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A quantitative measure of myelination development in infants, using MR images

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Abstract

The objective of this study was to measure myelination of frontal lobe changes in infants and young children. Twenty-four cases of infants and children (age range 12–121 months) were evaluated by a quantitative assessment of T2-weighted MR image features. Reliable quantitative changes between white and gray matter correlated with developmental age in a group of children with no neurological findings. Myelination appears to be an increasing exponential function with the greatest rate of change occurring over the first 3 years of life. The quantitative changes observed were in accordance with previous qualitative judgments of myelination development. Children with periventricular leukomalacia (PVL) showed delays in achieving levels of myelination when compared to normal children and adjusted for chronological age. The quantitative measure of myelination development may prove to be useful in assessing the stages of development and helpful in the quantitative descriptions of white matter disorders such as PVL.

Keywords

Pediatric brain; White matter disease; MRI; Myelination

Introduction

The relations between brain development and behavior in human infants and young children are of interest to developmental psychologists. For example, there are changes in brain development that relate to the acquisition of perceptual and cognitive processes [1,2]. Also of interest are developmental issues: how are the changes in myelination in the developing brain related to changes in social, emotional, and cognitive domains? Many of the changes in behavior, including social and emotional behavior, have been quantified; therefore, it would be useful to have a quantified measure of brain development to compare to the measures of behavior. A method of assessing developmental brain change is to assess the changing levels of myelination.

One approach to assessing myelination is to view the stained samples of brain tissue from specimens. Histologic studies of myelination of the forebrain have found no myelinated fibers before the seventh fetal month [3]. In the telencephalic division of the forebrain, myelinated fibers first appear in the white matter of the cerebral hemispheres in the tenth fetal month. In the supralimbic zone of the forebrain, which comprises the white matter of the cortical layers,

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the myelination of the subcortical white matter is synchronized with the myelination of cortical projections from the dorsolateral and posterior nuclei of thalamus.

Myelination of the long association fibers of white matter of the supralimbic zone continues through the first decade [3]. There are wide differences between brain areas in the time intervals between the onset and maturation of myelination [4]. For example, at age 40 post-conception weeks, 75% of infants evidence myelin in the posterior limb compared to 11% showing myelin in the lateral cerebellar white matter. The time interval between 7 months and 15 months postnatal is critical for the maturation of myelin in the posterior frontoparieto-occipital central white matter [4]. Subcortical association fibers complete the process of myelination in early adulthood [4]. Examination of the pathways in the temporal lobe in children ages 2 months to 3 years postnatal revealed differences between control cases and clinical cases including severe and prolonged perinatal pathology [5]. All clinical cases showed retardation of the myelination process by 2–20 months relative to the control group.

Another method of assessing stages of myelination is by magnetic resonance imaging [6]. Changes in MRI features are informative in determining the developmental changes in white and gray matter for normal and clinical cases [7,8]. Findings from qualitative studies show that myelination occurs earliest in the posterior fossa at 3 months postnatal, with well-defined white matter tracts including the corpus callosum appearing by the end of the first year, and continues development through adulthood [9,10,11,12,13,14,15,16,17]. In the first year after birth, water content of the brain decreases and white matter increases in myelin content. Generally, on T1-weighted images, an adult aspect of myelination appears by month 12, and on T2-weighted images, by age 24 months. Recent MR studies indicated that children 36–40 months show adult-like patterns [17]. In general, myelination proceeds in the posterior-to-anterior, inferior-to-superior, and central-to-peripheral directions [11,15].

Although the MR images are based on quantitative measures of anatomical tissue, myelination has been assessed by the qualitative judgments of experts. A more accurate measure of the changes in myelination that accompany increases in development is needed, one that relies less on qualitative judgments and more on a quantitative measure. Such attempts have been made looking at myelination [18,19]. Quantitative analyses of white matter myelination in the visual pathways were performed using MRI, and a positive relation was found between age and myelination development in the proximal optic radiation and the distal optic radiation [18]. However, for asphyxiated infants, the qualitative judgment was more predictive of neurodevelopmental outcome than was the quantitative assessment [19]. A relation between the quantitative assessments of frontal watershed injury with the 12-month mental developmental index was found. Çoskun et al. [19] suggested that accurate assessment of prefrontal regions might predict abnormalities in higher cortical functioning.

Overall, there are reliable findings of quantitative measures of gray–white differentiation and age, brain injury, and prediction of later cognitive functioning. The purpose of this paper is to report findings on the developmental changes in infants and young children, using a quantitative measure of myelination of the frontal lobe.

Method

Patients

The images from the first five children representing a wide age range (ages 12 months, 26 months, 44 months, 49 months, and 121 months) allowed us to examine changes in myelination over the first 10 years of life. The images from a second group of 19 children were assessed in order to examine individual differences in myelination within a restricted age range of 15–33 months. All subjects were referred to rule out neurological involvement. The first five cases

and 15 of the next 19 cases had no MR findings, while four cases had periventricular leukomalacia (PVL).

The institutional review board approved the protocol; parents gave written consent to review the MR images. Patients were treated in accordance with the ethical standards of the American Psychological Association, and the study was performed in accordance with the ethics standards indicated in the Declaration of Helsinki [20].

MR imaging

MR imaging was performed using a 1.5 T system (General Electric, Milwaukee, Wisconsin) with a standard head coil. T1-weighted and T2-weighted images were obtained for clinical review. The images used for quantitative analysis were the T2-weighted axial images with the following parameters: 20 cm FOV, 256·192 matrix, 4 mm thick slice with 1 mm skip, 2 NEX, TE 82–96 ms, TR 3,500–4,000 ms, echo train length of 12, 24 locations.

T2-weighted images were selected for several reasons. T2-weighted images provided information on degrees of myelination [10,16], and yielded more reliable graded judgments of myelin [13]. It is generally agreed that T1-weighted images are more useful in the first 6–8 months of age to image myelin, and T2-weighted images are more useful after 6 months of age [9,21].

Measurement technique

Details concerning the quantitative measurement and its mathematical derivation are available [22], and a brief description follows. The technique involves first, selecting axial sections and regions of interest, second, generating histograms of pixel intensities from corpus callosum (CC), gray matter, and white matter, and third, computing a measure of divergence between pairs of histograms in order to quantify the degree of myelination.

Selection of images and regions of interest

Five slices (atlas levels 2, 3, 6, 6_7, and 7_8, [23]) imaging frontal lobes were used to assess the degree of myelination in the frontal lobes. Gray matter and white matter were assessed in the frontal and parasagittal areas evident on the five levels. We selected the frontal areas for quantification of myelination due to the association of these brain structures with the development of psychological competencies in the second year of life, such as language acquisition and self-awareness [24]. The three MR slices that included the corpus callosum were the anterior forceps and body (level 6) and the genu (atlas levels 6_7 and 7_8).

Axial sections were divided into four main regions, defined as “left” and “right” by a vertical line through the interhemispheric fissure, and as “anterior” and “posterior” by a horizontal line immediately anterior to the ventricles. Rectangular regions of interest (ROI) enclosing approximately 200 pixels were located to lie wholly within selected brain regions. Two white matter regions immediately rostral to the horizontal line and on either side of the vertical line were selected, and two gray matter regions on either side of the image were selected rostral to the horizontal line and near the vertical line. For slices visualizing the CC, an ROI within the CC was analyzed. An example of a section from a case of a 10-year-old is shown in Fig. 1, with the horizontal and vertical reference lines and with five rectangles defining ROIs for CC, white, and gray matter superimposed on the anatomical image.

Generating histograms

After selection of the ROIs, histograms of pixel intensities were generated with pixel intensity on the *x*-axis and frequency counts on the *y*-axis.

Computing a measure of divergence

The divergence index is a measure of the separation of the pixel distributions between the pairs of histograms, such that a low divergence index indicates that the two histograms are similar in value, while a large divergence index indicates that the two histograms are widely separated. We expected small divergence values between a histogram representing the corpus callosum and a histogram representing white matter, and large divergence values between pairs of histograms representing the corpus callosum and gray matter. In this study, the divergence values between white and gray matter are direct measures of the degree of myelination of white matter. We expected the divergence index for white–gray differentiation to increase with developmental change. The quantitative measures of divergence were calculated between pairs of histograms. The theoretical lower limit of the divergence index is zero when two histograms have identical distributions, while the maximum theoretical value was calculated to be 1,420. The divergence index was calculated for pairs of histograms and then converted to a percentage scale, using the value of 1,420 to represent 100% divergence. Image noise does not influence the calculation of the divergence index. We assume that image noise is similar for gray matter and white matter. Since the divergence index is a measure of the differences in the distribution of signal intensities between gray matter and white matter, image noise does not confound the measure.

Results

Fig. 2 shows how divergence of white and gray matter increases as a function of age from 12–121 months. Curve fitting suggests an always-increasing non-linear fit ($p<0.01$) that indicates an exponential function. A two-way analysis of variance on the divergence values for white and gray matter in the first group of five children showed reliable effects for the factors of age, F (4, 25)=7.42, $p<0.001$, and atlas level, F (4, 25)=23.24, $p<0.001$. Post-hoc tests (Tukey LSD, $p<0.05$) indicated that atlas level 2 (M=32%) had significantly lower divergence values than atlas level 3 (M=77%), atlas level 6 (M=85%), atlas level 6_7 (M=80%), and atlas level 7_8 (M=89%). The interaction of age and atlas level was not significant.

Comparisons of the CC with gray matter yield similar findings, with reliable effects for age, F (4, 15)=5.72, $p<0.005$, atlas level, F (2, 15)=11.042, $p<0.001$, and their interaction, F (8, 15) =2.61, $p<0.06$. Post-hoc testing revealed that CC–gray matter divergence at atlas level 7_8 was the same at 12 months (M=99.9%) as at 121 months (M=97.6%). However, CC–gray matter divergence at atlas level 6 markedly changed from age 12 months (M=67%) to age 121 months (M=99.3%).

A two-way analysis of variance on the divergence values for CC and white matter showed reliable effects for the factors of age, F (4, 15)=6.86, $p<0.005$, and atlas level, F (2, 15)=60.80, $p<0.001$. Post-hoc tests (Tukey LSD) were employed to isolate the differences. Divergence for CC–white matter remained fairly stable over age range 12 months (M=46%) to 49 months (M=43%), with a significant decrease ($p<0.01$) by age 121 months (M=22%). Comparisons of atlas levels showed a significant decrease ($p<0.001$) in divergence for CC–white matter from atlas level 7_8 (75%), to level 6_7 (41%), to level 6 (14%). The interaction of age and atlas level was not significant.

Using the second group of 15 children who had no MR findings, the divergence values between white and gray matter were assessed for differences with age and atlas level, using a two-way analysis of variance. Even in the restricted ages (15–33 months), there was a significant age effect, F (8, 101)=4.15, $p<0.001$. Post-hoc regression analyses indicated increases in divergence by age ($p<0.05$). As was found with the first group of five children, there were clear differences in divergence for atlas level, F (4, 101)=17.25, $p<0.001$. Post-hoc analyses (Tukey LSD, $p<0.05$) found lowest values of divergence for atlas level 2 (M=41%), which were

significantly lower than all other atlas levels. Divergence at atlas level 3 (*M*=56%) was significantly lower than at atlas level 6 (*M*=81%), level 6_7 (*M*=73%), and level 7_8 (*M*=79%), which did not differ from one another. There was no significant interaction between the factors of age and atlas level. Finally, the divergence values for the 15 participants in this restricted age group fall within the values expected from the results of the first group of participants with a larger age range.

Given that the quantitative measure showed reliable changes with age in white–gray divergence in the frontal lobes of children without MR abnormalities, we wanted to know whether this measurement procedure would differentiate between patients with and without PVL. To answer this question, four patients who had PVL (*M*=24.8 months of age) were compared to the group of 15 normal children (*M*=22.0 months) for white–gray divergence values. To control for divergence differences due to age, a two-way analysis of covariance was applied to the divergence values for the factors of diagnostic group (PVL vs normal) and atlas level, with age as a covariate. Clear differences were found between groups, F (1, 171)=4.44, $p<0.05$, with lower divergence values for the PVL group (*M*=58%, 95% confidence interval (CI)=50–66%) compared with the normal group (*M*=68%, 95% CI=64–72%). The factor of atlas level over both groups was significant, F (4, 171)=11.02, $p<0.001$. Post-hoc tests (Tukey LSD, $p<0.05$) revealed that divergence at atlas level 2 (*M*=38%) was lower than at all other levels, and divergence at atlas level 3 (*M*=54%) was lower than at levels 6 (*M*=77%), 6_7 (*M*=75%), and 7_8 (*M*=71%), which did not differ from one another. The interaction of diagnostic group and atlas level was not significant. While controlling for the effects of age on divergence, it was found that the patients with PVL had less differentiation between white and gray matter than did typically developing patients.

Discussion

There are three main findings from this study. The first finding is that quantification of myelination development is possible using a measure that reflects changes in white matter and gray matter with age. We believe that this will relate to developmental changes in behavior, including social and emotional behavior.

Complementing this finding, our quantitative measures of MR signal differences are in agreement with the judgments of the stages of myelination relying on qualitative classifications by experts [9,10,11,12,13,14,15]. The divergence of white and gray matter is most rapid in the first 3 years of development, a finding that fits well with the qualitative judgments in previous studies. Divergence values decreased in the direction from inferior to superior regions of the frontal lobe, indicating decreased levels of myelination, which is in agreement with previous findings [11,15]. Of interest is the finding that there are myelination differences between the cases with PVL and cases with no neurological findings. As expected, the divergence values between white matter and the corpus callosum remained constant across age, which is in agreement with other studies. An understanding of the development of myelination aids in the determination of markers or signs of developmental delays or developmental disabilities, such as white matter disease [25].

Generalizability of the technique is restricted to cases of at least 12 months of age. It is well-known that the developmental changes in water content of the brain affect the MR signal and that most water content of the brain reduces in the first year [12,21]. The T1 values decrease steadily during the first year for white and gray matter, with no changes after age 1 year [26]. Histologic studies of the brains of infants less than 12 months of age found that the increase in white matter intensity on T1-weighted images is explained by water decrease in the brain, not by myelination [15]. The present study examined cases of infants with a minimum age of

12 months; therefore, the application of the measure to cases at least 12 months of age would be reliable.

Our third major finding is the difference in myelination measures between PVL cases and normal cases. It may be that the quantitative continuous measure is more sensitive than qualitative classification to subtle changes in white–gray differentiation. The quantitative measure may be useful in MR imaging studies that compare preterm and full-term infants for myelination patterns and dimensions of brain structures [13] and in the quantitative descriptions of white matter disorders such as PVL. The emergence of social function may be related to changes in myelination as measured by our quantitative assessment of MR image content. Current research needs to investigate the relations between the divergence values and measures of the onset of self-recognition, including the use of personal pronouns and pretend play [27].

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References

1. Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. Biol Psychol 2000;54:241–257. [PubMed: 11035225]
2. de Hann M, Thomas KM. Applications of ERP and fMRI techniques to developmental science. Developmental Science 2002;5:335–343.
3. Yakovlev PI, Lecours A (1967) The myelogenetic cycles of regional maturation of the brain. In: Minkowski A (ed) Regional development of the brain in early life. Blackwell, Oxford, pp 3–70
4. Kinney HC, Brody BA, Kloman AS, Gilles F. Sequence of central nervous system myelination in human infancy. J Neuropathol Exp Neurol 1988;47:217–234. [PubMed: 3367155]
5. Dambska M, Laure-Kamionowska M. Myelination as a parameter of normal and retarded brain maturation. Brain Dev 1990;12:214–220. [PubMed: 2360700]
6. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 2000;21:1099–1109. [PubMed: 10871022]
7. Barkovich AJ (2000) Pediatric neuroimaging, 3rd edn. Lippincott, Philadelphia
8. Barkovich AJ. Magnetic resonance imaging: role in the understanding of cerebral malformations. Brain Dev 2002;24:2–12. [PubMed: 11751019]
9. Barkovich AJ, Kjos BO, Jackson DE Jr, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 1988;166:173–180. [PubMed: 3336675]
10. Bird CR, Hedberg M, Drayer BP, et al. MR assessment of myelination in infants and children: usefulness of marker sites. AJNR Am J Neuroradiol 1989;10:731–740. [PubMed: 2505502]
11. Dietrich RB, Bradley WG, Zaragoza EJ 4th, et al. MR evaluation of early myelination patterns in normal and developmentally delayed infants. AJR Am J Roentgenol 1988;150:889–896. [PubMed: 2450448]
12. Holland BA, Haas DK, Norman D, et al. MRI of normal brain maturation. AJNR Am J Neuroradiol 1986;7:201–208. [PubMed: 3082150]
13. Konishi Y, Hayakawa K, Kuriyama M, et al. Developmental features of the brain in preterm and fullterm infants on MR imaging. Early Hum Dev 1993;34:155–162. [PubMed: 8275876]
14. Martin E, Kikinis R, Zuerrer M, et al. Developmental stages of human brain: an MR study. J Comput Assist Tomogr 1988;12:917–922. [PubMed: 3183125]
15. McArdle CB, Richardson CJ, Nicholas DA, et al. Developmental features of the neonatal brain: MR imaging. Part 1. Gray-white matter differentiation and myelination. Radiology 1987;162:223–229. [PubMed: 3786767]
16. van der Knaap MS, Valk J, Bakker CJ, et al. Myelination as an expression of the functional maturity of the brain. Dev Med Child Neurol 1991;33:849–857. [PubMed: 1743407]

17. Parazzini C, Baldoli C, Scotti G, Triulzi F. Terminal zones of myelination: MR evaluation of children aged 20–40 months. AJNR Am J Neuroradiol 2002;23:1669–1673. [PubMed: 12427621]

18. Yamada H, Sadato N, Konishi Y, et al. A milestone for normal development of the infantile brain detected by functional MRI. Neurology 2000;55:218–223. [PubMed: 10908895]

19. Çoskun A, Lequin M, Segal M, Vigneron DB, Ferriero DM, Barkovich AJ. Quantitative analysis of MR images in asphyxiated neonates: correlation with neurodevelopmental outcome. AJNR Am J Neuroradiol 2001;22:400–405. [PubMed: 11156790]

20. World Medical Organization. Declaration of Helsinki. BMJ 1996;313(7070):1448–1449.

21. Counsell SJ, Rutherford MA. Magnetic resonance imaging of the newborn brain. Current Paediatrics 2002;12:401–413.

22. Boddie-Willis AS (2001) Myelination of the frontal lobe in children with and without brain pathologies. Thesis, Rutgers University, New Brunswick, NJ, USA

23. Talairach J, Tournoux P (1988) Coplanar stereotaxic atlas of the human brain. Thieme, New York

24. Hershkowitz N. Neurological basis of behavioral development in infancy. Brain Dev 2000;22:411–416. [PubMed: 11102724]

25. Fuerst KB, Rourke BP (1995) White matter physiology and pathology. In: Rourke BP (ed) Syndrome of nonverbal learning disabilities: Neurodevelopmental manifestations. Guilford Press, New York, pp 27–44

26. Baierl P, Forster CH, Fendel H, et al. Magnetic resonance imaging of normal and pathological white matter maturation. Pediatr Radiol 1988;18:183–189. [PubMed: 3368242]

27. Lewis M, Ramsey D (1999) Intentions, consciousness, and pretend play. In: Zelazo PD, Astington JW, Olson DR (eds) Developing theories of intention: Social understanding and self-control. Erlbaum, Mahwah, NJ, USA, pp 77–94

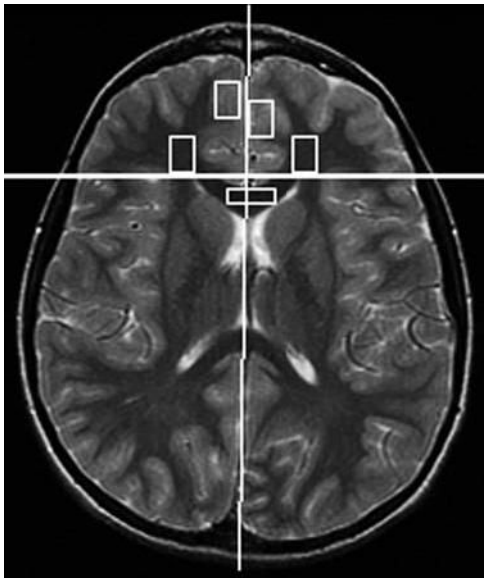

Fig. 1.
Example of T2-weighted MR axial image of a 10-year-old patient with *reference lines* and five regions of interest outlined by *rectangles*

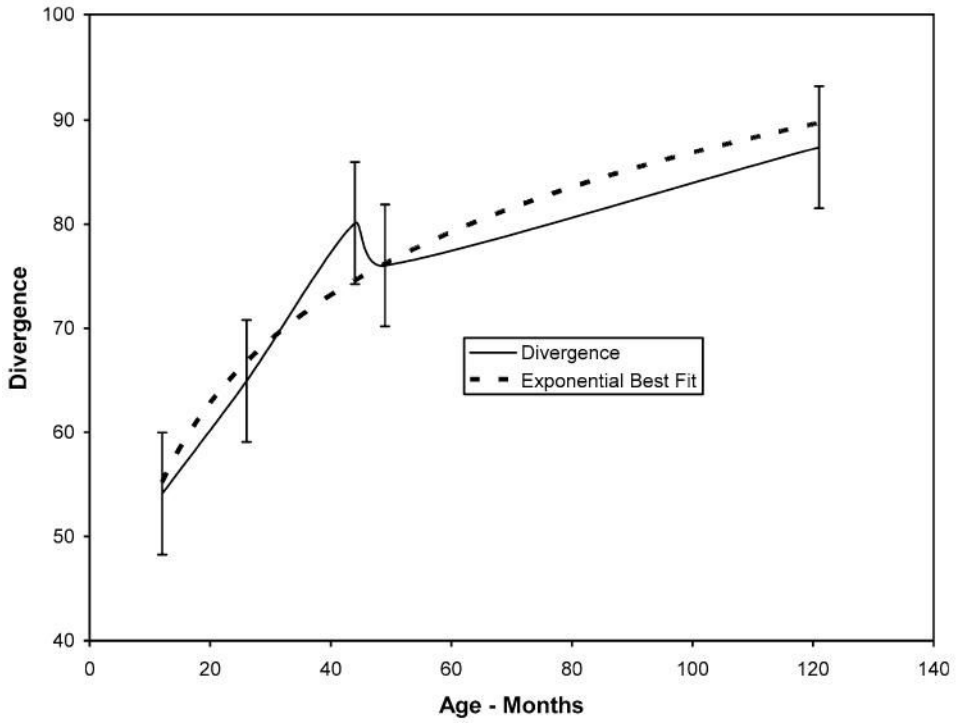

Fig. 2.
Age-related changes in white–gray matter divergence. *Error bars* indicate ±1 standard error