

Reduced Signal Intensity on MR Images of Thalamus and Putamen in Multiple Sclerosis: Increased Iron Content?

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High-field-strength (1.5-T) MR imaging was used to evaluate 47 patients with definite multiple sclerosis and 42 neurologically normal control patients. Abnormal, multiple foci of increased signal intensity on T2-weighted images, most prominent in the periventricular white matter, were apparent in 43 of 47 MS patients and in two of 42 control patients. A previously undescribed finding of relatively decreased signal intensity most evident in the putamen and thalamus on T2-weighted images was seen in 25 of 42 MS patients and correlated with the degree of white-matter abnormality. In the normal control patients a prominently decreased signal intensity was noted in the globus pallidus, as compared with the putamen or thalamus, correlating closely with the distribution of ferric iron as determined in normal Perls'-stained autopsy brains. The decreased signal intensity (decreased T2) is due to ferritin, which causes local magnetic field inhomogeneities and is proportional to the square of the field strength. The decreased T2 in the thalamus and striatum in MS may be related to abnormally increased iron accumulation in these locales with the underlying mechanism remaining speculative.

MR imaging has become the primary imaging technique for the diagnosis of multiple sclerosis (MS) [1, 2]. The basic MR abnormality, an increase in signal intensity on a T2-weighted image, results from an increase in mobile protons from either edema, gliosis, or neutral sudanophilic lipid (cholesterol esters and triglycerides) accumulation [3]. Our studies with high-field-strength (1.5-T) MR suggest that additional functional information concerning MS may be derived by delineating an abnormally decreased signal intensity on T2-weighted images in the thalamus and putamen. This investigation analyzes the origin of this decreased T2 relaxation time and its detectability in relationship to disease severity.

Subjects and Methods

We studied 47 patients aged 23–57 years old (mean, 40) with a clinical diagnosis of definite MS as established with standard diagnostic criteria [4]. MR studies were compared with those of 42 neurologically normal control individuals aged 21–58 (mean, 38) studied for headache, vertigo, depression, or orbital or middle-ear disorders.

MR imaging was performed with a high-field-strength (1.5-T) superconducting GE Signa or prototype system. After obtaining a multislice T1-weighted partial-saturation (PS) pulse sequence in the sagittal plane with a 500-msec repetition time (TR) and a 25-msec echo time (TE) (PS 500/25), a multislice T2-weighted spin-echo (SE) sequence was obtained with TR 2000 or 2500 and TE 100 or 80 msec (SE 2500/80) in both axial and coronal projections. Intermediate-weighted SE sequences with TR 2000 or 2500 and TE 30 or 40 msec (SE 2500/40) were also routinely obtained simultaneously with the T2-weighted images (a multislice, multiecho pulse sequence). An image acquisition matrix of 128 × 256 was used with a slice thickness of 5 or 10 mm and a single signal average. The total imaging time for the entire brain with all pulse sequences was only 19 min 12 sec.

The images were analyzed for areas of abnormal signal intensity. MS lesions were defined as localized regions of abnormally increased signal intensity (increased T2 relaxation time) on T2-weighted images. A visual rating of lesion number and severity was made and the MS

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patients and normal controls were separated into four groups on the basis of degree of MR abnormality (normal, mild, moderate, severe). The T2-weighted images were also evaluated to compare the relatively decreased signal intensity (decreased T2) in the thalamus and putamen with that in the globus pallidus. A simple three-point visual rating scale was used to analyze the T2-weighted images at the basal ganglia-thalamic level, in which *normal* = decreased signal intensity in the globus pallidus more prominent than in the putamen and far more prominent than in the thalamus, *equivocal* = decreased signal intensity in the globus pallidus slightly more prominent than in the putamen and more prominent than in the thalamus, and *abnormal* = decreased signal intensity in the globus pallidus equal to or less prominent than that in the putamen and caudate and only minimally more prominent or equally prominent to that in the thalamus.

Perls' stain [5-7] was used in four normal autopsy brains (18, 21, 43, and 44 years old) to determine the normal topographic distribution of ferric iron in the brain. In addition, an autopsy brain from one individual with MS was analyzed. Each brain was fixed in 20% formalin for at least 1 week, and horizontal 1-cm-thick sections were cut with at least two sections through the basal ganglia and thalamus. The brain sections were washed in tap water for 15 min and rinsed with three changes of distilled water. The specimens were immersed in Perls' stain for ferric iron with intermittent agitation over 30 min. The Perls' staining solution was decanted and the specimens washed for 5 min in tap water before color and black-and-white photography.

An estimate of the T2 relaxation time was made with the multislice SE 2500/40-80 msec pulse sequence in 13 normal control patients 23-54 years old (mean, 39) and in 13 of the MS patients 23-54 years old (mean, 39). Computed T2 and pseudodensity values were derived as described by MacFall [8] by performing a weighted linear regression on the logarithms of the source signal values for each pixel. The negative reciprocal of the slope of the fitted line represented T2, while the exponential of the intercept at TE equal to zero represented the pseudodensity. Operator-selected, region-of-interest cursors containing 12 (3 × 4) pixels were placed in the globus pallidus, putamen, and thalamus bilaterally to determine mean T2 and SD.

Relationships between number and severity (normal, mild, moderate, severe) of white-matter lesions and signal intensity ratings (normal, equivocal, or abnormal) on SE 2500/80 images were evaluated using Kendall's tau-b statistic, which is a measure of the association between two ordinal measurements [9]. It takes on values between -1 and +1 and is interpreted in the same way as a correlation coefficient: tau-b > 0 implies a direct relationship between the two measures under study and tau-b < 0 implies an inverse relationship. The closer tau-b is to +1 or -1, the stronger the association. In testing the hypothesis that there is no increasing or decreasing relationship between lesion severity and T2 rating (tau-b = 0), significance probabilities (*p* values) were obtained according to the approximation of Brown and Benedetti [10]. The nonparametric Wilcoxon rank sum test was used to compare MS and control groups with respect to the distributions of estimated T2 relaxation times in the globus pallidus, putamen, and thalamus, as well as in terms of the globus pallidus/putamen and globus pallidus/thalamus T2 ratios.

Results

There was no significant abnormality in the 42 neurologically normal patients except for a few scattered discrete areas of increased signal intensity in the cerebral white matter in two individuals. High-signal-intensity abnormalities on the SE 2500/80 and SE 2500/40 images were apparent in the cerebral white matter with a periventricular predominance in 43 of 47 patients with definite MS. The degree of MR abnormality

was rated as normal in four, mild in 21, moderate in 17, and severe in five. No lesions were seen on the PS 500/25 images that were not delineated on the T2-weighted images. The number and extent of white-matter lesions were characterized equally well on axial and coronal SE images. The majority of white-matter lesions were periventricular in location with additional abnormalities in the more peripheral centrum semiovale, internal and external capsules, brainstem, and cerebellum. There was no association between patient age and the number and extent of MS lesions.

The visual analyses of the decreased-signal-intensity ratings for the globus pallidus, putamen, and thalamus and their relationship to the number and severity of high-signal-intensity lesions in the white matter are summarized in Table 1. A dominant decrease in signal intensity in the globus pallidus as compared with the putamen was noted in 40 of 42 control patients and as compared with the thalamus in all 42 control patients (Fig. 1). A relative prominence of decreased signal intensity in the thalamus as compared with the globus pallidus was differentiated on the SE 2500/80 images on visual inspection in moderate (10 of 17) and severe (five of five) MS as compared with patients with fewer (one of 21) or no (zero of four) white-matter lesions (Figs. 2 and 3). Abnormally decreased signal intensity in the putamen was also prominent in moderate (12 of 17) and severe (five of five) MS (Figs. 3 and 4) and was noted also with less extensive white-matter involvement (seven of 21).

The correlational measures of association (Kendall's tau-b) between lesion severity (number and extent of white-matter lesions) and T2 ratings were 0.609 + 0.067 using T2 ratings for the putamen vs globus pallidus comparison and 0.687 + 0.048 for the thalamus vs globus pallidus contrast. Since *p* <

TABLE 1: Putamen/Thalamic vs Globus Pallidus Signal-Intensity (T2) (SE 2500/80) Ratings in Multiple Sclerosis

Region: Signal Intensity	No. of Lesions				
	Normal Control	Normal MS	Mild MS	Moderate MS	Severe MS
Putamen:					
Normal	39	3	13	3	0
Equivocal	1	0	1	2	0
Abnormal	2	1	7	12	5
Total	42	4	21	17	5
Thalamus:					
Normal	42	4	18	4	0
Equivocal	0	0	2	3	0
Abnormal	0	0	1	10	5
Total	42	4	21	17	5

Note.—MS = multiple sclerosis. Signal-intensity rating scale: *normal*—decreased signal intensity (T2) in the globus pallidus was strikingly more apparent than in the putamen or thalamus; *equivocal*—decreased signal intensity in the globus pallidus was only slightly more apparent than in the putamen or thalamus; *abnormal*—decreased signal intensity in the globus pallidus was similar to that in the putamen and thalamus; that is, increased thalamic and putamen iron. The statistical measures of association between severity and T2 ratings with a Kendall tau-b statistical analysis were tau-b 0.609 (0.687), asymptomatic error 0.067 (0.048), and significance probability *p* < .0001 (*p* < .0001) for the putamen (thalamus).

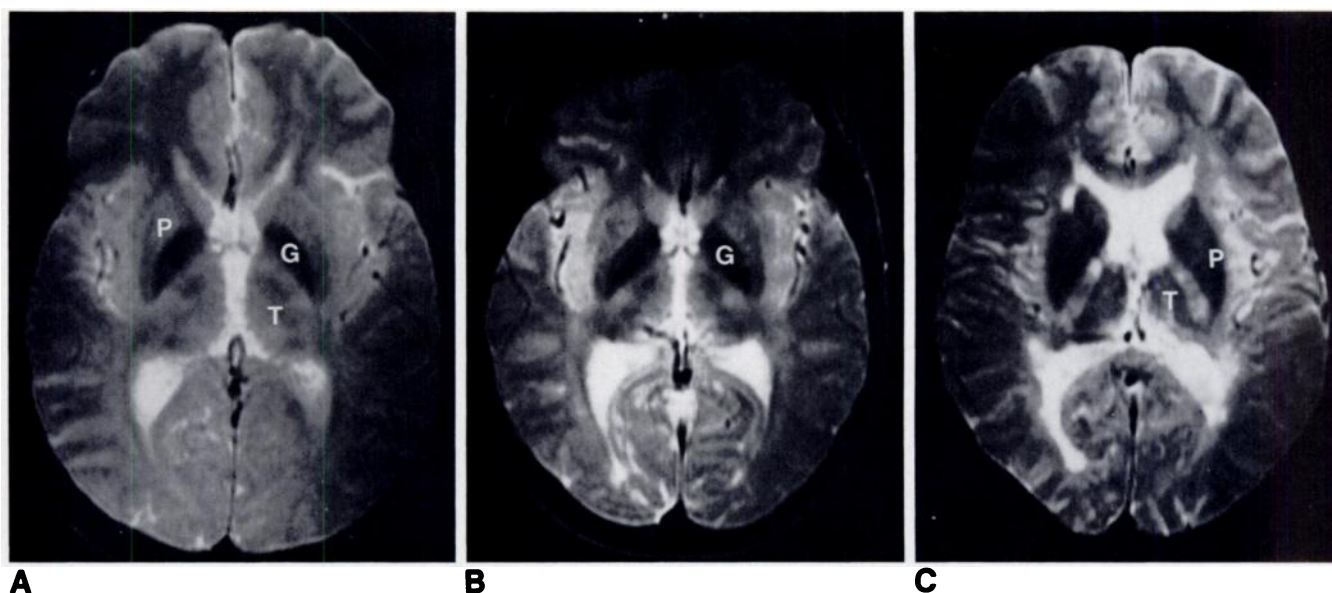


Fig. 1.—Normal, mild, and severe multiple sclerosis. SE 2000/100 msec (T2-weighted) axial MR images with 1.5-T MR unit.
A, Normal iron distribution—decreased signal intensity in globus pallidus (G) vs putamen (P) or thalamus (T)—in control patient (age 34).
B, Normal iron distribution in mild multiple sclerosis patient (age 32).
C, Abnormal decreased signal intensity (increased iron) as compared with normal in putamen and thalamus in 32-year-old patient with moderate multiple sclerosis.

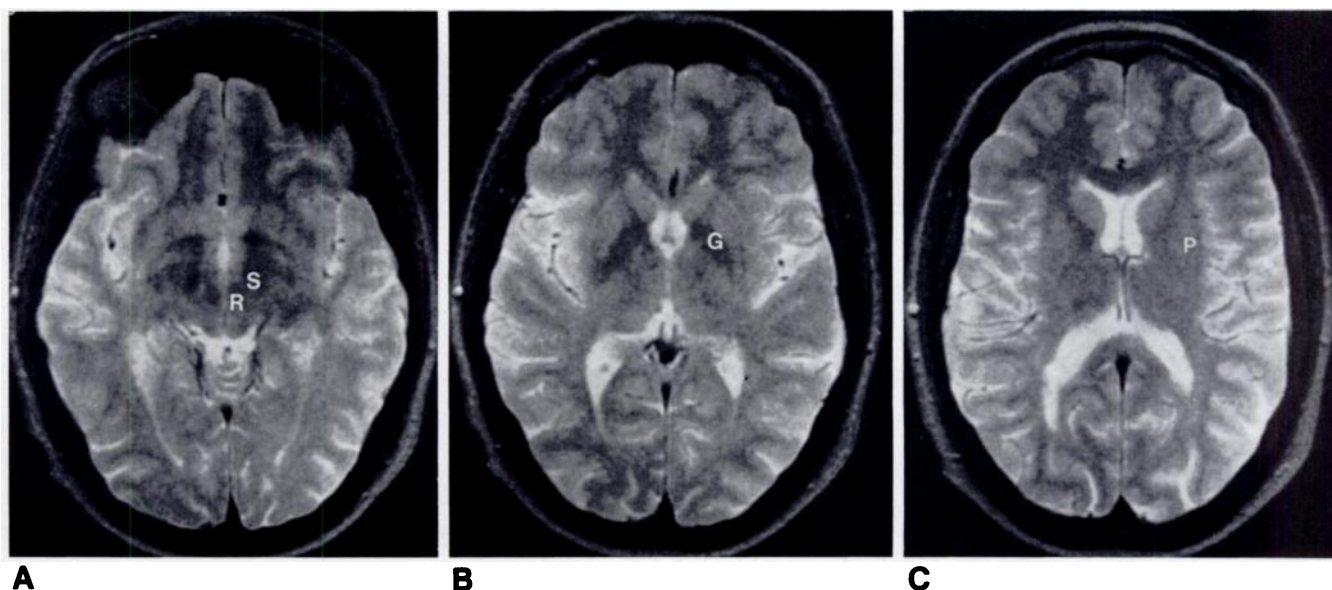


Fig. 2.—Mild multiple sclerosis (normal iron). SE 2500/80 msec (T2-weighted) axial MR images define normal distribution of decreased signal intensity in the red nucleus (R), substantia nigra (S), and globus pallidus (G) (age 35). P = putamen.

.0001 in both cases, these data provide very strong evidence of a positive association between lesion severity and T2 rating in both instances. There was no significant correlation with patient age or duration of disease.

Although the mean estimated T2 relaxation time in the thalamus was somewhat decreased in the MS group as

compared with normal controls (Table 2), no statistically significant differences between MS and control patients were found in the globus pallidus, the putamen, or the thalamus using the Wilcoxon test ($p > .10$). However, a significant elevation in the globus pallidus vs thalamus T2 ratio was found in the MS group relative to controls ($p < .05$). There

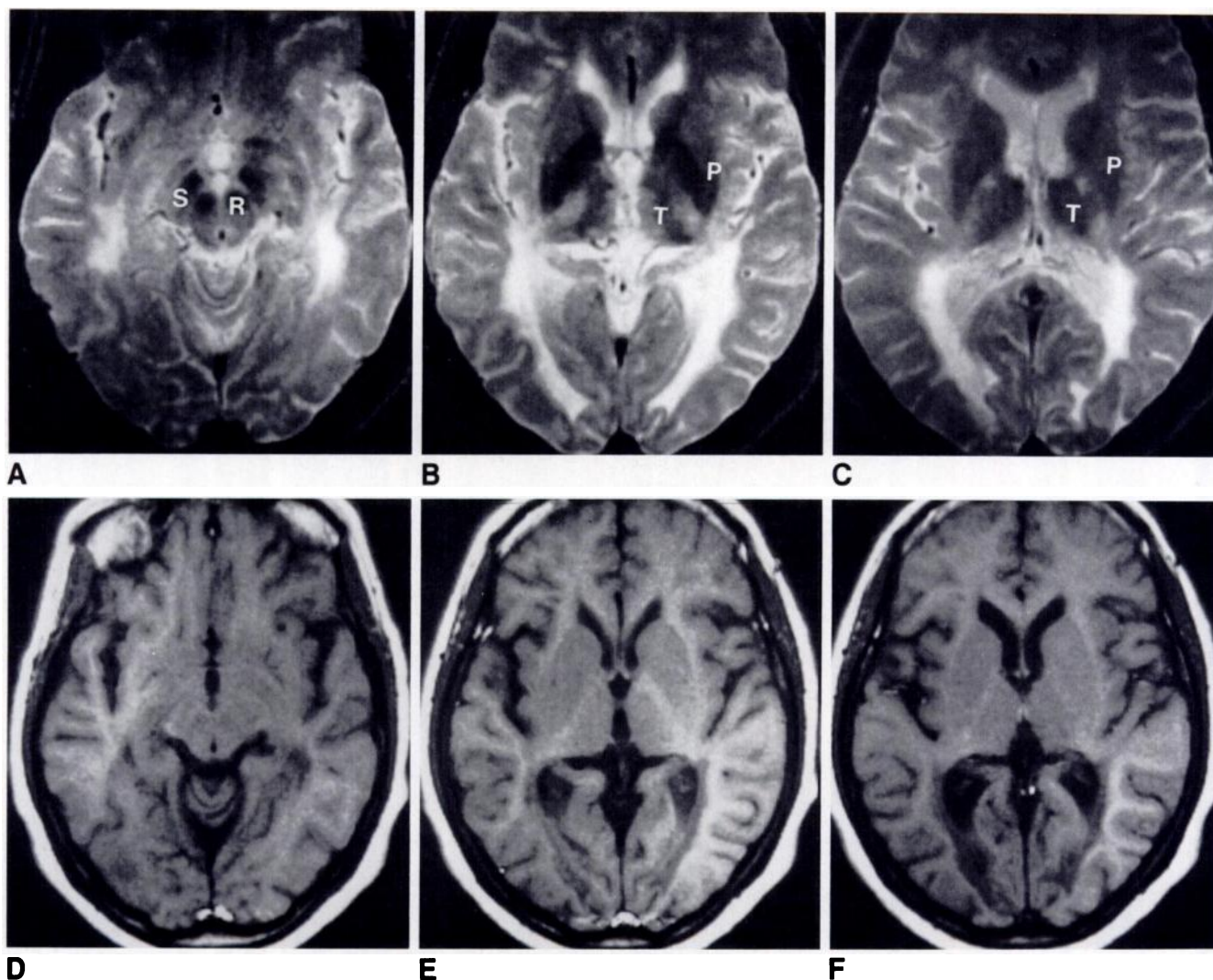


Fig. 3.—Moderate multiple sclerosis (abnormal iron).

A–C, SE 2500/80 msec (T2-weighted) images display abnormally decreased signal intensity in putamen (P) and thalamus (T) as compared with normal in 30-year-old patient. Decreased signal intensity in globus pallidus, red nucleus (R), and reticular substantia nigra (S) is prominent but within normal limits.

D–F, SE 500/25 msec (partial-saturation, T1-weighted) images at same levels show no evidence of abnormal signal intensity in basal ganglia structures.

was also some suggestion ($.05 < p < .10$) of an increase in the globus pallidus vs putamen T2 ratio for MS patients (Table 2). The T2 ratios were neither age nor gender dependent.

The intensity of blue staining in all four normal autopsy brains after Perls' staining for ferric iron correlated closely with the degree of decreased signal intensity seen in the 42 normal control brains using the SE 2500/80 (T2-weighted) pulse sequence. The most blueness (iron) was always noted in the globus pallidus with less blueness in the putamen and caudate and the least blue staining in the thalamus, cerebral cortex, and cerebral white matter (Fig. 5). The ferric iron distribution was increased in the putamen and thalamus as compared with the globus pallidus in the MS brain (Fig. 4).

Discussion

High-field-strength (1.5-T) MR imaging was abnormal (areas of increased signal intensity on T2-weighted images) in 43 (91%) of 47 patients with definite MS. This finding confirms other studies that have reported the sensitivity of T2-weighted MR imaging for the diagnosis of MS [1–3]. This series describes a previously unreported finding in MS, decreased signal intensity on T2-weighted images in the thalamus and putamen. The prominence of the decreased signal intensity directly correlated with the extent and number of white-matter lesions. This selective decrease in signal intensity is consistent with an abnormally increased accumulation of a transition

Fig. 4.—Moderate multiple sclerosis (abnormal iron). Comparison of normal control and moderate multiple sclerosis with SE 2500/80 msec (T2-weighted) coronal images.

A and B, Normal. Normal decreased signal intensity in globus pallidus (G) (30-year-old). T = thalamus.

C and D, Moderate multiple sclerosis. Abnormal decreased signal intensity relative to control in putamen (P) and thalamus (28-year-old). R = red nucleus.

E, Perls' stain in multiple sclerosis. Abnormally increased grayness (increased iron) in putamen relative to globus pallidus, which normally has more iron. Thalamic iron, though less prominent, is probably also relatively increased. (This patient was not from the MR study).

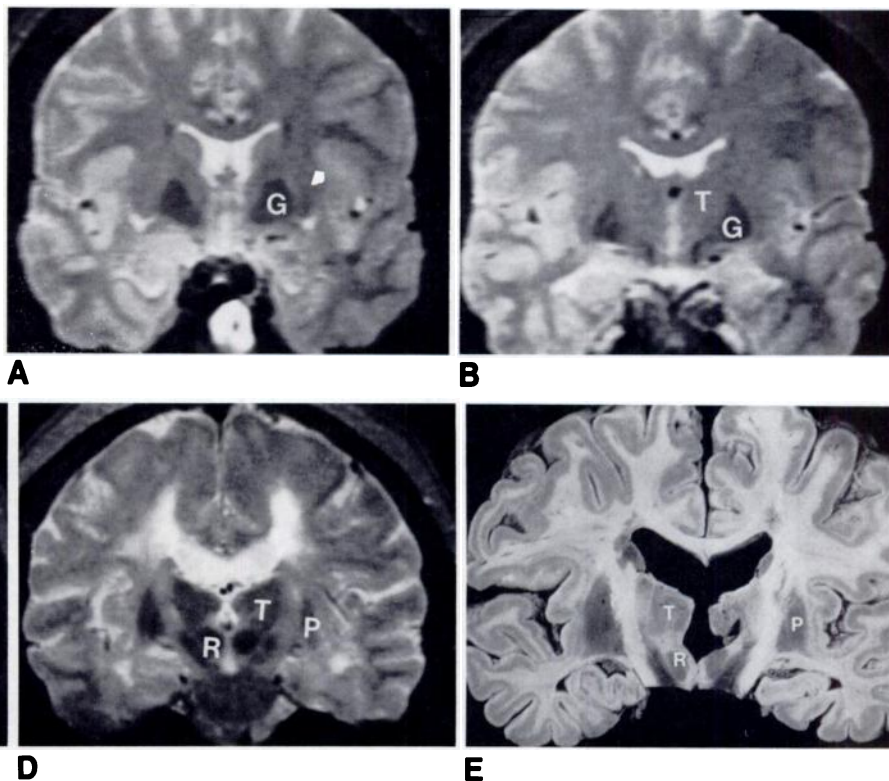


TABLE 2: T2 Relaxation Times in Multiple Sclerosis Estimated from SE 2500/40–80 Multislice Images

Region	Relaxation Times	
	MS (n = 13)	Controls (n = 13)
Globus pallidus	46.1 ± 3.2	45.1 ± 4.7
Putamen	52.4 ± 3.0	53.6 ± 6.1
Thalamus	56.5 ± 2.5	59.3 ± 6.8
T2 ratio of globus pallidus/		
Putamen	0.88 ± 0.05 ^a	0.84 ± 0.05
Thalamus	0.82 ± 0.06 ^b	0.76 ± 0.06

Note.—The ages for both multiple sclerosis (MS) and control groups were 23–54 years old (mean 39 years).

^a Wilcoxon text (.05 < p < .10).

^b Wilcoxon text (p < .05).

element, most likely iron, in the thalamus and striatum associated with MS.

When imaging with a 1.5-T-field-strength magnet, normal adults always exhibited a decrease in signal intensity on T2-weighted images (decreased T2 relaxation time) in a specific topographic distribution (globus pallidus, red nucleus, substantia nigra, and dentate nucleus of cerebellum) correlating with Perls' stain and other autopsy studies [5, 11–13]. The normal iron concentration in the brain is four times greater in the globus pallidus and 2.5 times greater in the putamen than in the thalamus [13]. No stainable iron is present at birth

[14], but there is a progressive accumulation of nonheme brain iron until stable adult levels are attained at about 20–25 years of age [13–15].

Brain iron concentration is most likely independent of hemoglobin metabolism and the iron reserves of other body organs. The passage of iron across the blood-brain barrier is poorly understood but may occur at sites of transferrin receptors on brain capillary endothelial cells [16]. Iron is present in other animal systems in a distribution similar to that found in humans [17, 18]. Finely granular brain iron is mainly in the form of ferritin [13, 15] and found predominantly in the mitochondria and microsomes of oligodendrocytes and glial cells, with much smaller deposits in the neuropil, inner and outer loops of myelin sheaths, and scattered neurons [13, 15, 18].

Iron and copper are the key trace metals used in brain metabolism. Iron enzymes play an important role in oxidative reactions [15]: (1) DPNH-cytochrome-C-reductase has a high iron content, (2) iron and lactoflavin contents of the brain are parallel except for low lactoflavin in the globus pallidus, and (3) iron-containing flavoproteins (DPNH dehydrogenase, succinic acid dehydrogenase) play a role in cellular respiration. Iron is an important cofactor in dopamine synthesis and degradation [19, 20] as well as in glutamate synthesis [21]. An important reaction in normal aging is the dismutation of superoxides to produce hydrogen peroxide, which in turn reacts with ferrous (II) iron to produce highly reactive and likely toxic hydroxyl free radicals and ferric iron [22].

Iron is the most likely candidate for producing the topographically specific, decreased signal intensity in basal ganglia

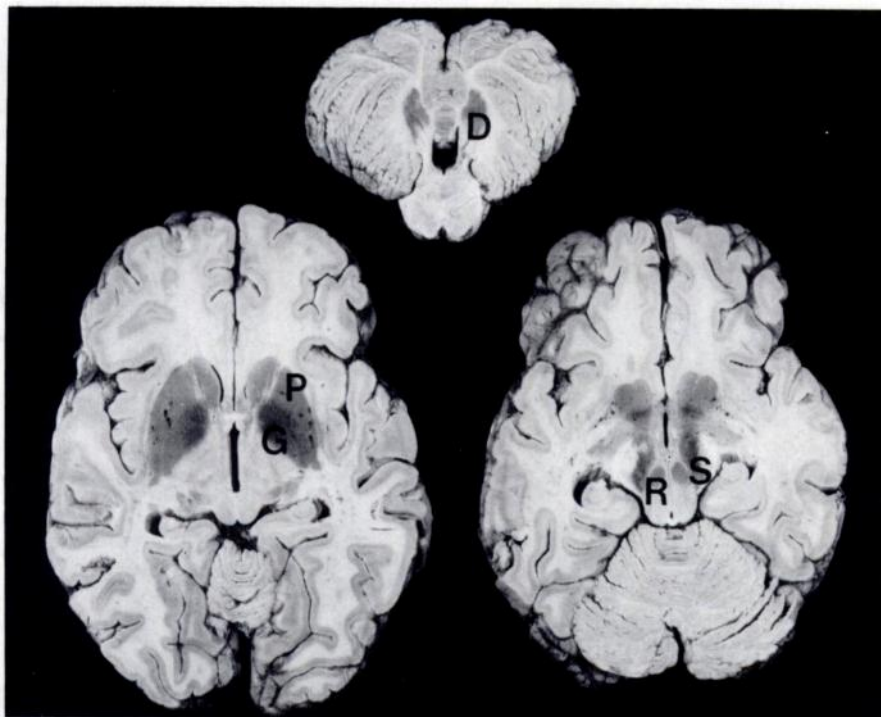


Fig. 5.—Perls' stain for ferric iron (normal brain). Greater intensity of blue staining (gray on black-and-white photographs) represents greatest concentration of ferric iron. Maximal blue (gray) staining in globus pallidus (G), red nucleus (R), reticular substantia nigra (S), and dentate nucleus (D) coincide with lowest signal intensity (decreased T2) on T2-weighted MR images. Gray staining in putamen (P) is less intense and in thalamus far less intense than in globus pallidus, consistent with normally lower iron concentrations in putamen and thalamus.

structures with high-field-strength MR imaging [3, 12]. Ferritin (molecular weight 480,000) is composed of a crystalline ferrioxhydroxide core with up to 4000 ferric ions per molecule. The ferritin is encased by a 25-Å protein shell, and therefore theories of paramagnetic relaxation effects would suggest no significant alteration in T1 or T2 relaxation time [23]. Intracellular iron, however, does create slow, statistical fluctuations in the magnetization of each ferritin core, resulting in local magnetic field gradients and inhomogeneities and a resultant decline in the transverse (T2) relaxation time and signal intensity on the T2-weighted image [5, 11, 23–26]. The effect of brain iron is better discerned at high field because this heterogeneity in magnetic susceptibility is proportional to the square of the magnetic field strength [25].

An abnormally increased concentration of brain iron has been reported in Hallervorden-Spatz disease [27], Huntington's disease [28], Parkinson's disease, and Parkinson's plus (multisystem atrophy) syndromes [12, 29, 30]. Individuals over 80 years old may normally have increased iron deposition in the striatum [12, 13]. There are, however, no disorders in which elevated iron concentration has been reported in the thalamus, although we have seen this finding after intracranial radiation therapy [12]. Rojas et al. [31] reported discrete foci of increased iron in only the ventrolateral thalamic nucleus with Parkinson's disease.

The question arises as to the reason for decreased signal intensity on T2-weighted images in the thalamus and putamen in a disease that predominantly affects the white matter. No trace metal or chemical compound in the brain other than iron normally preferentially accumulates as described [5, 13, 32] and preferentially affects T2 relaxivity. The decreased T2 in the thalamus and striatum is not related to calcium or vascu-

larity, which would similarly affect T1 relaxivity. The relative appearance of an abnormally decreased signal intensity in the putamen and thalamus does not seem highlighted by internal capsule plaques (increased signal intensity) as one would expect the globus pallidus decreased T2 to be equally accentuated.

Iron might accumulate as a result of a decline in iron-requiring oxidative reactions (hypometabolism) in deep gray-matter structures. MS is a disease of the oligodendroglia-myelin system. Since iron is predominantly found in the oligodendroglia, dysfunction may result in an excessive accumulation of iron in structures that normally have relatively high iron stores [18]. The increased iron accumulation might also result from an accelerated rate of hydroxyl free radical formation causing increased membrane peroxidation and ferric iron production [22]. Another possibility is that iron may pass into the brain more freely in MS because of an underlying blood-brain barrier abnormality [5].

Increased iron accumulation has been reported in ovoid bodies at a distance of about 150 μm from the MS plaque margin [33]. Walton and Kaufman [34] were unable to confirm this observation, although they occasionally found hemosiderin-laden macrophages within an acute plaque. Craelius et al. [33] reported iron along fiber tracts with occasional iron-containing microglia in close proximity to axons. The globus pallidus contains far fewer white-matter tracts than does the thalamus or putamen. Although these researchers did not see ovoid bodies in the gray matter, they noted that intravascular Prussian blue (iron) staining was extensive in the gray matter adjacent to the plaques. Enlarged, densely staining lysosomes, possibly containing iron, may be found in a perivascular location within glial cells near MS plaques. Craelius et

al. [33] proposed various potential mechanisms for iron accumulation in MS, including abnormal blood-brain barrier permeability, increased lysosomes and microglia that store iron, and increased iron in blood-vessel walls in the gray matter. They also mention that both hemochromatosis (disorder of iron metabolism) and MS are associated with similar histocompatibility loci, HLA-A3 and HLA-B7.

Whatever the mechanism, the results of high-field-strength MR studies strongly suggest that abnormally dominant decreased signal intensity on T2-weighted images in the thalamus and striatum is directly proportional to the severity of associated white-matter lesions. The possibility that iron accumulation is causally related to demyelination or disease progression in MS is unproved, although it provides an interesting new avenue for investigation. Even if iron accumulation proves epiphenomenal, the MR finding of decreased thalamic and striatal signal intensity may provide an important new diagnostic clue and marker of disease activity. Further studies are needed to determine the specificity of this finding for MS as compared with other white-matter disorders.

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