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Regional Gray Matter Growth, Sexual Dimorphism and Cerebral Asymmetry in the Neonatal Brain

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Development/Plasticity/Repair: Dr. Moses Chao**Regional Gray Matter Growth, Sexual Dimorphism and
Cerebral Asymmetry in the Neonatal Brain**

Abbreviated Title: Neonatal Brain Development

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Abstract

While there has been recent interest in the study of childhood and adolescent brain development, very little is known about normal brain development in the first few months of life. In older children, there are regional differences in cortical gray matter development, while cortical gray and white matter growth after birth has not been studied to a great extent. The adult human brain is also characterized by cerebral asymmetries and sexual dimorphisms, though very little is known about how these asymmetries and dimorphisms develop. We used magnetic resonance imaging and an automatic segmentation methodology to study brain structure in 74 neonates in the first few weeks after birth. We found robust cortical gray matter growth compared to white matter, with occipital regions growing much faster than prefrontal regions. Sexual dimorphism is present at birth, with males having larger total brain, cortical gray and white matter volumes than females. In contrast to adults and older children, the left hemisphere is larger than the right, and the normal pattern of fronto-occipital asymmetry described in older children and adults is not present. Regional differences in cortical gray matter growth are likely related to differential maturation of sensory/motor systems compared to prefrontal executive function following birth. These findings also indicate that while some adult patterns of sexual dimorphism and cerebral asymmetries are present at birth, others develop after birth.

Introduction

The first year of life is perhaps the most dynamic phase of postnatal brain development with rapid development of a wide range of cognitive and motor functions (Kagen and Herschkowitz, 2005). While there has been a great deal of recent interest in the study of childhood and adolescent brain development, very little is known about normal brain development in the first few months of life. Prior magnetic resonance (MR) imaging studies of a small number of healthy neonates being compared to prematurely born infants found gray and white matter volumes increased in the perinatal period (Huppi et al., 1998a; Peterson et al., 2003); a recent preliminary study white matter growth appeared to slow after 36 weeks gestational age (Nishida et al., 2006).

Cross-sectional neuroimaging studies of older children indicate that cortical gray matter volumes decrease after age 4-5 through puberty (Pfefferbaum et al., 1994, Reiss et al., 1996; Courchesne et al., 2000; De Bellis et al., 2001). A longitudinal study found regional differences in cortical gray matter development (Giedd et al., 1999). White matter volumes increase throughout later childhood and adolescent brain development (Pfefferbaum et al., 1994; Caviness et al., 1996; Giedd et al., 1999).

Sexual dimorphisms are present in the adult brain, with males having larger total brain volumes (Gur et al., 1999; Nopoulos et al., 2000; Goldstein et al., 2001). Older male children also have larger overall brain volumes and gray and white matter volumes than females (Giedd et al., 1996; Caviness et al., 1996; Reiss et al., 1996).

Structural asymmetries of the human brain appear to underlie functional asymmetries, including language and handedness (Toga and Thompson, 2003).

Cerebral asymmetries in the adult brain include the right hemisphere being larger than

the left, accounted for mainly by more white matter on the right, and fronto-occipital asymmetry or torque – the right prefrontal cortex is larger than the left, while the left occipital cortex is larger than the right (Nopoulos et al., 2000; Good et al., 2001; Raz et al., 2004; Toga and Thompson, 2003;). Adult patterns of cerebral asymmetry have been observed in older children (Giedd et al., 1996; Caviness et al., 1996; Matsuzawa et al., 2001; Reiss et al., 1996; Herbert et al., 2005).

Abnormalities of cortical gray and white matter have been described in neurodevelopmental disorders including schizophrenia (Honea et al., 2005) and autism (Hazlett et al., 2005). Similarly, abnormalities of normal cerebral asymmetries and gender differences have been observed schizophrenia (Bilder et al., 1994; Sommer et al., 2001; Goldstein et al., 2002), autism (Herbert et al., 2005; Rojas et al., 2005), Tourette syndrome (Hong et al., 2002), and developmental stuttering (Foundas et al., 2003). A better understanding of normal cortical gray and white matter development in the early postnatal period, as well as how and when normal cerebral asymmetries and sexual dimorphisms develop would provide important insights into these neurodevelopmental disorders. We present a study of regional cortical growth, sexual dimorphism, and cerebral asymmetry in a large cohort of healthy neonates.

Methods

Subjects: This study was approved by the Institutional Review Board of the University of North Carolina School of Medicine. Infants scanned for this study were part of a larger study of prenatal and neonatal brain development in children at high risk for neurodevelopmental disorders and controls. Control mothers were recruited during the second trimester of pregnancy from the outpatient OB-GYN Clinics at UNC

Hospitals. Exclusion criteria were the presence of abnormalities on fetal ultrasound or major medical or psychotic illness in the mother. Singleton subjects with a gestational age ≥ 37 weeks who had both T1 and T2/PD scans that were free of major motion were included in this analysis ($n = 78$). All scans were reviewed by a neuroradiologist (JKS). Additional exclusion criteria for this analysis included major delivery or neonatal complications or significant CNS abnormality on MRI ($n = 4$). 12 subjects had small incidental subdural hematomas or other intracranial bleeds, which are present in about 25% of vaginal births (Looney et al., 2006); these subjects were included in the analysis.

Image Acquisition: Neonates were scanned unsedated, fed prior to scanning, swaddled, 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. T1-weighted structural pulse sequences were a 3D magnetization prepared rapid gradient echo (MP-RAGE TR/TI/TE/Flip Angle 1820/400/4.38ms/7°) in the early phases of the study ($n=9$), then a 3D T1-weighted FLASH (TR/TE/Flip Angle 15/7msec/25°; $n=65$). Proton density and T2 weighted images were obtained with a turbo spin echo sequence (TSE TR/TE1/TE2/Flip Angle 6200/20/119ms/150°). Spatial resolution was 1 x 1 x 1mm voxel for T1 weighted images, 1.25 x 1.25 x 1.5mm voxel with 0.5 mm interslice gap for proton density/T2 weighted images.

The Siemens head-only 3T 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 have previously confirmed that the scan

sequences did not cause significant temperature increases with a phantom (Gilmore et al., 2005).

Image Analysis: Our segmentation method (Prawstawa et al., 2005) is an extension of a previously developed atlas-moderated automatic tissue classification technique which uses an iterative expectation maximization segmentation (EMS) algorithm (Wells et al., 1996; Van Leemput et al., 1999; Prastawa et al., 2004). The method operates on single or multi-channel MRI data and uses a co-registered probabilistic brain atlas as a spatial prior. The EM segmentation tool incorporates multi-channel image registration, registration of the probabilistic brain atlas to the subject, automatic bias inhomogeneity correction and brain stripping in one integrated framework, which offers significant advantages over processing pipelines where each of the tasks is solved as a separate, independent processing step. In neonate MRI, the low contrast-to-noise ratio of non-myelinated white matter to cortical and subcortical gray required significant changes. Parametric modeling of multivariate distributions is replaced by robust graph clustering and parameter estimation, resulting in an intermediate segmentation. This segmentation is finally refined using training sample pruning and non-parametric kernel density estimation. The segmentation of a two-channel MRI of the neonate brain is depicted in **Figure 1**. Validation by comparison to human-expert segmentation showed very good agreement (Prawstawa et al., 2005). The segmentation process is fully automatic, uses about 30 minutes on a standard PC workstation, and does not require human interaction which often limits reliability. EM segmentation requires a probabilistic brain atlas to define local geometric priors for each tissue category, but existing probabilistic atlases for adults are not appropriate for

pediatric studies. We followed the concept proposed by Evans et al. (1993) to build a new statistical brain atlas for the neonatal age group.

Parcellation of each subject's brain into regions is achieved by non-linear warping of a parcellation atlas template (Rueckert et al., 1999). The brain atlas template MRI, subdivided into regions by anatomical experts, serves as the template (see **Figure 1**). Left and right hemispheres were subdivided into four regions along the anterior-posterior axis (pre-frontal, frontal, parietal, occipital) and into infra- and supratentorial regions. The cerebellum, brainstem and combined sets of subcortical structures are represented separately. This parcellation template is registered to each individual subject's MRI by volumetric nonlinear by nonlinear deformation based on the mutual information criterion (Rueckert et al., 1999), combined with the individual tissue segmentation masks, and results in an estimate of gray, white and CSF volume for each region along the anterior-posterior axis.

Statistical Analysis: For cross-sectional analyses of gender differences on volumes, a two-group one-way analysis of variance was used, with ICV added as a covariate. For examinations of cerebral asymmetry, we used paired t-tests of right-left volumes, without covariates as these were entirely within-subject comparisons; analysis was repeated separately for each gender. For growth trajectory models, we fit mixed models with pre-frontal, frontal, parietal, occipital region (each overall region combines left and right inferior and superior subregions determined by the parcellation template) as the within-subjects variable of interest and age at MRI as a continuous predictor. In this model, we examined differences in slopes between regions with contrasts.

Results

The final study sample (n=74) included 40 males and 34 females; ethnic composition was 61 Caucasian, 12 African – American, and 1 Asian-American. Gestational age at MRI was (mean \pm SD) 42.8 \pm 1.6 wks (range 38.8 – 47.8 wks). There were no significant gender differences in the gestational age at birth (M: 39.7 \pm 0.9 wks; F: 39.6 \pm 1.0 wks; $p = 0.79$) or gestational age at MRI (M: 43.0 \pm 1.7 wk; F: 42.6 \pm 1.5 wk; $p = 0.28$). There was a significant difference in birth weight between males and females (M: 3587.7 \pm 465.5 g; F: 3278.7 \pm 407.39 g; $p = 0.0036$).

In the first several weeks after birth, total gray matter grew robustly compared to myelinated and unmyelinated white matter [inhomogeneity of slopes, $F(3,288) = 16.6$, $p < 0.0001$; **Figure 2**]. In the cortex, overall trajectories of gray matter growth were similar in males and females, though there was a trend for female cortical unmyelinated white matter growth to be more rapid than male [$F(1,70) = 3.2$, $p = 0.08$]. Interestingly, there is a posterior to anterior gradient for cortical gray matter development. There were significant differences in the regional growth rates, with the occipital and parietal regions growing significantly faster than the prefrontal region [$F(3,288) = 8.61$, $p < 0.0001$; **Figure 3**]. This overall posterior greater than anterior regional growth was also seen in the unmyelinated white matter compartment, though less pronounced compared to gray matter and not statistically significant [$F(3,288) = 1.5$, $p = 0.218$; **Figure 4**].

We found that sexual dimorphism was present in the early postnatal brain (**Table 1**), with males having intracranial volumes (ICV) 7.8% larger than females [two-group one-way ANOVA, $F(1,72) = 10.0$, $p = 0.0023$], comparable to the gender difference in birth weight of 9.42%. Males had significantly larger ICV compared to females, even controlling for birth weight [$F(1,71) = 4.3$, $p = 0.0418$]. Males had approximately 10.2%

more cortical gray matter [$F(1,72) = 11.35, p = 0.0012$] and 6.4% more cortical white matter [$F(1,72) = 6.0, p = 0.0169$] than females. Males also had 7.8% larger subcortical gray matter volumes [$F(1,72) = 4.28, p = 0.0423$] than females. These differences were related to the ICV of males, as there were no significant gender differences when controlling for ICV (**Table 3**). There was no significant gender difference in lateral ventricle or cerebellum volume in the first weeks of life, though males tended to have larger volumes (**Table 1**).

Cerebral asymmetry was present at birth (**Table 2**), with the left hemisphere approximately 4.3% larger than the right [$T(73) = 14.2, p < 0.0001$], – the opposite of the right greater than left asymmetry observed in older children and adults. This left greater than right hemisphere asymmetry was a very consistent finding, present in 70 subjects (94.6%). Left greater than right asymmetry was present in hemispheric gray matter (4.6%, $T(73) = 9.3, p < 0.0001$) and white matter [1.2%, $T(73) = 2.8, p = 0.0065$], though more pronounced in gray matter compared to white. Left greater than right asymmetries of the subcortical gray matter [6.8%, $T(73) = 11.4, p < 0.0001$] and lateral ventricles [37.9%, $T(73) = 2.9, p = 0.0054$] are also evident in the early postnatal period. Males and females had similar patterns of asymmetry in total hemisphere volume, hemispheric gray matter, hemispheric white matter, subcortical gray matter, and lateral ventricles (data not shown).

We did not observe torque in the neonatal brain. While the left occipital region was larger than the right as expected [10.4%, $T(73) = 18.8, p < 0.0001$], the left prefrontal region was actually non-significantly larger than the right [0.92%; $T(73) = -1.9, p = 0.0603$] – the opposite pattern of that observed in adults (**Table 3**). The magnitude

of the asymmetry was more pronounced in the female brain in both regions, with a significant gender differences in asymmetries in the prefrontal [$T(72) = 2.2, p = 0.0272$] and occipital regions [$T(72) = -2.3, p = 0.0243$].

Discussion

The early postnatal period is characterized by a robust growth of cortical gray matter compared to white matter, as well as by a posterior to anterior regional specificity of cortical gray matter growth. Sexual dimorphisms are generally similar to those found in later stages of brain development, indicating that adult patterns of sexual dimorphism arise before birth and persist throughout postnatal brain development. The patterns of cerebral asymmetry in this period of brain development are different from those observed in older children and adults suggesting that adult patterns of cerebral asymmetry arise after birth.

Overall brain volume in the neonatal period is roughly 35% that of normal adults scanned on the same scanner (Mortamet et al., 2005), indicating there is enormous overall growth of the brain between birth and adulthood. Early results from follow-up scans at one year of age suggest that total brain size increases 100% in the first year of life to approximately 73% of adult size (Gilmore et al., unpublished results).

In the first weeks after birth, there is a robust increase in cortical gray matter volumes, likely the result of exuberant development of new synapses in the cortex, which has been observed in human and non-human primates (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Bourgeois and Rakic, 1993; Bourgeois et al., 1994). Interestingly, there is regional specificity to this gray matter growth, with occipital and parietal regions growing significantly more than prefrontal regions. This pattern

suggests that gray matter is maturing faster in the sensory and motor regions than in the prefrontal regions, reflecting the rapid maturation of visual and motor functions relative to the executive functions of the prefrontal cortex in the early postnatal period (Kagen and Herschkowitz, 2005). This pattern of gray matter development is also consistent with a similar posterior to anterior maturation of cortical white matter tracts, with the occipital poles myelinating before the frontotemporal poles (Sampaio and Truwit, 2001).

The regional differences in gray matter growth is consistent with previous studies of synapse development in human brain, in which synapse numbers peak at 3-4 months in the occipital cortex, and at 4-5 years in the prefrontal cortex (Huttenlocher and Dabholkar, 1997). In non-human primates, there does not appear to be regional differences in synapse development (Bourgeois and Rakic, 1993; Bourgeois et al., 1994), and whether there are real regional differences in humans has been debated (Rakic et al., 1994). While overall volume gray matter changes are an indirect measure of synapse proliferation, our results are supportive of regional differences in synapse development in humans.

Sexual dimorphism is present in the neonatal brain. After birth, males have about 9% larger intracranial volumes than females. This difference in ICV is similar to that observed in adults – 11.9 to 14.6 % (Gur et al., 1999; Raz et al., 2004). Infant males had 10% more cortical gray matter than females, which is similar to the 10 -11% differences in gray matter in observed in older children (Giedd et al., 1999; Reiss et al., 1996) and the 7-10% differences noted in adults (Gur et al., 1999; Allen et al., 2003). Males also had 6% more cortical white matter, similar to the 7.5% differences in older

children (Reiss et al., 1996), but less than the 17-15% differences found in adults (Gur et al., 1999; Allen et al., 2003). Sexual dimorphism in head circumference has been observed as early as the second trimester in human and non-human primates on ultrasound (Joffe et al., 2005). Our study suggests that adult patterns of sexual dimorphisms of overall intracranial and cortical gray matter volumes are present at birth, while adult patterns of cortical white matter and lateral ventricle volumes develop after birth.

The left hemisphere greater than right hemisphere asymmetry present after birth is the opposite of the right greater than left asymmetry observed in older children and adults (Nopoulos et al., 2000; Good et al., 2001; Raz et al., 2004; Giedd et al., 1996; Caviness et al., 1996; Matsuzawa et al., 2001). The magnitude of cerebral asymmetries in the early postnatal period are also greater than the asymmetries observed in older children and adults, which are modest (Reiss et al., 1996; Gur et al. 1999; Matsuzawa et al., 2001). For example, while we found a 5% L > R difference in hemispheric gray matter in the neonatal brain, Gur et al. (1999) found a 0.19% R > L difference in adults. There was a significant asymmetry in cortical white matter in our cohort, while white matter volumes are symmetric in adults (Gur et al., 1999).

Adult patterns of overall fronto-occipital asymmetry or torque are not present in the neonate. While we did find the expected right greater than left asymmetry in the occipital region, the expected prefrontal region asymmetries are not present. Prefrontal asymmetry appears to develop after birth, and this lack of asymmetry may reflect a relative “immaturity” of the prefrontal regions compared to occipital regions, consistent with the slower trajectory of prefrontal gray matter growth pattern versus posterior

cortical regions. Interestingly, the magnitude of asymmetry in each region was significantly larger in females, in contrast to studies in adults that found no gender difference in the magnitude of torque (Raz et al., 2004).

Cerebral asymmetries are present at birth in humans, indicating they arise during prenatal brain development. A prior ultrasound study found that this left greater than right hemisphere asymmetry is present as early as 20-22 weeks gestational age (Hering-Hanit et al., 2001). Left greater than right asymmetry of the lateral ventricles has also been observed in the fetus using ultrasound (Achiron et al., 1997). In a postmortem study of fetal and neonatal tissue, the right frontal region was found to be larger than the left, while the left occipital region was larger than the right (Weinberger et al., 1982). This contrasts with our finding that the left prefrontal region is the same volume or even larger than the right.

Asymmetry patterns present in the neonatal brain are likely due to genetic programs that operate during prenatal brain development as gene expression in human embryonic cortex is asymmetric as early as 12 weeks (Sun et al., 2005; Sun and Walsh, 2006). Adult patterns of asymmetry are also likely the result of genetic programming of and environmental influences on postnatal brain development. A recent study of cerebral asymmetry in 14 year olds who were born very preterm found normal fronto-occipital asymmetry, suggesting that environmental insults to the developing brain at this very early age does not affect adult asymmetry patterns (Lancefield et al., 2006). Children with posttraumatic stress disorder have a loss of normal frontal lobe asymmetry, suggesting that postnatal stress may influence development of adult patterns of asymmetry (Carrion et al., 2001).

While the automatic segmentation approach used is the best available for reproducible, highly automated segmentation with good validity given the processing needs of a study with a large number of subjects, there are a few limitations to this approach. There appears to be a slight overestimation of the region of early white matter myelination, especially in the region of the lower anterior part of the internal capsule. Binary classification, i.e. tissue label maps, may misclassify tissue in regions that do not exhibit a clear assignment to gray or white matter. This problem will be addressed in future studies by calculating regional tissue volumes through integration of tissue probability values, produced by the currently applied EM segmentation, instead of hard labels. Such a procedure also might much better cope with partial voluming at the very thin cortical gray matter layer, which in label color maps leaves the impression of overestimation of gray matter.

The current parcellation is based on a Talairach-based box parcellation of the brain volume with separation of subcortical regions, brain stem and cerebellum. Our results provide information about overall regional growth in the cortex, but does not provide detailed information about specific lobes or subregions within the cortex. Growth trajectories of cortical lobes such as those defined in the semi-automated approach of Nishida and colleagues (Nishida et al., 2006) may differ from the results presented in this study, but the overall pattern of posterior greater than anterior growth should be consistent.

In summary, brain development in the first weeks of life is characterized by rapid cortical gray matter growth that is regionally specific. Overall sexual dimorphism of brain size at this age is similar to that found in older children and adults, though there

are some subtle differences in patterns of cerebral gray and white matter volumes. The pattern of cerebral asymmetry in neonates is opposite that of older children and adults and suggests that adult patterns of cerebral asymmetry are the result of ongoing neurodevelopmental processes active after birth, driven by genetic programming as well by experience. There is much to learn about human brain development in the first years of life. We are currently following this cohort with longitudinal imaging and developmental assessments at ages one and two years.

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Table 1. Sexual Dimorphism

	Male mean (SD)	Female mean (SD)	Difference %, M>F	p value	p value ICV controlled*
Birthweight (grams)	3587.7 (465.5)	3278.7 (407.7)	9.42 %	0.0036	na
ICV (mm ³)	525524 (58637)	487378 (41848)	7.83 %	0.0023	na
Hem GM (mm ³)	218212 (28693)	197945 (197944)	10.24 %	0.0012	0.2734
Hem umWM (mm ³)	163987 (18420)	154146 (15745)	6.38%	0.0169	0.8365
Subcort GM (mm ³)	24390 (4229)	22628 (2823)	7.79%	0.0423	0.5868
Lat Ventricle (mm ³)	2927 (2054)	2771 (3944)	5.67%	0.8277	0.3553
Cerebellum (mm ³)	28227 (4050)	26893 (3156)	4.96 %	0.1235	0.6712

Table 2. Cerebral Asymmetry

	Left mean (SD)	Right mean (SD)	Difference %, L>R	p value*
Total Hemisphere (mm ³)	237395 (26573)	227623 (25826)	4.29	<0.0001
Hem GM (mm ³)	106833 (14213)	102067 (13689)	4.67	<0.0001
Hem umWM (mm ³)	80225 (9092)	79240 (8988)	1.24	0.0065
Subcort GM (mm ³)	12180 (1919)	11401 (1860)	6.83	<0.0001
Lat Ventricle (mm ³)	1655 (2134)	1200 (1011)	37.91	0.0054

GM – gray matter; umWM – unmyelinated white matter

* paired t-test

Table 3. Fronto-Occipital Asymmetry (Torque)

	Left mean (SD)	Right mean (SD)	Difference %, L>R	p value
Prefrontal (mm ³)				
All	29001 (3710)	28736 (2823)	0.92	0.0603
Male	29697 (3668)	29713 (3706)	-0.05	*
Female	28183 (3642)	27586 (3686)	2.16	*
Occipital (mm ³)				
All	63407 (8177)	57048 (7642)	10.45	<0.0001
Male	65682 (8501)	60341 (7788)	8.85	**
Female	60730 (6989)	53956 (58899)	12.55	**

* Gender difference in prefrontal asymmetry, $T(72) = 2.2$, $p = 0.0272$

** Gender difference in occipital asymmetry, $T(72) = -2.3$, $p = 0.0243$

Figure 1. T1 weighted (A) and T2 weighted (B) images are automatically segmented (C) into CSF (blue), gray matter (yellow), unmyelinated white matter (green) and myelinated white matter (pink). (D) Template of the neonatal brain for automatic parcellation into 16 cortical regions, right and left subcortical regions, brainstem and cerebellum.

Figure 2. Tissue specific growth rates in whole brain (n=74). There is a significant overall difference in slopes [inhomogeneity of slopes, $F(3,288) = 16.6$, $p < 0.0001$]. There are significant differences in growth rates between gray matter (GM) and unmyelinated white matter [umWM; $F(1,288) = 28.0$, $p < 0.0001$] and between GM and myelinated white matter [mWM, $F(1,288) = 44.9$, $p < 0.0001$].

Figure 3. Regional growth of cortical gray (n=74). There is a significant overall regional difference in slopes [inhomogeneity of slopes, $F(3,288) = 8.6$, $p < 0.0001$]. There were significant differences between occipital and prefrontal [$F(1,288) = 18.9$, $p < 0.0001$], occipital and frontal [$F(1,288) = 5.8$, $p = 0.0166$], and between parietal and prefrontal [$F(1,288) = 17.9$, $p < 0.0001$] matter growth rates.

Figure 4. Regional growth of cortical unmyelinated white matter (n=74). There was not a significant regional difference in slopes for unmyelinated white matter [inhomogeneity of slopes, $F(3,288) = 1.5$, $p = 0.2180$].







