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Detailed semiautomated MRI based morphometry of the neonatal brain: Preliminary results

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In the neonate, regional growth trajectories provide information about the coordinated development of cerebral substructures and help identify regional vulnerability by identifying times of faster growth. Segmentation of magnetic resonance images (MRI) has provided detailed information for the myelinated brain but few reports of regional neonatal brain growth exist. We report the method and preliminary results of detailed semiautomated segmentation of 12 normative neonatal brains (gestational age 31.1–42.6 weeks at time of MRI) using volumetric T1-weighted images. Accuracy was confirmed by expert review of every segmented image. In 5 brains, repeat segmentation resulted in intraclass correlation coefficients >0.9 (except for the right amygdala) and an average percent voxel overlap of 90.0%. Artifacts or image quality limited the number of regions segmented in 9/12 data sets and 1/12 was excluded from volumetric analysis due to ventriculomegaly. Brains were segmented into cerebral exterior (N = 8), cerebral lobes (N = 5), lateral ventricles (N = 8), cerebral cortex (N = 6), white matter (N = 6), corpus callosum (N = 7), deep central gray (N = 8), hippocampi (N = 8), amygdalae (N = 8), cerebellar hemispheres (N = 8), vermis (N = 8), midbrain (N = 8), pons (N = 8) and medulla (N = 8). Linear growth (P < 0.05) was identified in all regions except the cerebral white matter, medulla and ventricles. Striking differences in regional growth rates were noted. These preliminary results are consistent with the heterochronous nature of cerebral development and provide initial estimates of regional brain growth and therefore regional vulnerability in the perinatal time period.

Keywords: Morphometry; Brain; Development; Neonate; MRI; Gompertz

Introduction

The size and form of the human brain are the result of a complex series of overlapping histogenetic processes influenced by genes, environmental exposures and epigenetic rules (heritable modifications of DNA bases that can lead to rapidly reversible changes in gene expression). Although cerebral development begins in the early embryonic period and continues through the second decade of postnatal life (Sidman and Rakic, 1982), it is during the period of rapid growth that the brain is most vulnerable to errors arising from genetic defects, environmental exposures and abnormal gene expression. This vulnerable period of rapid growth occurs between the third trimester of pregnancy and the early postnatal months. During this phase, the brain weight increases by 6% of adult weight/month, and there are associated radical changes in shape and surface features (Caviness et al., 1996a,b,c). The rate of growth decelerates by a factor of 2 by 10 months and by a factor of 4 by 18 months. The asymptote of brain growth, approximately 80%, is reached by the third year of life, with the brain increasing only some 8–10% in volume beyond the 9th year of life (Caviness et al., 1996a,b,c). During the phase of rapid growth, there is also rapid development of axono-dendritic connections and myelination followed by neuronal specification which results in programmed cell death and pruning of axonal and dendritic arbors (Bourgeois and Rakic, 1993; LaMantia and Rakic, 1990, 1994). Therefore, not only is the brain most vulnerable from the third trimester to the early postnatal months, but also insults occurring during this time period have profound effects on the orchestration of neuronal connectivity and the integration of neural activity.

It has been estimated that any process impairing brain growth such that the head circumference is not normal by 8 months will result in life long disabilities in the cognitive if not other domains of cerebral function (Hack and Breslau, 1986; Hack et al., 1989, 1991). Recent MRI studies in patients with ADHD have detected abnormal caudate volumes prior to adolescence and focal changes in white

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matter and gray matter volumes (Castellanos et al., 2002; Filipek et al., 1997; Spencer et al., 2002; Wilens et al., 2002), suggesting that regional volumetric differences on MRI are associated with variations in cerebral function. There is also evidence based on MRI morphometry that volumetric changes precede clinical expression in certain grave neuropsychiatric disorders. In particular, volumetric changes in schizophrenia appear to have predictive power for eventual clinical expression among first degree family members of probands (Pantelis et al., 2003). Therefore, it follows that the pace of regional brain growth as measured with MRI may be a sensitive indicator of the biological state of the brain and may provide predictions of those neonates and young children at risk for abnormal cerebral function. Volumetric measures based upon MRI in the first weeks and months of life may thus be a more sensitive index of future neurological outcome than formal behavioral testing and neurological examination as these latter indices are notoriously insensitive as predictors of neurological outcome.

Almost all automated and semiautomated MRI segmentation techniques for cerebral morphometry have been developed for volumetric T1 studies of the fully myelinated mature brain (Filipek et al., 1994; Fischl et al., 2002; Gogtay et al., 2004; Sowell et al., 2004). The most comprehensive and systematic but labor intensive approach is the detailed computer-assisted semiautomated technique developed by the Center for Morphometric Analysis (Caviness et al., 1989; Filipek et al., 1989, 1991, 1992, 1994; Kennedy, 1986; Kennedy et al., 1989; Kennedy and Nelson, 1987). In this technique, segmentation is partially automated on a slice by slice basis with the investigator interacting with the segmentation process and guiding the segmentation with judgments that are knowledge based. This technique assesses reliability in the sense of percent voxel concordance among operators knowledgeable with regard to anatomy. This detailed semiautomated approach is highly accurate because an experienced reader guides and confirms accurate segmentation on a slice by slice basis but is very costly in terms of time required of experienced analysts. As a result, this computer-assisted detailed semiautomated technique does not allow the rapid and less expensive evaluation of large numbers of MRI studies that automated and semiautomated techniques allow. Instead, this approach allows the most accurate evaluation of a small number of MR studies and the creation of a set of "gold standards" which can be used to develop and validate more rapid and practical semiautomated and automated techniques.

Analysis techniques developed for the mature brain are not directly transferable to the incompletely myelinated brain. This is particularly true for the newborn brain where the gray–white matter contrast is inverted with white matter lower in T1 signal than cortex. In addition, the regional variation in myelin maturation results in much more regional variation in both gray and white matter T1 signals compared to adults. Further difficulty is added by the smaller head sizes, lack of myelin, and need for shorter scan times to avoid motion which result in T1 images with lower signal to noise ratios. Where semiautomated techniques for the immature brain have been described, these have provided useful approximates of the volumes of major brain regions (Huppi et al., 1998; Peterson et al., 2003) and have been useful in searching for differences between two groups of patients (Huppi et al., 1998; Inder et al., 1999; Murphy et al., 2001). However, these methods do not include slice by slice validation by an experienced reviewer and therefore although reproducible may not be accurate in their volume estimates of specific brain structures, in particularly those that are relatively small.

The purpose of this study was to develop a knowledge based, reliable segmentation process for newborn brains based on the methods previously developed for adult brains at the Center for Morphometric Analysis, of the Massachusetts General Hospital. This paper will describe our new in vivo MR-based technique for segmentation of the minimally myelinated neonatal brain and the results obtained from segmenting normative neonatal brains at various gestational ages.

Materials and methods

Subjects

A total of 12 neonates, 6 female and 6 male, with gestational ages at birth ranging from 31.1 to 42.6 weeks, imaged between 1 and 39 days of life were included in this study. All were imaged for clinical indications, and the study was approved by our institutional review board. Clinical indications typically included evaluation of suspected seizures, perinatal depression, suspected hemorrhage, or questionable ultrasound findings. On expert review by a pediatric neuroradiologist (PEG), the MR images showed no structural abnormalities apart from one case with mildly enlarged ventricles. This case was included in the reliability measures for the segmentation procedure but was excluded from the normative data analysis. None of the studies had diffusion-weighted imaging (DWI) abnormalities, apart from a small thalamic stroke in two patients, none had MR spectroscopy abnormalities and none had hemorrhage. Only one patient required mechanical ventilation for respiratory distress for more than 24 h. None met the clinical criteria for hypoxic–ischemic encephalopathy, and none were septic or had persistent hypoglycemia. There was no imaging or clinical evidence of congenital malformations or metabolic disorders. None had abnormal neurological exams. Three of four neonates with confirmed seizures had normal EEGs and normal neurological exams at follow-up evaluation. The remaining case had an improving EEG with the expectation that seizure medications would be terminated by 18 months of age. Three with suspected neonatal seizures had no further events suggestive of seizures.

MR image acquisition

An axial 3D SPGR (volumetric spoiled gradient echo) sequence was performed as part of the clinical protocol on a 1.5-T MR System (General Electric, Milwaukee). This is a T1-weighted image with imaging parameters as follows: TR/TE = 30/8, flip angle = 25 to 30, matrix = 256 × 192, bandwidth 10.42, slice thickness = 1.2 to 1.4 mm, FOV = 220 × 165 mm or 200 × 150 mm, NEX = 1. Therefore, spatial resolution was between 0.8 and 0.9 mm × 0.8 to 0.9 mm × 1.2 mm. For five neonates, imaging was performed with a Pediatric Head Coil (Scan Med) but when possible (N = 7) imaging was performed with a Neonatal Head Coil (Advanced Imaging Research) due to the marked improvement in SNR with the smaller neonate-specific head coil. Both coils are receive only coils and therefore do not result in different image distortions.

Positional normalization

To reduce variability due to differences in head position, all brains are repositioned in three dimensions using a reference plane that bisects the decussations of the anterior commissure (AC) and posterior