Age-related R2* Values Variation in Gray Matter from Birth to 5 Years Detected by Using an Atlas-based Analysis

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Target audience: MR physicians and pediatric neurologists.

Introduction Iron plays an important role in brain development and metabolism[1], so estimating the iron deposition may be important to assess the development and the neural diseases for infants and preschool children. The effective transverse relaxation rate (R2*) could reflect the iron deposition in the deep gray nuclei[2]. Our previous study showed R2* was a feasible parameter to estimate the iron content for infants[3]. However, this manual delineation method using one single slice may be subjective and less repeatable, which also doesn't base on the entire anatomical structure as volumetric measurement. Moreover, the age-related variation of the R2* in cerebral cortex was rarely known. In this study, we intend to extract the R2* values by using an atlas-based analysis; and to evaluate the age-related R2* changes and the potentiality for monitoring iron deposition in the cerebral cortex and deep gray nuclei after birth.

Methods 83 young children without abnormalities in brain MR images were enrolled in this study and examined with informed consent from parents according to local ethics procedures. They were divided into 6 groups (age: 3 days- 51months; group 1: 0-1m, 2: 6m-<1y, 3: 1y-<2y, 4: 2y-<3y, 5: 3y-<4y, 6: 4y-<5y). A 3D gradient-echo sequence of enhanced T2* weighted angiography (ESWAN) and a 3D-T1 FSPGR were employed using a 3.0T MR system (GE Signa HDxt). ESWAN: TR=51ms, number of echoes=6, TE=6~60ms, FA=20°, slice/gap=2mm/0mm, NEX=0.69, FOV=18×18cm^2, matrix=256×256; and 3D-T1:TR=10ms, TE=4.6ms, FA=15°, slice/gap=1mm/0mm, NEX=1, FOV=18×18cm^2, matrix=256×256. For each subject, we performed a fitting of the data acquired at the 6 TEs to obtain a monoexponential signal decay curve (i.e. $S(t)=S_0e^{-tR2^*}$, where S=measured data, S_0=multiplicative constant, t=echo time). Preprocessing of R2* data was corrected to T1 data for subsequent processing, and the procedure followed 4 steps by FMRIB's Software Library (FSL). Step 1, 3D-T1 templates were made for each group. The template of group 6 was made based on the adult MNI152_T1_1mm_brain template, and the template of the group 5 based on the group 6, and so on[4]. Step 2, the 3D-T1 map for each subject was registered to the templates of its group and to the next templates one by one. For example, the 3D-T1 data of one subject in group 1 should be registered to the template of group 2 firstly, then to the template in the order of group 3, 4, 5, 6 and the adult template finally (Fig 1). Step 3, The R2* data were unified to 3D-T1 and performed the final registration by the deformation matrix of T1, which should be finally registered to adult template step by step. Step 4, according to the adult atlas MNI-maxprob-thr25-1mm from FSL, R2* values were measured in the seven regions: the frontal, parietal, temporal and occipital cortex（FC, PC, TC and OC）, caudate nucleus (CN), lenticular nucleus (LN) and thalamus (THA) by Matlab (fig 2). For each subject, the curves were fitted by using the monoexponential model for R2* versus age described by Aquino D[2]. Furthermore, the correlation analysis was performed between the R2* values and the reference iron concentrations[5].

Results Firstly, we successfully measured the R2* values by using the atlas-based analysis. Secondly, the curves for R2* values versus age showed exponential increase with increasing age, and the R2* values increased with a different pattern in the selected gray matter (Fig.3). The regression equations were also shown in Table 1. Furthermore, the R2* values of various gray matter exhibited strongly positive correlations with the reference values of the iron concentrations (P<0.001) (Table 1).

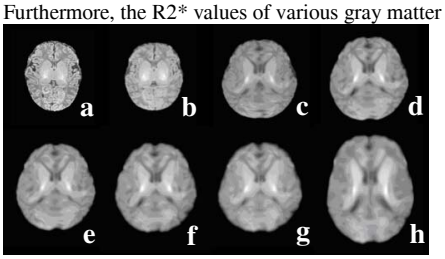

Fig 1 The 3D-T1 data for a 27-day-old neonate were registered to the templates step by step. a: 3D-T1 data; b: "a" registered to the template of group 1; c-g: "b" registered to the template of group 2, and so on. h: "g" registered to the adult template.

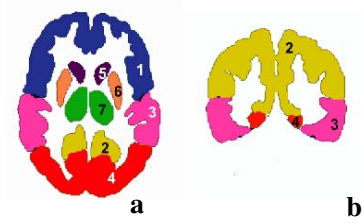

Fig 2 R2* values were measured in the seven regions. a: axial view; b: coronal view. 1: frontal cortex, 2: parietal cortex, 3: temporal cortex, 4: occipital cortex, 5: caudate nucleus, 6: lenticular nucleus, and 7: thalamus.

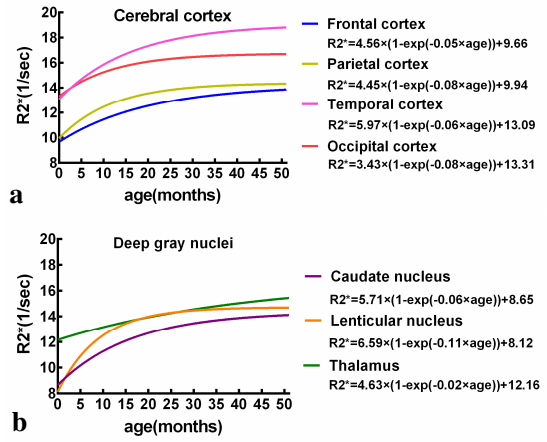

Fig 3 The monoexponential curves of regional R2* values fitting by the age (P<0.001). a: cerebral cortex; b: deep gray nuclei.

Discussion It is the first time that the R2* values are extracted by using an atlas-based analysis based on the 3D-T1 anatomical images in infants and preschool children. The results in the deep gray nuclei agreed with findings in previous studies in which regions of interest were manually delineated[3]. The exponential curves of R2* to age were fitting to the iron model from Hallgren and Sourander[5], and a strongly positive correlation between the R2* values and the iron concentrations was found, which reflected more fast deposition of iron especially in infants. Our results revealed that the gray matter presented fast different patterns of age-related iron deposition. In the cortex, the variation tendency of R2* values (OC>PC>FC) was due to the differences of iron content in those regions, which had been demonstrated in the adults[5]. As we known, in adults, the iron contents in the deep regions were much more than those in the cortex[5]. But in our study, the R2* values in the TC and OC were in a higher level, which maybe attributed to the more rapid maturation of cortex after birth[6]. Furthermore, R2* didn't present the absolute iron concentrations[7], which was also affected by other factors[2] including magnetic field inhomogeneities from tissue-tissue and air-tissue interfaces. Also, the orientation of penetrating cortical white matter fibers in cortex would affect estimates of monoexponential R2*[8]. In deep gray nuclei structures with largely isotropic structures, R2* didn't have an orientation dependence but retained a better linear dependence on iron concentration[8].

Regions	R	R^2	regression equation
FC	0.825	0.681	R2*=6.232+6.913×Iron
PC	0.777	0.603	R2*=7.560+5.787×Iron
TC	0.806	0.650	R2*=9.328+8.636×Iron
OC	0.676	0.457	R2*=11.461+3.726×Iron
CN	0.842	0.709	R2*=8.590+3.103×Iron

Table 1 R2* values vs. iron concentration calculated by equations in cerebral cortex and CN. Iron concentration (mg/100g fresh tissue). R is the correlation coefficient. R^2 is the regression coefficient.

Conclusion In infants and preschool children, the R2* values could reflect the age-related and spatial difference of the development of the gray matter, which likely presented the different iron deposition patterns. This atlas-based analysis may be a feasible method for R2* measurement in early brain development.

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