (M. Lo).

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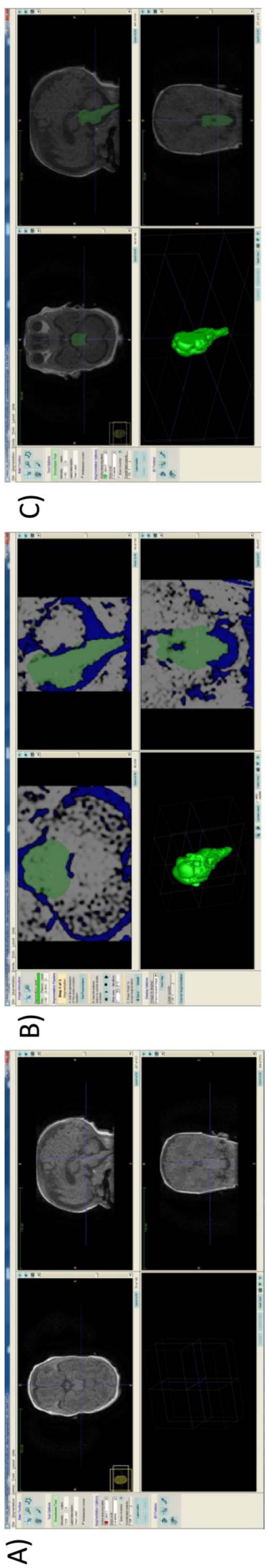

Fig. 1. (A) Original unprocessed T1-weighted MRI. (B) Output after pre-segmentation phase and active contour phase. Foreground regions (regions of interest) are white. Background regions are blue. The green regions depict the result of automatic seed expansion within the regions of interest. The unedited 3D output can be seen bottom-left. (C) Final manually-edited output of brainstem segmentation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

have not been well documented, and remain poorly understood. Recently, there has been one study investigating changes in brainstem shape resulting from prematurity in a cohort of 8 year-old children born preterm (Garg et al. 2016). Another study has also anecdotally noted a pattern of reduced anterior-posterior dimensions on sagittal projections of the brainstem in 2 month–2 year old children born preterm (Messerschmidt et al. 2005). To our knowledge, however, there are no studies directly measuring the effect of prematurity and perinatal brain injury on brainstem shape in neonates, and this was the goal of the present study.

In this report, structural MRI was used to measure the anatomy of the brainstem in infants from the neonatal intensive care unit (NICU). Past studies have shown abnormalities in brainstem function in neonates under intensive care (Jiang et al. 2012, 2013). We hypothesized a link between intensive care and brainstem structure as well, and that certain aspects of the clinical course would affect the shape of the brainstem in structures quantifiable on sagittal projections – namely the medulla, the midbrain, and the pons.

2. Methods

2.1. Cohort

Sixty-six inpatients were recruited from the NICU at Victoria Hospital, London, ON, Canada. The subjects spanned from 24 to 41 weeks gestational age (GA), and ranged from neurologically healthy to severely brain-injured. Parents were invited to participate in this research study if their infant met the following inclusion criteria: requirement for a clinical MRI, as determined by the neonatology and neurology team at Victoria Hospital, London, Canada, and fulfillment of the criteria to be enrolled in the Canadian Neonatal Follow-Up Network: being born < 29 weeks GA, or being at elevated risk of neurodevelopmental complications (e.g. secondary to asphyxia during birth). Infants with ferromagnetic implants of any sort were excluded. The infant's caregiver signed informed consent. Ethical approval was obtained from the Health Sciences Research Ethics Board of Western University.

2.2. Magnetic resonance imaging

All subjects underwent a T1-weighted MRI scan (GE MR 450W, 1.5T scanner, 3D SPGR sequence TE = 4.2 ms, TR = 8.4–11.5 ms, FA = 12/25°, matrix size 512 × 512, 99–268 slices, voxel size typically 0.39 × 0.39 × 0.5 mm) during unsedated natural sleep at term-equivalent age at Victoria Hospital. Infants were wrapped in a MedVac vacuum blanket to minimize motion, and wore infant ear protection (MiniMuffs, Natus, 7 dB attenuation) and ear defenders (29 dB attenuation, http://www.scansound.com/index.php/mri-noise-reduction-headphone.html). During scanning sessions, infants were monitored by an attending NICU nurse using pulse-oxymetry, electrocardiogram, and a noise-cancelling microphone (FOMRI–III, Optoacoustics) attached to the head coil.

Of the $N = 66$ MRI scans obtained, 9 were corrupted due to participant motion and 2 failed automatic inter-subject brainstem registration (described later). This left 55 usable brainstem images. Of these, however, full clinical data (details in Supplementary Table) was available for $N = 45$. This is the final sample used in the analyses.

2.3. Semi-automatic segmentation

T1-weighted structural MRI images were semi-automatically segmented to isolate the brainstem. ITK-SNAP (http://www.itksnap.org/) is a software tool used to render medical images in 3D. It is a reliable and efficient alternative to the traditional method of manual tracing on slices, which is prone to error and user bias (Yushkevich et al. 2006).

ITK-SNAP v.2.4.0 was used to perform the segmentations in the