Available online at www.sciencedirect.com
SCIENCE DIRECT®
Psychiatry Research: Neuroimaging 132 (2004) 81–85
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Brief report

3 Tesla magnetic resonance imaging of the brain in newborns

John H. Gilmore[a,b,*], Guihua Zhai[c], Kathy Wilber[c], J. Keith Smith[c], Weili Lin[c], Guido Gerig[a,b,d]

[a]UNC Schizophrenia Research Center, University of North Carolina, Chapel Hill, NC 27599-7160, USA
[b]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7160, USA
[c]Department of Radiology, University of North Carolina, Chapel Hill, NC 27599-7160, USA
[d]Department of Computer Science, University of North Carolina, Chapel Hill, NC 27599-7160, USA

Received 28 March 2003; received in revised form 27 February 2004; accepted 23 April 2004

Abstract

While it has been hypothesized that brain development is abnormal in schizophrenia and other neurodevelopmental disorders, there have been few attempts to study very early brain development in children. Twenty unsedated healthy newborns underwent 3 Tesla magnetic resonance imaging (MRI), including diffusion tensor imaging (DTI). The left ventricle was significantly larger than the right; females had significantly larger ventricles than males. Fractional anisotropy (FA) increased significantly with gestational age in the genu and splenium of the corpus callosum. It is feasible to study brain development in unsedated newborns using 3 T MRI.

Keywords: Lateral ventricles; Asymmetry; Diffusion tensor imaging; Neurodevelopmental disorders; Schizophrenia; Neonates

1. Introduction

The neurodevelopmental hypothesis of schizophrenia suggests that the abnormal brain structure observed in people with schizophrenia arises during fetal or neonatal brain development. However, there is little direct evidence to support this idea. We have previously hypothesized that structural brain abnormalities associated with schizophrenia and other neurodevelopmental disorders, including lateral ventricle enlargement, can be detected very early with ultrasound (Gilmore et al., 1998, 2001b) and have shown that 3D ultrasound provides comparable measures of lateral ventricle volume to those obtained with magnetic resonance imaging (MRI) in infants (Gilmore et al., 2001a). Compared with MRI, ultrasound provides limited information about the developing brain. Therefore, it is critically important to develop MRI methods to study neonatal brain structure and development in normal children and in

* Corresponding author. Department of Psychiatry, CB# 7160, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7160, USA. Tel.: +1 919 966 6971; fax: +1 919 966 9604.
E-mail address: jgilmore@med.unc.edu (J.H. Gilmore).

0925-4927/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2004.04.004

children at high risk for schizophrenia and other neurodevelopmental disorders. The relatively long scan times of conventional 1.5 Tesla (T) scanners combined with the need to image neonates unsedated for research purposes makes this a difficult task. Most MR studies of the neonatal brain have utilized scans performed for clinical reasons. There have been only a few prior quantitative MRI and diffusion tensor imaging studies of unsedated newborns (Hüppi et al., 1998a; Hüppi et al., 1998b; Neil et al., 1998; Peterson et al., 2003).

3 T scanners offer the advantage of allowing several scan sequences in the short time period required when scanning unsedated newborns for research purposes. This study was conducted to determine the feasibility of using 3 T MRI to study brain structure and white matter development in unsedated healthy newborns. Group comparisons of diffusion tensor imaging (DTI) data between neonates in this study and adults are presented in Zhai et al. (2003).

2. Methods and materials

This study was approved by the Institutional Review Board of the University of North Carolina School of Medicine. Twenty healthy neonates were recruited from the newborn nursery at UNC Hospitals (10 males and 10 females; 13 Caucasian, 4 African-American, 3 Hispanic; birth weight: 3430.05±361.06 g [mean±S.D.]). No sedation was used. Neonates were fed before scanning, were swaddled, were fitted with ear protection and had their heads secured in a vacuum-fixation device. A physician or nurse was present during each scan; a pulse oximeter was used to monitor heart rate and oxygen saturation. Most neonates slept during the scan. The small bore size of the head-only scanner allowed a parent to sit close to the child during the scan.

Images were acquired on a Siemens head-only 3 T scanner (Allegra, Siemens Medical System, Erlangen, Germany). Three imaging sequences were used: a magnetization prepared rapid gradient echo (MP-RAGE) T1-weighted, a turbo spin echo (TSE), dual-echo (proton density and T2 weighted), and a single shot echo planar (EPI) diffusion tensor (DTI) sequence. Total scan time was approximately 15 min. The imaging parameters for the MP-RAGE sequence were: repeat time (TR)/echo time (TE)/inversion time (TI)/slice thickness (TH)=11.1 ms/4.3 ms/400 ms/1 mm, inplane resolution=1.27×0.90 mm^2. A total of 128 sagittal images were acquired to cover the entire brain. The imaging parameters for the TSE sequence were: TR/TE/TH=7 s/15 and 90 ms/3 mm, in-plane resolution 1×1 mm^2, 28 slices. The imaging parameters for the DTI sequence were: TR/TE/TH=4219 ms/92.2 ms/5 mm, in-plane resolution=1.72×1.72 mm, 12 averages, and 20 slices. Seven images were acquired for each slice, one without diffusion gradient (b=0) while the remaining six with b=1000 s/mm^2 and diffusion gradients along $\{1/\sqrt{2},0,1/\sqrt{2}\}$,$\{-1/\sqrt{2},0,1/\sqrt{2}\}$, $\{0,1/\sqrt{2},1/\sqrt{2}\}$, $\{0,1/\sqrt{2},-1/\sqrt{2}\}$, $\{1/\sqrt{2},1/\sqrt{2},0\}$, $\{-1/\sqrt{2},1/\sqrt{2},0\}$, separately.

The Siemens head-only 3 T scanner is FDA approved for use in all age groups. Specific absorption rates are kept within safe levels for body weight by both hardware and software features of the scanner. We confirmed that the scan sequences did not cause significant temperature increases with a cylindrical gel phantom made with ~80% of water content, similar to that of the neonatal brain. The diameter and the length of the phantom were 10.5 and 16 cm, respectively, and three copper thermocouple probes were placed on the surface, the center and the bottom of the phantom. The long axis of the phantom was aligned along the direction of the magnetic field. The mean (±S.D.) temperature increase at the probes was 0.19±0.20 °C, with a range of 0.0 to 0.5 °C. Actual in vivo temperature increases are likely less than this due to biological heat removal capabilities (Kangarlu et al., 2003). Specific absorption rates (SAR) for the T1, T2/PD, and DTI sequences were 0.2, 2.6, and 2.7 W/kg, respectively, well within FDA criteria for nonsignificant risk (US FDA, 2003).

Intracranial volume (ICV) and the left and right lateral ventricle volume were segmented using an automated level set evolution method SNAP (Ho et al., 2002) applied to the T2 image and T1 images, respectively. Intra-rater reliability for lateral ventricle volumes were good, with intraclass correlation coefficients of 0.99 for both the left and right ventricles. The SNAP tool is freely offered at http://www.cs.unc.edu/~gerig/.

For DTI, trace images were created by averaging all six diffusion-weighted images, and subsequently apparent diffusion coefficient (ADC) and fractional diffusion anisotropy (FA) were determined (Zhai et al., 2003). Eight regions of interest (ROIs) were placed in white matter on a single transverse section through the level of the basal ganglia, including the anterior and posterior limbs of the internal capsule (IC), left and right occipital and frontal WM adjacent to the cortical gray matter (averaged to give single IC, frontal and occipital WM values) and the genu and splenium of the corpus callosum (Zhai et al., 2003). These white matter structures were chosen because they exhibited visible anisotropy and were easily identified on diffusion-tensor images.

Volumes of the lateral ventricles were compared with *t*-tests; Pearson correlations were performed for DTI parameters and gestational age. Significance was set at $P<0.05$ using a two-tailed test for all analyses.

3. Results

We were able to obtain quality images without significant motion in 13 of the 20 neonates (6 M, 7 F; age at MR 17±8 days). Overall, images could be obtained if the infant slept through the scan; most of the scan failures were due to an inability to get the infant to sleep before scanning. Representative T1, T2, and proton density weighted images are shown in Fig. 1. Note the relatively low intensity of white matter compared with gray matter in the T1 image, which is opposite to that seen in adults. White matter in the neonate is heterogeneous as well, with hyperintensity of central myelinated white matter. The T2 weighted image shows hypointensity of central myelinated white matter, hyperintensity of cerebrospinal fluid, and excellent contrast between white matter and cortical and subcortical gray matter.

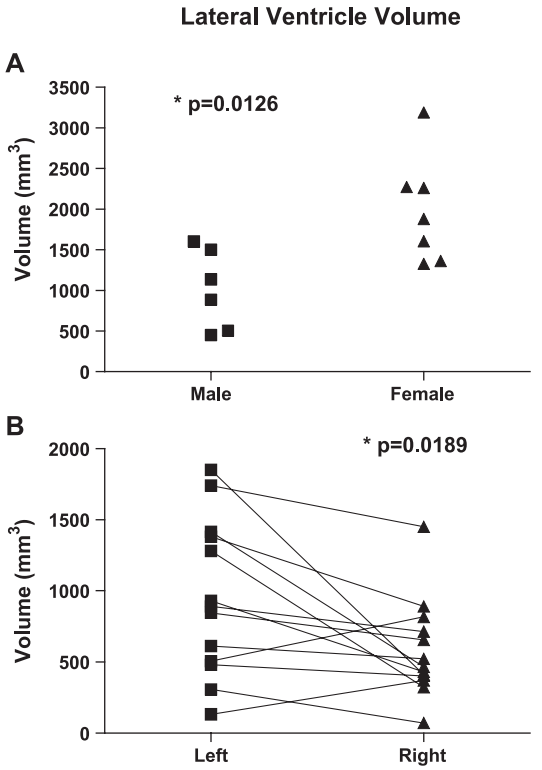

Fig. 2. Gender differences (A) and left–right asymmetry (B) in neonatal lateral ventricle volume. Female newborns have larger lateral ventricles than males ($P=0.0126$). The left ventricle was significantly larger than the right ($P=0.0189$, paired *t*-test).

There was asymmetry of the lateral ventricles with the left having a larger volume than the right ($P=0.0173$, paired *t*-test; Fig. 2). Female neonates

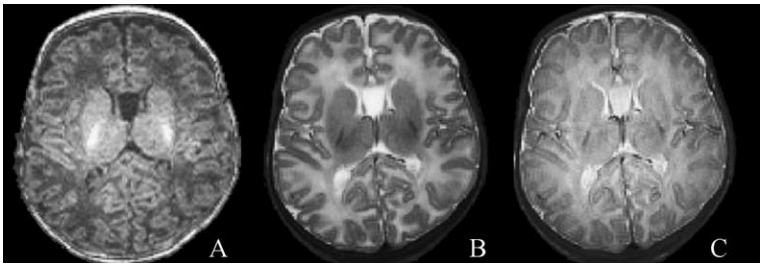

Fig. 1. T1-weighted (A), T2-weighted (B), and proton density weighted (C) axial images of a neonate. Note the reversed intensity of white and gray matter in the T1-weighted image (A); white matter in the neonate is heterogeneous as well, with hyperintensity of central myelinated white matter. The T2 weighted image (B) shows hypointensity of central myelinated white matter, hyperintensity of cerebrospinal fluid, and excellent contrast between white matter and cortical and subcortical gray matter. Also note large cavum septum pellucidum in this child.

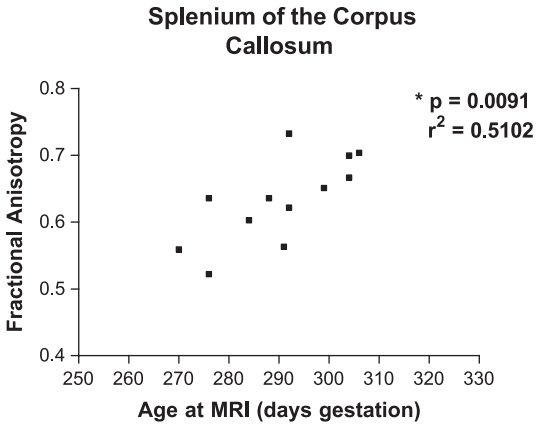

Fig. 3. There was a significant correlation between gestational age at MRI and FA in the splenium of the corpus callosum (r^2=0.5102; p=0.0091). There was a similar significant correlation in the genu (r^2=0.3639; p=0.0291; data not shown).

had larger lateral ventricle volumes than males (P=0.0126; Fig. 2). There were no significant gender differences in gestational age at birth (males 279±9 vs. females 271±11 days), birth weight (mean±S.D.; males 3396.2±551.6 vs. females 3546.1±203.3 g), age at MRI (males 19±10 vs. females 16±6 days), or ICV (males 484.8±37.8 vs. 470.76±58.8 ml).

There was a significant correlation between gestational age at MRI and FA in the genu (r^2=0.3639; P=0.0291; data not shown) and the splenium of the corpus callosum (r^2=0.5102; P=0.0091, Fig. 3). There was no significant correlation for FA or ADC and gestational age at MRI in any other ROI.

4. Discussion

This study indicates that 3 T MRI can be used to evaluate brain structure and white matter development in unsedated newborns. Compared with 1.5 T, the improved signal-to-noise ratio (SNR) of 3 T field strength allows a shortening of the total data acquisition time by a factor of 4 while maintaining an SNR comparable to 1.5 T (Lin et al., 2003). The shorter acquisition time of 3 T is a major advantage over 1.5 T in attempts to study unsedated newborns, especially in an outpatient setting where the infants were brought to the scanner by their parents. 3 T field strength also allows improved special resolution when keeping data acquisition time similar to 1.5 T (Lin et al., 2003). Finally, the improved SNR of 3 T offers improved DTI quality and improved white matter fiber tacking (Lin et al., 2003). The use of 3 T MRI will likely provide a vastly improved understanding of early brain development and its relationship to neuropsychiatric disorders.

In our sample, there was significant ventricular asymmetry at birth, with the left ventricle being larger than the right. This ventricle asymmetry is present in older children (Giedd et al., 1996) and indicates that lateralization of the brain is present at birth. Interestingly, female newborns had larger lateral ventricles than males, even in the face of similar intracranial volumes and birth weights. Studies in older children have found no gender difference (Giedd et al., 1996) or that males have larger ventricles than females (Reiss et al., 1996). Our study suggests there is a gender difference in brain maturation at birth and that there are dynamic changes in brain structure taking place in the neonatal period through childhood that are not well understood at this time and deserve further study.

Previous studies in infants and older children find that white matter FA increases and ADC decreases with age (Hüppi et al., 1998a; Neil et al., 1998; Schmithorst et al., 2002). In the very limited age range available in our study, we observed a significant increase in FA in the genu and splenium of the corpus callosum, but not in other white matter tracts. This suggests that the white matter of the corpus callosum is undergoing significant maturation in the period after birth that may represent a window of vulnerability to perinatal insults that have been associated with neurodevelopmental disorders, including schizophrenia.

These findings are interesting, but must be considered as preliminary given the small sample size and need to be replicated in a larger sample. Our findings do suggest that imaging studies in newborns and young children will reveal a wealth of currently unknown information about early human brain development. Studies of neonatal brain structure and development in healthy children and in children at high risk for schizophrenia are currently underway.

The neonatal brain presents unique challenges for image analysis (Hüppi et al., 1998b). Standard automated segmentation methods fail as there is a reversed intensity of white and gray matter and less

contrast between white and gray matter in neonates compared with adults. White matter is also heterogeneous, with hyperintense myelinated white matter relative to unmyelinated white matter. We are currently developing a tool for the automatic segmentation of gray matter, myelinated white matter, and unmyelinated white matter in the neonatal brain.

Acknowledgments

This work was supported by NIH Conte Center MH064065, Neurodevelopmental Disorders Research Center HD 03110, the Stanley Medical Research Institute, and the Foundation of Hope. The authors thank Jeffrey Lieberman, MD, Elizabeth Webster, PhD, and Joseph Piven, MD, for their support and helpful discussions.

References

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., Rapoport, J.L., 1996. Quantitative magnetic resonance imaging of human brain development: ages 4–8. Cerebral Cortex 6, 1047–3211.

Gilmore, J.H., van Tol, J., Kliewer, M.A., Silva, S.G., Cohen, S.B., Hertzberg, B.S., Chescheir, N.C., 1998. Mild ventriculomegaly detected in utero with ultrasound: clinical associations and implications for schizophrenia. Schizophrenia Research 33, 133–140.

Gilmore, J.H., Gerig, G., Specter, B., Charles, H.C., Wilber, J.S., Hertzberg, B.S., Kliewer, M.A., 2001a. Neonatal cerebral ventricle volume: a comparison of 3D ultrasound and magnetic resonance imaging. Ultrasound in Medicine & Biology 27, 1143–1146.

Gilmore, J.H., van Tol, J., Lewis-Streicher, H., Williamson, K., Cohen, S.B., Greenwood, R., Charles, C.R., Kliewer, M.A., Whitt, J.K., Silva, S.G., Hertzberg, B.S., Chescheir, N.C., 2001b. Outcome in children with fetal isolated mild ventriculomegaly: a case series. Schizophrenia Research 48, 219–226.

Ho, S., Bullitt, E., Gerig, G., 2002. Level set evolution with region competition: automatic 3-D segmentation of brain tumors. In: Kasturi, R., Laurendeau, D., Suen, C. (Eds.), Proceedings of the 16th International Conference on Pattern Recognition ICPR 2002, IEEE Computer Society, pp. 532–535.

Hüppi, P.S., Maier, S.E., Peled, S., Zientara, G.P., Barnes, P.D., Jolesz, F.A., Volpe, J.J., 1998a. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. Pediatrics 44, 584–590.

Hüppi, P.S., Warfield, S., Kikinis, R., Barnes, P.D., Zientara, G.P., Jolesz, F.A., Tsuji, M.K., Volpe, J.J., 1998b. Quantitative magnetic resonance imaging of brain development in premature and normal newborns. Annals of Neurology 43, 224–235.

Kangarlu, A., Shellock, F.G., Chakeres, D.W., 2003. 8.0-Tesla human MR system: temperature changes associated with radiofrequency-induced heating of a head phantom. Journal of Magnetic Resonance Imaging 17, 220–226.

Lin, W., An, H., Chen, Y., Nicholas, P., Zhai, G., Gerig, G., Gilmore, J., Bullitt, E., 2003. Practical consideration for 3T imaging. Magnetic Resonance Imaging Clinics of North America 11, 615–639.

Neil, J.J., Shiran, S.I., McKinstry, R.C., Schefft, G.L., Snyder, A.Z., Almli, C.R., Akbudak, E., Aronovitz, J.A., Miller, J.P., Lee, B.C.P., Conturo, T.E., 1998. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology 209, 57–66.

Peterson, B.S., Andersen, A.W., Ehrenkranz, R., Staib, L.H., Tageldin, M., Colson, E., Gore, J.C., Duncan, C.C., Mukuch, R., Ment, L.R., 2003. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 111, 939–948.

Reiss, A.L., Abrams, M.T., Singer, H.S., Ross, J.L., Denckla, M.B., 1996. Brain development, gender and IQ in children: a volumetric study. Brain 119, 1763–1774.

Schmithorst, V.J., Wilke, M., Dardzinski, B.J., Holland, S.K., 2002. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. Radiology 222, 212–218.

U.S. Food and Drug Administration, 2003. Criteria for significant risk investigations of magnetic resonance diagnostic devices, http://www.fda.gov/cdrh/ode/guidance/793.pdf.

Zhai, G., Lin, W., Wilber, K., Gerig, G., Gilmore, J.H., 2003. Comparisons of regional white matter fractional anisotropy in healthy neonates and adults using a 3T head-only scanner. Radiology 229, 673–681.