Published in final edited form as:

Dev Sci. 2014 March ; 17(2): 161–174. doi:10.1111/desc.12106.

Different early rearing experiences have long term effects on cortical organization in captive chimpanzees (*Pan troglodytes*)

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Abstract

Consequences of rearing history in chimpanzees (*Pan troglodytes*) have been explored in relation to behavioral abnormalities and cognition, however, little is known about the effects of rearing conditions on anatomical brain development. Human studies have revealed that experiences of maltreatment and neglect during infancy and childhood can have detrimental effects on brain development and cognition. In this study, we evaluated the effects of early rearing experience on brain morphology in 92 captive chimpanzees (ages 11–43) who were either reared by their mothers ($n = 46$) or in a nursery ($n = 46$) with age-group peers. Magnetic resonance brain images were analyzed with a processing program (BrainVISA) that extracts cortical sulci. We obtained various measurements from 11 sulci located throughout the brain, as well as whole brain gyrification and white and grey matter volumes. We found that mother-reared chimpanzees have greater global white-to-grey matter volume, more cortical folding and thinner grey matter within the cortical folds than nursery-reared animals. The findings reported here are the first to demonstrate that differences in early rearing conditions have significant consequences on brain morphology in chimpanzees and suggests potential differences in the development of white matter expansion and myelination.

Keywords

Brain; Cortical sulci; White matter; Chimpanzee; Infant rearing; Early life stress

Introduction

One of the main characteristics that define the order Primates is their slow rate of overall development, resulting in a longer period of infant dependency on their mothers. The human brain triples in mass from birth to five years of age, which is driven by intense myelination

of axon fiber tracks, thus increasing white matter throughout the cortex (Durstun et al., 2001; Giedd et al., 1999). These early years are critical in cortical development and disruption to this process can be detrimental as is demonstrated by negative consequences of a range of adverse childhood experiences. Childhood stress, in the form of neglect, social deprivation, abuse or trauma affects both cognitive functioning (Ammerman, Cassisi, Hersen, & Van Hasselt, 1986; De Bellis, Hooper, Spratt, & Woolley, 2009; Kaufman & Charney, 2001; McCrory, De Brito, & Viding, 2011; Pechtel & Pizzagalli, 2011) and multiple aspects of brain development (De Bellis et al., 1999). In humans, a number of brain regions, including the hippocampus (HC), cerebellum (CB), prefrontal cortex (PFC), and corpus callosum (CC) are affected by early life stress (Teicher et al., 2003) and presumably underlie the deficits found in socio-emotional development and cognition of those who had harmful childhood experiences.

Comparatively, as the brain gets larger through the family Hominidae, or great apes, infant dependency is further amplified as manifested by the relatively immature brain size at birth and the long post-natal period of development (Leigh, 2004). For instance, human and chimpanzee brains are only 30% of their adult weight at birth, compared to 50% in more distantly related monkey species such as the rhesus and capuchin monkeys (Leigh, 2001, 2004; Robson & Wood, 2008; Sakai et al., 2011). As in humans, the relatively immature brain at birth coupled with the longer post-natal period of development in chimpanzees makes cortical development during this period of the lifespan particularly sensitive to the influences of a variety of social and environmental experiences. Indeed, a great deal of research has demonstrated that different social rearing experiences have profound effects on emotional and psychological well-being in both human (Ammerman et al., 1986; Baumrind, 1993; Hofer, 1994; Kochanska, 2001) and non-human primates (Bellanca & Crockett, 2002; Nash, Fritz, Alford, & Brent, 1999; Novak, Meyer, Lutz, & Tiefenbacher, 2006; Sackett, Novak, & Kroeker, 1999).

Decades of controlled experimental studies in rodents and primates have clearly established the deleterious consequences of social deprivation on the development of species-typical social behavior, learning, socio-affective processes, neurochemistry, and a range of other health outcomes (Abello & Colell, 2006; Bennett & Pierre, 2010; Harlow & Harlow, 1962; Harlow & Suomi, 1971; Latham & Mason, 2008; Marriner & Drickamer, 1994; Meder, 1989; Meyer, Novak, Bowman, & Harlow, 1975; Mitchell, Ruppenthal, Raymond, & Harlow, 1966; Nash et al., 1999; Ruppenthal, Arling, Harlow, Sackett, & Suomi, 1976; Sánchez, Ladd, & Plotsky, 2001), as well as on cognition (Bennett & Pierre, 2010; Davenport & Rogers, 1970; Davenport, Rogers, & Rumbaugh, 1973; Meder, 1989; Menzel, Davenport, & Rogers, 1970; Morimura & Mori, 2010; Rumbaugh, 1970; Russell et al., 2005). Much less is known, however, about how different early social rearing experiences influence specific aspects of brain development, particularly among great apes. While little is known about the long-term consequences of early rearing experiences on chimpanzee brain morphology and development, a number of findings from studies of rhesus monkeys indicate significant differences between mother-reared animals and those who were nursery-reared or without maternal relationships in infancy. For example, in rhesus monkeys, a number of investigations have demonstrated effects of early differential rearing on various measures of brain morphology and composition, including differences in the caudate-putamen (Ginsberg, Hof, McKinney, & Morrison, 1993; Ichise et al., 2006; Martin, Spicer, Lewis, Gluck, & Cork, 1991) and corpus callosum (Sánchez, Hearn, Do, Rilling, & Herndon, 1998). Spinelli and colleagues (2009) examined magnetic resonance images (MRI) from 28 rhesus (*Macaca mulatta*) monkeys (ages 23-32 months) that were either reared by their mother or in a group with three age-mate peers (peer-reared). Using region-of-interest (ROI) analyses, they found that the vermis of the cerebellum, dorsomedial prefrontal cortex, and dorsal anterior cingulate cortex, were enlarged in the peer- compared

to mother-reared monkeys. No significant differences were evident between these groups in the corpus callosum or in hippocampus volumes. Spinelli and colleagues (2009) suggest that the enlarged stress-sensitive brain regions identified in nursery-reared monkeys may be associated with behavioral differences in stress reactivity that, in humans, are linked to a higher risk of developing neuropsychiatric disorders. Together, the results of these studies suggest not only that early experience may significantly alter brain development in chimpanzees, but also that uncovering the specific effects of early rearing history is important to understanding individual variation in great ape brain morphology and cortical organization.

Rather than focus on specific regions of interest, here we examined the long-term consequences of different rearing experiences on cortical folding and grey matter thickness in a sample of captive chimpanzees. Cortical folding, or gyrification index (GI), reflects the ratio in the folded grey matter surface of the cortex relative to the outer contour of the brain. Previous studies have shown that humans have a larger GI than apes, who in turn have a larger value than Old and New World monkeys (Armstrong, Zilles, & Schleicher, 1993; Rilling & Insel, 1999; Rogers et al., 2010). Moreover, among humans and monkeys, GI values increase with post-natal age (Sawada et al., 2010; White, Su, Schmidt, Kao, & Sapiro, 2010) and therefore this measure of cortical organization may be sensitive to different rearing experiences in chimpanzees. Grey matter thickness reflects the localized variation in the grey matter distance between the pial surface and white matter boundary. Though we are unaware of any published studies examining the influence of different rearing experiences on grey matter thickness in human or nonhuman primates, studies have shown that rats raised in deprived or enriched physical environments exhibit significant differences in cortical thickness throughout the cortex (Renner & Rosenzweig, 1987). Lastly, we measured the overall grey and white matter volumes as well as the ratio of white to grey matter in the chimpanzee brains. It has been hypothesized that both grey matter thickness and cortical folding are related to variation in white matter such that increased white matter results in increased folding of the cortex and a small but significant degree of thinning in the grey matter thickness (Herculano-Houzel, Mota, Wong, & Kaas, 2010; Seldon, 2005). Based on these assumptions in cortical organization, we hypothesized that if different early social experiences have long-term consequences on the development of cortical organization, then significant differences would be found in cortical folding, white to grey matter ratio and grey matter thickness between chimpanzees raised with their mothers and those raised in peer groups. We hypothesized that mother-reared chimpanzees will have more white matter, greater cortical folding, and thinner sulcal grey matter thickness when compared to nursery-reared subjects.

Methods

Subjects

We used a matched design in this study. There were 92 captive chimpanzees in this study, including 58 females and 34 males, housed at either the Yerkes National Primate Research Center (YNPRC) or The University of Texas M. D. Anderson Cancer Center (UTMDACC). There were 46 mother-reared (MR) and 46 nursery-reared (NR) chimpanzees that were matched on scanner type (1.5T or 3T), age, and sex. Ages at the time of their magnetic resonance image scans ranged from 11 to 43 years with the mean age for mother- and nursery-reared chimpanzees being 20.98 ($SD = 6.74$) and 21.91 ($SD = 7.12$) years, respectively. Factoring in evidence that captive chimpanzees mature earlier than in the wild and following Goodall's (1986) age classification, adulthood is reached around age 13 years for females and 15 years for males. Though the MR and NR subjects were matched on age,

because of the large range in ages of our sample, we used age as a covariate in all of the statistical analyses (see below).

We defined a nursery-reared chimpanzee as an animal that was separated from his or her mother within the first 30 days of life, due to unresponsive care, injury, or illness (Bard, 1994; Bard, Platzman, Lester, & Suomi, 1992). These chimpanzees were placed in incubators, fed standard human infant formula (not supplemented with DHA as far as we know), and cared for by humans until they could sufficiently care for themselves, at which time they were placed with other infants of the same age until they were three years of age (Bard, 1994; Bard et al., 1992). At three years of age, the nursery-reared chimpanzees were integrated into larger social groups of adult and sub-adult chimpanzees. Mother-reared chimpanzees were not separated from their mother for at least 2.5 years of life and were raised in ‘nuclear’ family groups of chimpanzees, with group sizes ranging from 4 to 20 individuals. It should be noted that some of the chimpanzees in this study were nursery-reared because their biological mothers did not exhibit adequate maternal care at birth and this required intervention in order to protect the infants’ well-being. Thus, the chimpanzees in this study were not nursery-reared with the goal of subsequently determining the effects of early life experiences on development. The study we present here is opportunistic and retrospective; that is to say, we took advantage of the fact that some of the chimpanzees received different rearing experiences in order to determine whether this might have long-term consequences on cortical development.

Magnetic Resonance Image Collection

All chimpanzees were scanned during one of their annual physical examinations. Magnetic resonance image (MRI) scans followed standard procedures at the YNPRC and UTMDACC and were designed to minimize stress. Thus, the animals were first sedated with ketamine (10 mg/kg) or telazol (3-5mg/kg) and were subsequently anaesthetized with propofol (40–60 mg/(kg/h)). They were then transported to the MRI scanning facility and placed in a supine position in the scanner with their head in a human-head coil. Upon completion of the MRI, chimpanzees were briefly singly-housed for 2-24 hours to permit close monitoring and safe recovery from the anesthesia prior to return to the home social group. All procedures were approved by the Institutional Animal Care and Use Committees at YNPRC and UTMDACC and also followed the guidelines of the Institute of Medicine on the use of chimpanzees in research. Forty chimpanzees were scanned using a 3.0 Tesla scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania, USA). T1-weighted images were collected using a three-dimensional gradient echo sequence (pulse repetition = 2300 ms, echo time = 4.4 ms, number of signals averaged = 3, matrix size = 320×320 , with $0.6 \times 0.6 \times 0.6$ resolution). The remaining 52 chimpanzees were scanned using a 1.5T G.E. echo-speed Horizon LX MR scanner (GE Medical Systems, Milwaukee, WI). T1-weighted images were collected in the transverse plane using a gradient echo protocol (pulse repetition = 19.0 ms, echo time = 8.5 ms, number of signals averaged = 8, matrix size = 256×256 , with $0.7 \times 0.7 \times 1.2$ resolution). Though two different scanners were used, recall that the mother- and nursery-reared chimpanzees were matched on the scanner and image acquisition protocol so as to remove this potential confound when comparing the two subject groups.

MRI Processing

BrainVISA 4.0.1 (BV) is freely distributed software (<http://brainvisa.info>) that measures cortical folding of the brain (Mangin et al., 2004). Initially, using Analyze 8.1, all chimpanzee scans were skull-stripped, cropped, and reformatted at 0.7 cubic isotropic resolution and subsequently imported into BV. Extracting the sulci from the cortex in the brain scans involves a series of steps in a pipeline process within BV (Mangin et al., 2004)

(see Figure 1) and these methods are described in detail elsewhere (Bogart et al., 2012). Initially, the anterior and posterior commissures were manually specified on the MRI where they intersect with the mid-sagittal slice to align the brain. The first step was to correct for special inhomogeneities in the signal intensity providing a spatially smooth bias field with a stable distribution of tissue intensities (Figure 1b). Next, the analysis of the signal histogram and mathematical morphology was computed to obtain a binary mask of the brain (Figure 1c). The mask was then split into the left and right hemispheres and the cerebellum (Figure 1d). A negative mould of the white matter was computed from the split-brain mask. The outside boundary of this mould results from a 5 mm morphological closing of the masked hemisphere, filling up the folds. The grey/white interface is the inside boundary preserving deformations assuring the spherical topology of the mould (Figure 1e). Finally the mould was skeletonised to detect cortical folding, while topological constraints guarantee the resulting surfaces have no holes (Figure 1f-e). The deepest part of the fold indicates the buried gyrus given the grey/white interface. The final steps results in creating the cortical fold graph with the extracted sulci (Figure 1h).

In this study, 11 sulci of the chimpanzee brain were manually labeled following Bailey et al.'s (1950) definitions (Figure 1h). The sulci selected in the frontal lobe were the central (CS), superior precentral (SPC), precentral inferior (PCI), inferior frontal (IFS), and fronto-orbital (FO) sulci. The superior precentral sulcus in the chimpanzees is triradiate in formation, one branch extends toward the frontal pole (Bailey et al., 1950), while the posterior end runs medial to lateral. We included all limbs of SPC in this study. PCI often includes the superior limb running parallel to the central sulcus, however, we were interested in including only that portion of PCI that is used to define the inferior frontal gyrus (IFG) in chimpanzees (Keller, Roberts, & Hopkins, 2009). Thus, measures were obtained on the inferior limb, which is considered the posterior border of the IFG in the chimpanzee brain. Furthermore, PCI can be bifurcated (Keller et al., 2009; Sherwood, Broadfield, Holloway, Gannon, & Hof, 2003), and we included all inferior branches of the PCI in our measurement of this sulcus. FO in the chimpanzee constitutes the anterior border of IFG and is analogous to the human ascending ramus (Keller et al., 2009). Further, we only include the portion of IFS that forms the superior border of IFG. The temporal lobe sulci consisted of the sylvian fissure (SF) and superior temporal sulcus (STS), while the parietal lobe sulci included the superior postcentral (SPCS), inferior postcentral (IPCS), superior parietal sulcus (SPS) and intraparietal (IPS) sulci.

Sulcus Measures

Two measures were obtained from each sulcus using BrainVISA's (BV) morphometric tools, and these included: 1) mean depth (mm) and 2) grey matter thickness (mm). Mean depth is the average depth of the sulcus along its principal axis of projection (i.e., dorsal-ventral, anterior-posterior, see Figure 2a). Sulcus grey matter thickness (GMT) was quantified by measuring the mean distance between the pial surface and the grey/white interface around the buried sulcus (see Figure 2b).

Global Cortical Measures

Using BV, we further calculated hemispheric grey and white matter volumes (mm^3), overall gyrification index (GI), and average whole brain grey matter thickness (mm) for each subject. To calculate the grey (GM) and white matter (WM) volumes, the program used the grey/white interface generated in the sulci extraction pipeline process to generate a cerebral spinal fluid (CSF) interface, providing the total volumes in each hemisphere. The cerebellum and related brain stem structures were excluded from calculations in total GM and WM volume. The ratio in white-to-grey matter (WMGM) was derived by dividing the WM by GM volume. As has been done in many previous studies, the overall gyrification

index (GI) was determined by measuring the surface area sulcal internal contours of the cortex and dividing it by the total surface area for each hemisphere, which BV calculates (Armstrong et al., 1993; Rilling & Insel, 1999; Rogers et al., 2010; Zilles, Armstrong, Moser, Schleicher, & Stephan, 1989). Overall average cortical grey matter thickness (CGM) was computed using a plugin developed for BV by Kochunov and colleagues (2012). This plugin measures the CGM within each hemisphere using the pial and grey-white interface created in the pipeline process for each brain. Whole brain CGM was calculated for the explicit purpose of adjusting individual sulcal grey matter thickness (see Statistical Analyses below).

Statistical Analyses

For all analyses, the left and right hemisphere values for each subject were averaged to derive a single mean outcome measure. For the overall white and grey matter volumes and GI measures, we used multivariate analysis of covariance (MANCOVA) with sex (male, female) and rearing history (MR, NR) as between group factors while age served as a covariate. An ANCOVA was used to test for group differences in WMGM ratio with rearing history and sex serving as between group factors while age was again the covariate.

For sulcus mean depth and grey matter thickness measures, we computed adjusted values for each sulcus. Adjusting the values for the whole brain measure eliminates the assumption of an effect on the entire cortical space and allows for assessment of the relative variation between cortical sulci. The overall cortical GI and average global cortical grey matter thickness (CGM) were used as adjustment variables for the mean depth and grey matter thickness measures, respectively. For each subject, we subtracted the CGM from the mean grey matter thickness (GMT) for each sulcus, thereby adjusting the GM thickness for each sulcus for the overall grey matter thickness of the brain (AGMT). Adjusted mean depth (AMD) was computed by dividing the sulcus mean depth by the mean overall GI for each subject. Thus, each subject's sulcus measurement was adjusted for individual cortical variability using their own global brain measurements. To compare the adjusted sulci measures, we used a mixed-model analysis of covariance (ANCOVA) with sulcus as the repeated measure because the same variable (AGMT or AMD) was measured more than once (for 11 sulci) for each subject. Sex (male, female) and rearing history (MR, NR) served as between group factors. Age was the covariate. Alpha was set to $p < 0.05$ and any post-hoc tests were conducted using Tukey's Honestly Significant Difference test.

Results

Global Cortical Measures

The MANCOVA on GI and mean grey and white matter volumes revealed a significant main effect for rearing $F(3, 85) = 5.743, p = 0.002$. Subsequent univariate F -tests revealed that mother-reared (MR) chimpanzees have significantly higher mean white matter volumes $F(1, 87) = 7.785, p = 0.007$ than nursery-reared (NR) chimpanzees (see Table 1). The covariate age was also significant $F(3, 85) = 2.947, p < 0.04$. The univariate F -tests revealed significant associations between age and mean grey matter volume $F(1, 87) = 4.085, p < 0.05$ as well as the GI score $F(1, 87) = 7.71, p < 0.008$. Increasing age was negatively associated with both mean grey matter volume and GI scores. We would emphasize that comparing ages between NR and MR male and female chimpanzees revealed no significant differences. Thus, age was correlated with the mean grey matter and GI scores but this appeared to be consistent between the different sex and rearing groups. The ANCOVA on the WMGM ratio revealed similar results with MR chimpanzees having significantly higher ratios than NR individuals $F(1, 87) = 14.910, p < 0.001$ (see Table 1). Age was also a

significant covariate $F(1, 87) = 6.789, p < 0.02$. In this case, increasing age was associated with higher WG ratio scores. No sex differences were revealed in any of these analyses.

Sulci Measures

Grey Matter Thickness—For adjusted sulcus grey matter thickness (AGMT), the mixed-model ANCOVA revealed a significant main effect for sex $F(1, 88) = 4.83, p < 0.04$ with females ($Mean = 0.838$ mm, $SE = 0.046$) having thicker grey matter than males ($Mean = 0.669$ mm, $SE = 0.061$). Further, there was a significant two-way interaction between sulcus and rearing history $F(10, 880) = 2.32, p < 0.02$. For the rearing by sulcus interaction, post-hoc analysis indicated that NR chimpanzees had significantly larger AGMT values than MR chimpanzees for the CS, SPC, PCI, IPCS and SPCS sulci (see Figure 3). Finally, a two-way interaction was found between sulcus and the covariate age $F(10, 880) = 2.04, p < 0.03$. Subsequent Pearson Product Moment correlations revealed a significant negative association between age and adjusted GM thickness for PCI (see Table 2).

Mean Depth—As with the grey matter thickness, we conducted a mixed-model ANCOVA with sulci as the repeated measure while sex and rearing history were the between group factors. Age again served as a covariate. The ANCOVA revealed a significant two-way interaction between rearing history and sulcus $F(10, 870) = 2.799, p < 0.003$. The mean adjusted sulcus depth (AMD) for MR and NR chimpanzees are shown in Figure 4. Post-hoc analysis indicated that MR chimpanzees had larger AMD for the CS, PCI, FO, IPS, SF and STS sulci compared to the NR apes. No significant differences were found between the MR and NR chimpanzees for the remaining sulci. As was the case for the grey matter thickness data, we also found a significant two-way interaction between sulci and the covariate age $F(10, 870) = 5.300, p < 0.001$. Subsequent bivariate correlations revealed significant positive associations between age and the AMD for the CS, PCI, SF, and STS sulci (see Table 2).

Associations between white-grey matter ratio, sulcal grey matter thickness and mean depth

We calculated partial correlation coefficients between the WMGM ratio measurement and the adjusted grey matter thickness (AGMT) for each sulcus to assess whether these variables were correlated with each other. Because the previous analyses showed that age was associated with both WMGM ratio and at least some of the grey matter thickness and mean depth measures, we statistically controlled for age in these correlation analyses. Significant negative associations were found between WMGM ratio and AGMT for the CS and SPC (Table 3). Borderline significant associations were found between WMGM and AGMT for the IPCS and SPCS. For all 4 associations, higher ratios values in WMGM were associated with thinner sulcus AGMT. In contrast, significant positive correlations were found between WMGM ratio and adjusted mean sulcus depth (AMD) for all of the sulci with the exception of IFS and IPCS (Table 3).

We also performed partial correlations between the AMD and AGMT scores for each sulcus. Significant negative associations were found between these two variables for CS ($r = -0.390, p < 0.001$), STS ($r = -0.275, p < 0.009$), PCI ($r = -0.256, p < 0.02$), SPC ($r = -0.391, p < 0.001$), IFS ($r = -0.311, p < 0.004$), and SPS ($r = -0.437, p < 0.001$). Thus, in all cases, increased cortical folding depth values were associated with lower AGMT values.

Analysis of Residual Grey Matter Thickness

Specific sulci that differ between MR and NR chimpanzees were not consistent between the two measures analyzed. Because variation in AGMT and AMD values were negatively correlated for a number of sulci, we performed one more analysis in order to examine

whether MR and NR chimpanzees differed in AGMT scores after adjusting for individual differences in sulcus mean depth. For this analysis, we regressed the AMD value on the AGMT score for all subjects on each of the 11 sulci. We then saved the unstandardized residual values from the regression analysis, which reflected the degree to which a subject had higher or lower AGMT values than would be predicted for given that subject's adjusted mean depth value. As before, we performed an ANCOVA with sulcus as the repeated measure while sex and rearing history were between group factors, while age was the covariate. As before, a significant two-way interaction was found between sulcus and rearing history $F(10, 870) = 2.86, p < 0.003$ and between sex and rearing history $F(1, 87) = 4.36, p < 0.04$. For the interaction between sulcus and rearing history, post-hoc analysis indicated that NR chimpanzees had higher residual AGMT scores for the CS, SPC, IPCS and SPCS compared to MR individuals (see Figure 5). For the sex by rearing interaction there was no significant difference between MR ($Mean = -.069$) and NR ($Mean = -.104$) males, but for females, MR individuals ($Mean = -.082$) had significantly lower values than NR ($Mean = .183$).

Discussion

The findings reported here provide the first evidence of significant long-term effects of different early rearing experiences on chimpanzee cortical organization. Specifically, our results demonstrate that MR chimpanzees had higher ratios in white-to-grey matter, deeper cortical folds and thinner grey matter compared to NR chimpanzees. We further found that age was positively associated with increased sulcus depth and negatively associated grey matter thickness for a number of sulci. Moreover, when statistically controlling for age, mean sulcus depth was negatively associated with grey matter thickness such that subjects with greater sulcus depth had thinner grey matter within the fold. Finally, when statistically controlling for individual differences in mean sulcus depth, MR chimpanzees had thinner grey matter within the folds compared to the NR subjects. In general, the results supported the majority of our initial hypotheses.

The differences in grey matter thickness, mean sulcus depth, and WMGM ratio reported here between MR and NR chimpanzees likely reflect common ontogenetic processes underlying cortical development. Specifically, it has been suggested that as brain size increases during development, it is largely attributable to the expansion of white matter and connections between locally and distantly connected functional networks (Durst et al., 2001). As the brain expands outward, the outer surface area (grey matter) has to spread out. Assuming a finite volume of grey matter within a given brain, the thickness of the cortex has to thin in order to accommodate the expanding surface area (Seldon, 2005). Alternatively, Van Essen (Van Essen, 1997) has hypothesized that cortical folding or increased gyrification is linked to the formation of strong connections between adjacent cortical regions. Increased connectivity creates a torque or gravitational force that results in the surface of the cortex folding inward and hereby forming the cortical folds. Thus, increasing white matter would reflect increasing connectivity between adjacent functional regions, which results in localized changes in cortical folding.

For grey matter thickness and mean sulcus depth, the differences between MR and NR chimpanzees were sulci specific and not entirely consistent between the two measures. For the AGMT measure, the primary regions that differed between MR and NR chimpanzees were sulci used to define the premotor and primary motor (CS, SPC, PCI) and somatosensory (IPCS, SPCS) cortex. In contrast, for the depth of cortical folding, the sulci that differed between MR and NR apes were CS, PCI, FO, IPS, SF and STS. The results were much more specific when comparing the grey matter thickness values after adjusting for the depth of the sulcus (see Figure 5). In this case, differences between NR and MR

chimpanzees were found for the CS, SPC, IPCS and SPCS, respectively. In short, the differences between NR and MR chimpanzees were largely found for sulci that are landmarks for the definition of primary and secondary motor and somatosensory cortex. Thus, these brain regions appear to be most influenced by early social rearing experiences in chimpanzees.

Mechanisms of rearing effects on brain development

Brain development can be influenced by a number of factors in an infant's environment (De Bellis, 2005) and we offer two possible mechanisms for our findings including: (1) limited attachment and sensorimotor experience or (2) nutritional factors. The majority of studies reporting deleterious consequences of differential rearing in infancy have centered on alterations in pathways involved in stress response. Thus, one explanation for the findings reported here is that with the disruption in the development of species-typical mother infant bonding in NR chimpanzees, stress is induced that alters the course of normal cortical development. Similar mechanisms have been posited to explain differences in cortical volumes of specific regions of interest in humans, monkeys and rodents and this is the most parsimonious explanation for the results reported here (Chugani et al., 2001; De Bellis et al., 1999; Kaufman & Charney, 2001; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Increased stress concurrently results in increased levels of glucocorticoids (e.g. cortisol), or stress hormones, which can have adverse effects on the developing brain (Gunnar & Barr, 1998; Gunnar, Morison, Chisholm, & Schuder, 2001; Gunnar & Quevedo, 2007). For example, maltreated children that have post-traumatic stress disorder exhibit smaller intracranial and cerebral volumes than matched controls (De Bellis et al., 1999). Our data indicates an impact in the primary and secondary motor and somatosensory cortex, which somewhat coincides with previous research suggesting stress-sensitive areas of the human brain (Teicher et al., 2003). Unfortunately, one limitation is that we do not have any data reflecting postnatal stress levels in the MR and NR chimpanzees in this study, so we cannot validate with stress hormones or other measures that the NR chimpanzees experienced more stress than the MR individuals early in their lives.

The second possible mechanism at work entails nutritional differences between the two groups. As noted above, during the first few years of life in both chimpanzees and humans the brain grows rapidly due to white matter expansion, which is the result of myelination of axons (Durstun et al., 2001; Leigh, 2004). Myelin contains large amounts of lipids (70% of dry weight), in which 25% of the lipid content is cholesterol (Morell & Jurevics, 1996) and cholesterol availability is essential to myelination during brain development (Saher et al., 2005). Breast milk in both humans and chimpanzees contains significant quantities of cholesterol while commercially available infant formulas contain very little or none (Davis et al., 1994; Hinde & Milligan, 2011; Uauy, Mize, & Castillo-Duran, 2000). Studies in humans have demonstrated that breast-fed infants have higher cholesterol than formula-fed infants (Harit, Faridi, Aggarwal, & Sharma, 2007; Saher et al., 2005) and that human infants who receive their mother's milk also have larger white matter volumes (Anderson, Johnstone, & Remley, 1999; Isaacs et al., 2010) and higher cognitive scores (Anderson et al., 1999) than formula-fed infants. Further, it has been hypothesized that fatty acid supplementation with docosahexaenoic acid (DHA) in infant diets enhances motor skills and learning ability in mice and nonhuman primates (Carrié, Guesnet, Bourre, & Francès, 2000; Champoux et al., 2002). The use of DHA supplement in humans has similarly been associated with better attention skills and benefits in neurodevelopment (Brenna, 2011; Jensen et al., 2010).

Though we do not know the specific chemical composition of the formula provided to the NR chimpanzees in this study, fatty acid supplemented commercial infant formula was not readily available before the 1990's. In addition, to assess whether these potential early

nutritional factors were evident in the NR and MR chimpanzees, we retrospectively went back through the animal records at the YNPRC and UTMDACC and determined the circulating cholesterol levels during development of NR and MR chimpanzees. Cholesterol levels are one of the standard biological measures assayed from blood collected from the chimpanzees at their annual physical examination. These data are stored in the records and we were able to access data on mean cholesterol levels for the NR and MR chimpanzees at years one ($n = 39$, 17 MR and 22 NR), two ($n = 42$, 19 MR and 23 NR), and three ($n = 47$, 23 MR and 24 NR) of life are shown in Table 4. Separate ANOVA's on the cholesterol data for years one $F(1, 38) = 7.024$, $p < 0.02$, two $F(1, 41) = 6.758$, $p < 0.02$ and three $F(1, 46) = 9.08$, $p < 0.005$ revealed significant rearing differences with NR chimpanzees having lower values than MR chimpanzees. Therefore, NR chimpanzees in this study had lower cholesterol levels within the first 3 years of life. As a result, the lower white matter volumes of these chimpanzees may possibly reflect limited amounts of fatty acids in the formula they received versus what is typically provided in breast milk. Using the cholesterol levels as a covariate on our ANCOVA analysis of the WMGM ratio did not change the results we found between the rearing cohorts, year one $F(1, 38) = 9.774$, $p < 0.005$, year two $F(1, 41) = 8.971$, $p < 0.006$, and year three $F(1, 46) = 9.355$, $p < 0.005$. Thus, the nutritional aspect on infant brain development is presumably compounded by other various factors, such as genetics or environmental factors. For example, a genetic variant in the gene *FADS2* in humans has been demonstrated as an influencing factor in fatty acid pathways for breastfed children and their IQ scores (Caspi et al., 2007). Thus, several factors could be working together, but the evidence suggests rearing history influences neurodevelopment.

Though we lack strong documentation on every subject's experiences throughout their lifetime, we do know that all subjects would have received relatively uniform social and cognitive experiences following federal guidelines for social housing, diet, and enrichment. NR chimpanzees were integrated into larger social groups with adults after age three, which was similar to the social groups MR subjects lived in. Thus, there was little variation between the rearing groups in relation to social interaction (excluding mother interaction) and cognitive stimulation. Inferences on how these confounds may have contributed to brain development would be limited, but should not be discounted completely.

Behavioral and Functional Consequences

This study focused solely on cortical organization but the implications from these findings are that rearing experiences could have long-term consequences for behavioral and cognitive functions in chimpanzees. We know from several studies performed in the early 1970s that social deprivation can have deleterious effects on learning abilities and cognition in chimpanzees (Davenport & Rogers, 1970; Davenport et al., 1973; Menzel et al., 1970; Morimura & Mori, 2010). For example, Davenport and colleagues (1973) tested a social group of 14 chimpanzees who were reared in two different conditions. The six subjects with restricted rearing were isolated in enclosed cribs for the first two years of life, while the other eight individuals were born in the wild and lived with their mother for the first year of life. The study tested the chimpanzees around age 13 on a learning task referred to as the transfer index described by Rumbaugh (1970). Wild-born animals performed significantly better on the transfer index task than the chimpanzees raised in the restricted condition.

Of course, the type of rearing experiences of the chimpanzees raised by Davenport and colleagues in the 1960-70s and the NR chimpanzees in this study were quite different. As a result of these early studies that identified the social and environmental conditions that would promote better animal welfare, laboratory chimpanzees, including those in this study, were reared with peers not in isolation and had significant daily contact with adult human caregivers early in life. These chimpanzees also lived in physical environments that were

larger and more complex, with a range of enrichment designed to encourage species-typical behavior. Indeed, in two recent studies examining social and physical cognition in many of the same chimpanzees used in this study, no significant differences were found in performance between NR and MR chimpanzees (Lyn, Russell, & Hopkins, 2010; Russell, Lyn, Schaeffer, & Hopkins, 2011); however, it should be noted that enculturated chimpanzees in these two studies out-performed both 'normal' NR and MR chimpanzees on these tasks. Enculturated chimpanzees were those apes raised by humans in complex socio-communicative environments (Russell et al., 2005) and none of these apes were included in this study. Nonetheless, this type of enculturation typically has a facilitative effect on cognitive performance, particularly for social cognition. Based on the results reported here, it raises the possibility that enculturated apes may show an even different pattern of cortical organization than either NR or MR chimpanzees raised in standard captive settings such as laboratories and zoos.

It is also of note that the most consistent differences found between MR and NR chimpanzees were in the primary and secondary motor and somatosensory cortex, brains regions less likely involved in some of the higher order cognitive tasks previously described. Based on the anatomical data reported here, it seems more likely that behavioral differences might be evident for motor and sensory tasks, such as tool use or grasping skills.

It might be argued that the potential rearing differences reported here might be attributable to inherent genetic differences between the offspring born to females who rejected their offspring and those who raised them. In this scenario, presumably there would be less genetic variability within either the NR or MR chimpanzees. We do not think this is likely because the subjects in the analyses were from 70 different females, including 39 different mothers with offspring in the MR cohort and 42 separate mothers with offspring in the NR group (11 mothers had offspring in both cohorts). Though the NR and MR offspring within each group were not completely heterogeneous, the degree of genetic diversity was comparable between them.

Conclusion

In conclusion, the first few years of a chimpanzee's life are important for cortical development and our data suggest early rearing experiences have long-term consequences on the development of cortical organization. The functional consequences of these changes in cortical organization remain unclear but should be investigated in future studies, perhaps with a focus on socio-emotional behavior or motor and somatosensory tasks. Further, specific regions of the brain appear more susceptible to early rearing environments and future research should perhaps focus on region of interest analyses rather than focusing on cortical sulci, as was the case in this study. Additional studies will contribute to our understanding of the role of early social rearing experiences in the development of mental health and psychological well-being, in human and nonhuman primates. Finally, the results of this study underscore the importance of explicitly considering early rearing influences when examining the wide range of biobehavioral processes that show significant individual differences.

Acknowledgments

This research was supported by NIH grants MH-84980, NS-42867, NS-73134, HD-56232 and HD-60563 and Cooperative Agreement RR-15090. American Psychological Association and Institute of Medicine guidelines for the treatment of animals were followed during all aspects of this study. We would like to thank Yerkes National Primate Research Center and the University of Texas MD Anderson Cancer Center and their respective veterinary and care staffs for assistance in MR imaging. Michelle Haddad, Anna J. Hall, and Ruth Reveal of Agnes Scott College assisted in MRI processing of chimpanzee brains.

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Figure 1.

BrainVISA's pipeline processing steps a) MR image of a skull-stripped chimpanzee brain, b) stable tissue intensities creating bias field, c) binary mask of the brain, d) split mask of left and right hemispheres and cerebellum, e) grey and white interface, f) a negative mould of the white matter, g) skeletonised mould of cortical folding, h) cortical fold graph of chimpanzee sulci manually labelled. Sulci: red = central, light green = superior precentral, orange = fronto-orbital, yellow = precentral inferior, light purple = inferior frontal, dark blue = sylvian fissure, dark pink = superior temporal, light blue = inferior postcentral, dark purple = superior postcentral, dark green = intraparietal, and brown = superior parietal.

Figure 2.

The central sulcus is extracted to demonstrate sulcus measures computed. a) Mean depth is the calculated average of the depth measures along the entire length of the sulcus. b) The grey matter thickness (yellow arrows) is quantified by measuring the mean distance between the pial surface and the grey/white interface (blue) around of the buried sulcus (red).

Figure 3.

Rearing history results for adjusted sulcus grey matter thickness (AGMT) (mm $\pm$ s.e.) in mother- (MR) and nursery- (NR) reared chimpanzees. Sulci: CS = central, SPC = superior precentral, IFS = inferior frontal, PCI = precentral inferior, FO = fronto-orbital, SF = sylvian fissure, STS = superior temporal, SPCS = superior postcentral, IPCS = inferior postcentral, IPS = intraparietal, SPS = superior parietal sulcus. * indicates sulci that differed at $p < 0.05$ between NR and MR chimpanzees.

Figure 4.

Rearing history results for adjusted sulcus depth (AMD) (mm $\pm$ s.e.) in mother (MR) and nursery (NR) reared chimpanzees. Sulci: CS = central, SPC = superior precentral, IFS = inferior frontal, PCI = precentral inferior, FO = fronto-orbital, SF = sylvian fissure, STS = superior temporal, SPCS = superior postcentral, IPCS = inferior postcentral, IPS = intraparietal, SPS = superior parietal sulcus. * indicates sulci that differed at $p < 0.05$ between NR and MR chimpanzees.

Figure 5.

Rearing history results for mean AGMT residual scores (AGMT) (mm $\pm$ s.e.) in mother (MR) and nursery (NR) reared chimpanzees. Sulci: CS = central, SPC = superior precentral, IFS = inferior frontal, PCI = precentral inferior, FO = fronto-orbital, SF = sylvian fissure, STS = superior temporal, SPCS = superior postcentral, IPCS = inferior postcentral, IPS = intraparietal, SPS = superior parietal sulcus. * indicates sulci that differed at $p < 0.05$ between NR and MR chimpanzees.

Table 1

Means ($\pm$ standard errors) for grey and white matter volume (mm^3), white-to-grey matter ratio and gyrification index in mother- and nursery-reared chimpanzees ($n = 92$).

Measure	Mother-Reared	Nursery-Reared
Grey Matter Volume	67541.40 (± 1718.26)	72558.17 (± 2529.44)
White Matter Volume	76050.59 (± 1441.90)	69915.57 (± 1516.27) **
WMGM Ratio	1.15 (± 0.034)	1.00 (± 0.029) **
GI	1.07 (± 0.015)	1.09 (± 0.021)

** indicates significant difference with $p < 0.01$

Table 2

Correlation coefficients between age and adjusted grey matter thickness (AGMT) and adjusted mean depth (AMD) for each sulcus.

Sulcus	AGMT	AMD
CS	−0.191 ⁺	+0.234 [*]
SPC	−0.194 ⁺	+0.196 ⁺
IFS	−0.131	+0.085
PCI	−0.239 [*]	+0.281 [*]
FO	−0.110	−0.032
SF	+0.028	+0.431 ^{**}
STS	−0.119	+0.241 ^{**}
IPCS	−0.126	+0.150
SPCS	−0.061	+0.136
IP	−0.096	+0.104
SPS	−0.115	+0.098

^{**}
 $p < 0.01$

^{*}
 $p < 0.05$

⁺
 $p < 0.10$

Table 3

Partial correlation coefficients between global cortical white-to-grey matter ratio (WMGM) and the adjusted grey matter thickness (AGMT) and adjusted mean depth (AMD) values of each sulcus.

Sulcus	AGMT	AMD
CS	−0.289 **	+0.304 **
SPC	−0.252 *	+0.295 **
IFS	−0.108	+0.117
PCI	−0.120	+0.349 **
FO	−0.035	+0.337 **
SF	+0.024	+0.458 **
STS	−0.140	+0.312 **
IPCS	−0.193 +	+0.005
SPCS	−0.202 +	+0.233 *
IP	−0.136	+0.265 *
SPS	−0.082	+0.246 *

**
 $p < 0.01$

*
 $p < 0.05$

+
 $p < 0.10$

Table 4

Mean cholesterol levels (mg/dL) during the first three years of life ($\pm$ standard errors) in a subsample of mother- and nursery-reared chimpanzees (n = 39, 42, and 47, respectively).

	Year One	Year Two	Year Three
Mother-Reared	256.18 (± 9.65)	262.37 (± 12.16)	261.57 (± 10.84)
Nursery-Reared	222.14 (± 8.48)	219.65 (± 11.05)	215.88 (± 10.61)