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Age distribution and iron dependency of the T2 relaxation time in the globus pallidus and putamen

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Summary. Heavily T2-weighted spin echo sequences of the brain show age-dependent low signal intensity in many extrapyramidal nuclei. Although it has been suggested that this low intensity results from non-haem iron, the specific influence of non-haem iron on the T2 relaxation time has not been quantified and remains controversial. The T2 relaxation times of the globus pallidus and putamen were measured from MRI at 1.5 T in 27 healthy patients, by using a mathematical model. They were then plotted as a function of age and compared to the curve of age-dependent iron concentration determined post mortem. The curves of T2 relaxation time in the basal ganglia are congruent with published curves of iron concentration, indicating a high probability that the changes in T2 relaxation times and the low signal in the basal ganglia result from the local, age-dependent iron deposition. Individual measurements of T2 relaxation time show less variation before than after 45 years of age, indicating the influence of a second, more individual factor.

Key words: Brain iron – Basal ganglia – Magnetic resonance imaging

Magnetic resonance imaging (MRI) provides some data on the change in the chemical composition of the central nervous system during life. Heavily T2-weighted spin echo sequences show substantial, age-dependent low intensity in two different groups of brain structures. The first, characterized by shortening of the T1 and the T2 relaxation times with age, includes myelinated pathways such as the anterior commissure, optic radiations, inferior and superior fronto-occipital fasciculi, the uncinate and longitudinal superior fasciculi, internal capsules, mammillo-thalamic tracts, brachium pontis and corpus callosum [1–3]. The shortening of the T1 and T2 relaxation time is caused by increasing myelination and simultaneously decreasing water content [2].

The second group, characterized by shortening of T2 but not of T1 relaxation times with age [4–8], consists of the nuclei of the extrapyramidal system such as the globus pallidus, substantia nigra, red nucleus, and putamen as well as the caudate, dentate and subthalamic nuclei.

At birth, no iron can be found in the brain. Autopsy studies have shown that iron begins to be deposited in the globus pallidus approximately 6 months after birth, in the zona reticulata of the substantia nigra between the 9th and 12th months and in the red nucleus after the 2nd year [6]. Anatomical and histological tests using the Perl iron stain to visualize the non-haem iron existing as haemosiderin and ferritin confirm that the zones of hypointensity within the extrapyramidal nuclei correspond to areas of high iron concentration [7]. These observations led to the belief that the low T2 values are caused by a high iron concentration.

Whether measured T2 values correlate with the concentration of iron in vivo remains controversial, because quantitative iron measures are only possible post mortem, and are difficult to obtain in all the age groups necessary. Some groups [5, 7] suggest that the T2 values are mainly determined by iron, because T2 relaxation times are not shortened in young patients with (presumed) low iron concentrations and are abnormally short in diseases such as Parkinson's disease, multiple sclerosis, Huntington's chorea, Alzheimer's disease, Hallervorden-Spatz disease, etc., in which iron deposition is known to be increased. Others find incomplete [8] or absent [9, 10] correlation between measured T2 values and iron concentration. They acknowledge a certain influence of iron on the T2 relaxation time, but accept it as a cause of hypointensity only in certain pathological conditions [8, 9]. Instead they suggest that the distribution, diffusion and metabolic characteristics of water are the main factors responsible for the T2 relaxation times under normal physiological conditions [9]. The relationship between iron concentration and T2 is complex, and is dependent on the absolute quantity of iron, its physical state, form, and microscopic distribution, among other factors. The percentage of the iron fraction which can be detected using MRI and the individual variations in the ground tissue produced by proteins and lipids are unknown. Therefore no statement about the

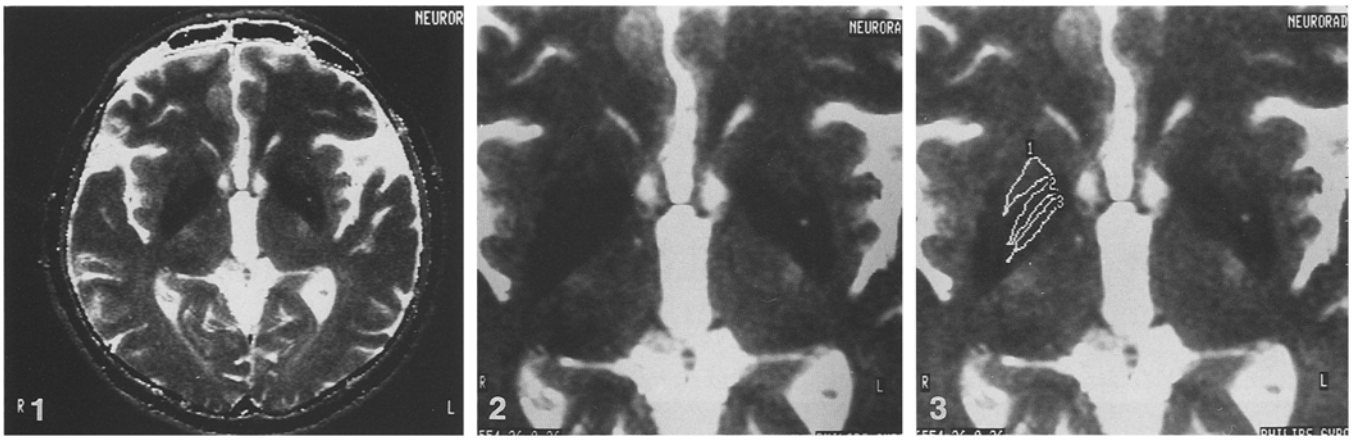


Fig. 1. T2 image 2 mm above and parallel to the intercommissural plane

Fig. 2. Same image as Fig. 1, magnified by a factor of 2

Fig. 3. Same image as Fig. 1, with ROI: *1*, putamen; *2*, lateral globus pallidus; *3*, medial globus pallidus

correlation of T2 relaxation time with iron concentration can be made with certainty [9].

Because the decrease in signal in the extrapyramidal nuclei is obviously age dependent and appears likely to result from the corresponding iron concentration, the authors undertook to establish an age-dependent curve of normal T2 values for the globus pallidus and putamen and to compare this to the curve of Hallgren and Sourander [11], who measured the iron concentration in these structures post mortem. Congruence of these curves would determine the validity of the contention that T2 relaxation times were determined by the iron concentration in the putamen and the globus pallidus.

Materials and methods

To establish the age-dependent curve of normal values, T2 relaxation times were measured in the globus pallidus and the putamen of both hemespheres of 27 patients (14 males, 13 females) selected from a consecutive series of routine MRI examinations. Criteria for inclusion into the study were: (1) no clinical evidence of basal ganglion disease or disease secondarily affecting the basal ganglia; (2) normal brain study on T1- and T2-weighted MRI. The youngest patient was 2 years, the oldest 74 years old. All studies were performed on a 1.5 T MR-unit. A single slice SE sequence was applied with TR 1500 ms; eight echos with TE: 20 ms, 40 ms, 60 ms, 80 ms, 100 ms, 120 ms, 140 ms and 160 ms; slice thickness 4 mm; field of view 200–220 mm and matrix 256 × 256.

The slice chosen was 2 mm above and parallel to the intercommissural line. T2 values were calculated by the MR-unit and visualized directly on a screen as an image, displaying the T2 values on a grey scale (Fig. 1), which was then magnified by a factor of 2.0 (Fig. 2). The putamen, lateral globus pallidus (lateral nucleus), and medial globus pallidus (medial nucleus) were identified by standard anatomic criteria using a statistical region of interest (ROI) program to measure T2 values (Fig. 3). Three measurements of the T2 relaxation times were made in each putamen, lateral and medial globus pallidus of each hemisphere; the three measurements were averaged.

Subsequently, the curve of age dependency of T2 values (Figs. 4a, 5a, 6a) was mathematically modelled and the constant of the exponential curve were calculated by a least square fitting procedure. The calculated curve was then compared with the empirical curve of Hallgren and Sourander (Figs. 4b, 5b, 6b).

Results

Medial globus pallidus (Fig. 4a)

The curve of T2 relaxation times versus age shows an exponential fall. T2 begins to decline from 93–97 ms during the 1st year of life, is reduced to 90% at 20 years, and reaches a saturation level of 63 ± 3 ms between 35 and 40 years. During the first half of life, individual variations are small, but after 45 years, the values distribute more widely around the saturation level.

Lateral globus pallidus (Fig. 5a)

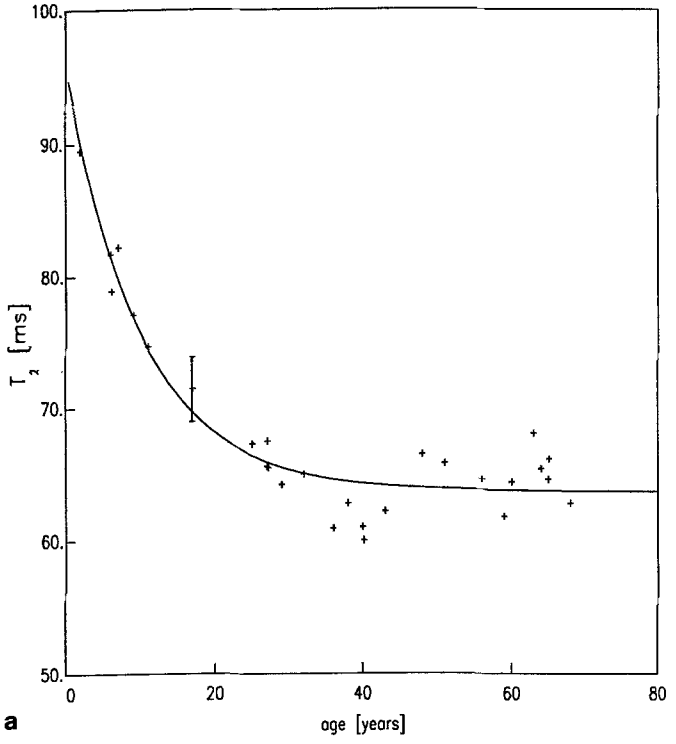
The curve shows a similar configuration, the only difference being that the T2 values are 2–4 ms lower than those of the medial globus pallidus and vary less. The lateral globus pallidus reaches a saturation level of 62 ± 3 ms. As in the medial globus pallidus, the T2 values vary only slightly during the first half of life and deviate more widely from the saturation level in the second half.

Putamen (Fig. 6a)

The curve of the T2 values shows a similar exponential fall, the values beginning to decline after birth from an initial value of 96–100 ms. The reduction in T2 of the putamen is obviously slower than in the globus pallidus, so that the curve is flatter. At the age of 50–60, a plateau of 75 ± 3 ms is reached. The variations in T2 are generally less pronounced after 45 years than in the globus pallidus.

The iron concentration curve of Hallgren and Sourander [11] compared to the T2 curves (Figs. 4b, 5b, 6b)

The reciprocal T2 values measured from MRI were fitted according to the method described by Hallgren and Sourander [11]. The result of this non-linear least squares



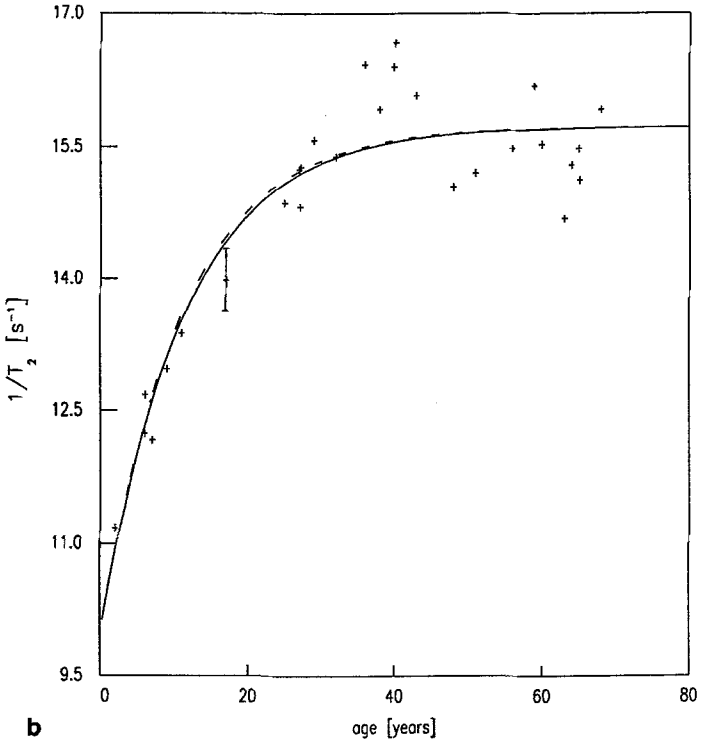


Fig. 4a, b. Medial globus pallidus. **a** Age-dependent curve of T2 values. **b** Reciprocal T2 curve *(continuous line)* compared to the iron concentration curve of Hallgren and Sourander [16] *(dotted line)*

approximation for the different structures studied is presented in Figs. 4b, 5b, and 6b as a dotted line.

The time constants B of the measured T2 values can be calculated using the following equation:

$1/T_2 = A(1 - \exp(-Bx)) + C$, where x = age in years.

The time constant B, calculated from the measured T2 values, plus the time constants of the iron concentration curve provided by Hallgren and Sourander [11], are shown in Table 1.

Discussion

Iron metabolism

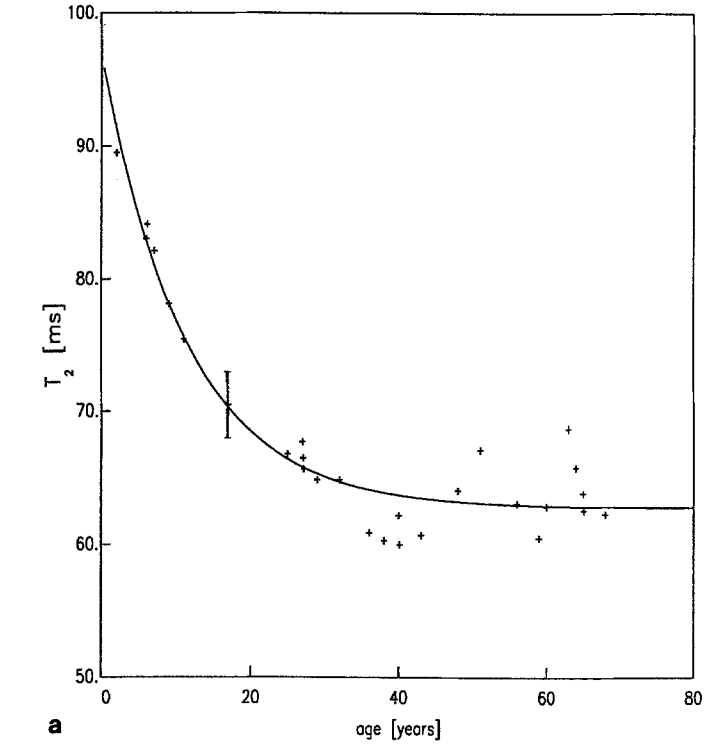
The amount of iron in the body is maintained mainly by variations in iron absorption, rather than by regulation of iron excretion. Iron is absorbed as Fe^{2+} in the upper part of the small intestine. Upon contact with blood, it is complexed by transferrin, which transports it to the cells, where it is partially deposited in protoporphyrin-IX and converted to haem iron. Excess iron, in the form of non-haem iron, forms complexes with haemosiderin, apoferritin and ferritin, and is called "storage iron". Ferritin is produced by intracellularly synthesized apoferritin, when micellar iron occupies the center of the protein complex.

Ferritin cannot penetrate the blood-brain barrier [7]. The mechanism by which iron accumulates in the central nervous system has not yet been completely explained. However, it is known that iron is resorbed by capillary endothelial cells in the thalamus and basal ganglia, after transferrin has been bound to a specific receptor at the cell surface. Only this transferrin-receptor complex can then be resorbed [6].

Iron is necessary for oxidative metabolism at each step of the electron-transport chain [7, 8, 12, 13]. However, the high iron concentration in the motor nuclei cannot be explained only by an increased respiratory consumption of oxygen (respiratory enzymes). Other regions with similarly high metabolic demands, such as the respiration centre, have a much lower iron content than the motor nuclei [12]. In addition, iron plays an important role in neurotransmitter metabolism [7]. Iron is also a cofactor for the monoamine-synthesizing and -degrading enzymes such as tyrosine-hydroxylase, tryptophan-hydroxylase and aldehyde-oxidase [7, 13]. Among other factors, it is responsible for maintaing the monoamine-oxidase level and for the function of serotonin and dopamine receptors [7]. It is also known that the regions with the highest iron resorption are not those with the highest iron deposition and consumption [7, 14]. It is therefore assumed that iron is resorbed by the dendrites and transported along the axons to the region of the cortical projections, where it is deposited in oligodendrocytes [7, 14]. If this iron transport pathway is interrupted by a defect in the axonal projection, abnormal iron accumulation can be found at the site of resorption in the basal ganglia [14].

Brain iron on MRI

Ferritin has a molecular weight of 480000 and is composed of a crystalloid ferricohydroxyde body with 4000 Fe^{3+} iron molecules in a high-spin state. The most common explanation for the low signal caused by iron on



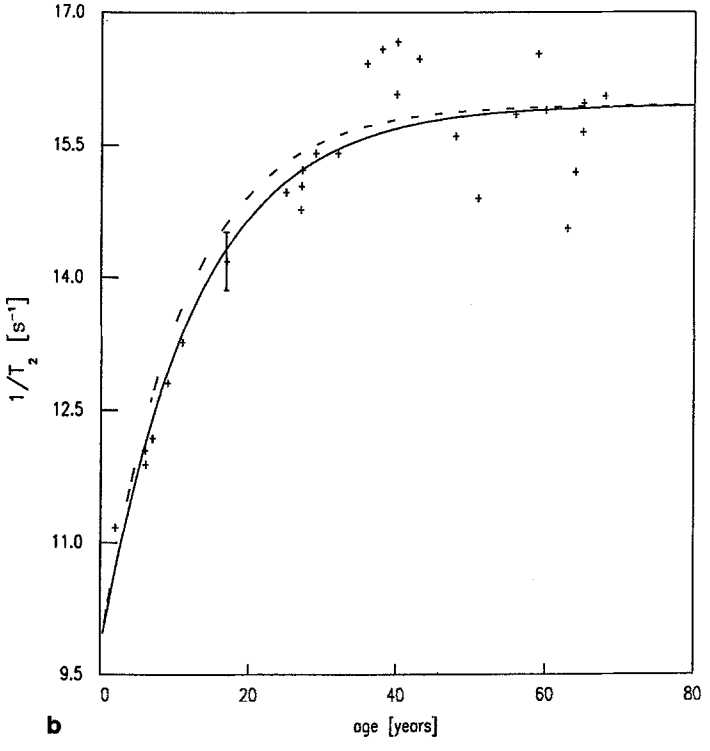
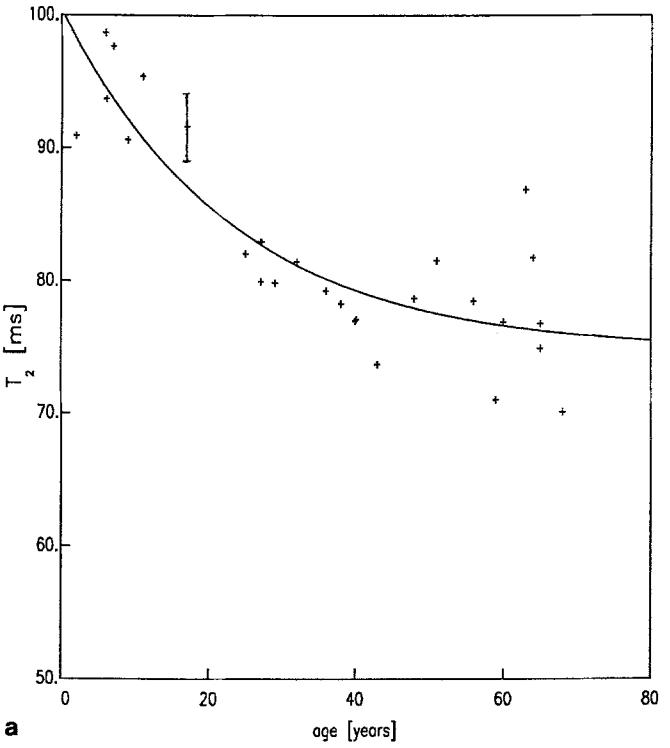


Fig. 5 a, b. Lateral globus pallidus. **a, b** as in Fig. 4



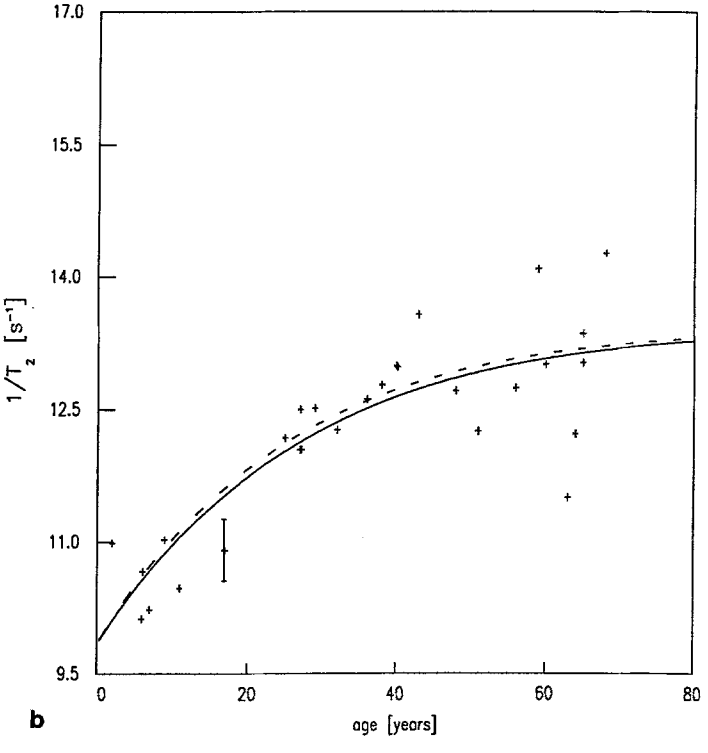


Fig. 6 a, b. Putamen. **a, b** as in Fig. 4

heavily T2-weighted MRI is paramagnetism. Protons in regions with high ferritin content are dephased by slow, random fluctuations producing magnetization of each ferritin body. This phenomenon leads to a local magnetic field gradient and inhomogeneities of the magnetic field. Water molecules, which diffuse into regions with high ferritin concentrations, therefore produce local statistical fluctuations (i.e. heterogeneities) in the magnetic field; this decreases the T2 relaxation time, without influencing T1. This effect is proportional to the square of the magnetic field and therefore becomes more obvious at higher field strengths [15]. However, a recent study has shown that there is no quadratic relationship between signal intensity and ferritin at different field strengths. Because

Table 1. Comparison of the time constants of the iron concentration curve and the reciprocal T2 values in different regions

Region	Time constant of Fe-concentration [11] [year^{-1}]	Time constant B of fit [year^{-1}]	χ^2 of the fit
Medial globus pallidus	0.09	0.087 ± 0.01	1.5
Lateral globus pallidus	0.09	0.079 ± 0.01	1.2
Putamen	0.04	0.038 ± 0.005	1.5

ferritin is known to be antiferromagnetic, a superparamagnetic mechanism for the low-signal intensities has been suggested [16].

In this study it was assumed that the changes in T2 values were produced by the non-haem iron only, and were therefore proportional to the reciprocal of the iron concentration. If this assumption is correct, the reciprocal T2 curves for the different structures and the curve of Hallgren and Sourander [11] should show the same age dependency, with identical rising constants. The fitted 1/T2 curves in the globus pallidus and putamen are indeed congruent with the curve published by Hallgren and Sourander [11] (Table 1). Corresponding to that curve of Hallgren and Sourander, the fitted curve of T2 values falls immediately after birth in the globus pallidus and reaches 90% of the saturation level at the age of about 20 years. Complete saturation, however, is only reached at the age of 50 [7, 11]. The slightly lower T2 values in the lateral than in the medial globus pallidus are probably due to the myelinated fibres of the anterior commissure passing through the former [2, 3]. In the putamen, the slope of the fitted curve of T2 values falls more slowly, and the curve becomes obviously flatter with age. The 1/T2 values, however, increase during life, as do the iron concentrations [11]. There is therefore a high probability that the changes in T2 values are caused only by changes in iron content; that means the hypointensity is caused by iron such that

$$T_{2[Fe]} = C*1/[Fe],$$

where C is a proportionality factor.

This is true up to the age of 45 years, below which the values deviate only slightly from the fitted 1/T2 curves. Above 45 years, however, the T2 values of the different structures begin to deviate more widely with greater individual variation, although the fitted curves are still congruent with the Hallgren and Sourander curve. These average deviations could be of a statistical nature, but, since the T2 values tend always to fall, a different, more individual factor must be present to influence them.

The relaxation time in a biological tissue is complex. It can be expressed as a sum of the reciprocal T2 values of the different contributing factors [16]:

$$\frac{1}{T_{2\,(tot)}} = \frac{1}{T_{1\,[Fe]}} + \frac{1}{T_{2\,(rest)}}$$

where T2 (tot) = measured T2, T2 (Fe) = T2 of iron and T2 (rest) = T2 of all other factors such as water, protein, etc.

Because the fitted curves are congruent with the curves of Hallgren and Sourander, T2 (rest) seems to be constant and is not believed to be responsible for changes of T2 (tot) values under normal conditions.

With increasing age, however, the T2 (rest) becomes more important due to higher individual variations of the tissues, reflecting structural changes in the basal ganglia, on the one hand, and saturation of the iron concentration [and therefore constant T2 (Fe)], on the other. The individual changes in T2 (rest) reflect the difference between "usual ageing" and "successful ageing", proposed by Rowe and Kahn [17]. People with typical age-related diseases such as cardiac insufficiency, arteriosclerosis, hypertension, adult-onset diabetes, decreasing renal function etc. are assumed to suffer from "usual ageing". In contrast, older people who do not suffer from these diseases show "successful ageing", and may have only a small change in T2 (rest) values; in these individuals changes in T2 (tot) are influenced mainly by iron concentration. For people with "usual ageing" the T2 (rest) becomes more important, so the scattering of measured T2 (tot) from the fitted curves is of greater relevance. It can be assumed that increased T2 values result from senile atrophy with enlarged Robin-Virchow spaces and/or microscopic lacunar infarcts and consequently higher water content in the brain. Microcalcification may also be responsible for decreased T2 values.

Drayer [18] puts the beginning of ventricular enlargement, which is a measure for atrophy, between the 5th and 7th decade. This also corresponds with the beginning of the rise of the T2 values. Arteriosclerotic changes of the parietal brain arteries are found in half of people more than 50 years old [18]. Jorgensen and Torvik [19] found 320 cases with ischaemic vascular disease in 994 consecutive autopsies, of which 124 showed no symptoms during life. With increasing age some people show evidence of inhomogeneity, such as hyperintense foci in the basal ganglia. Several groups have described small, highly hyperintense lesions in 30–80% of older people with no neurological problems; they were most frequent in the deep white matter of the frontal and parieto-occipital lobes and in the basal ganglia, especially the globus pallidus and putamen [18].

Because in the first half of life the fitted curves are congruent with those of Hallgren and Sourander it must be assumed from the mathematical formula discussed before, that T2 (rest) is nearly constant. Any increase in T2 values is due to a change of 1/T2 (rest) and is structurally determined. In contrast, a decrease in T2 is described by 1/T2 (Fe) and indicates increased iron deposition, reflecting malfunction on a metabolic level, or microcalcification.

Preliminary examinations of patients have shown that measurement of the T2 values can be a diagnostic aid, precisely because normal values show little deviation until the age of 45 years. Small abnormalities resulting from diseases such as multiple sclerosis, Parkinson's disease, vascular and inflammatory processes can easily be detected in the early stages. This is possible even if no pathological changes can be diagnosed visually on MRI.

Breger et al. [20] found small, reproducible deviations of T2 values, when measurements were repeated within a

short time. In long-term studies over 15 months, applying different examinations and using different software packages, they observed a considerable increase over time in the same patient. The reason for this may be that the relaxation times were measured with only four widely varying echos. Therefore, early as well as late falls in signal and the corresponding T2 values were inaccurate. The smaller deviation of the T1 relaxation times, determined using earlier echos lying close together, favours this explanation.

Until now, only qualitative determination of iron content was possible, but these qualitative assessments were subjective and poorly reproducible because they depended so heavily on image quality [21]. With the establishment of normative data and confirmation of the validity of age-dependent iron-T2 relaxation curves, it is now possible to determine iron content quantitatively or semiquantitatively, provided only that, for qualitative assessments, changes must reach a certain threshold to be detectable [5].

This study demonstrates that changes in signal intensity in the basal ganglia on T2-weighted MRI are very likely to be produced by iron, that the T2 values are reciprocally proportional to the iron concentration in the basal ganglia, and that potentially they can be used as a diagnostic aid, because of the very small deviations in normal values until the age of about 45 years. Of course, further investigations are needed to improve the accuracy of the normal curve, and establish more complete confidence levels.

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