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High Signal Regions in Normal White Matter Shown by Heavily T2-Weighted CSF Nulled IR Sequences

Joseph V. Hajnal, Beatrice De Coene, Paul D. Lewis, Christine J. Baudouin, Frances M. Cowan, Jacqueline M. Pennock, Ian R. Young, and Graeme M. Bydder

Abstract: Inversion recovery (IR) sequences with an inversion time (TI) designed to markedly reduce or null the signal from CSF (TI of ~2,100 ms at 1.0 T) and a very long echo time (TE) of 240 ms were used to image the brain of two normal adult volunteers, one 34-year-old man with an intrinsic tumor, and one 3-month-old infant with an infarct. Using these very heavily T2-weighted pulse sequences, adult gray and white matter showed similar signal intensity in many areas of the brain, but normal white matter in regions of the centrum semiovale, posterior internal capsule, parietopontile tract, occipitothalamic radiation, and brain stem showed a much higher signal intensity than surrounding gray or white matter. The infant displayed a low signal intensity in myelinated regions in the internal capsule and occipitothalamic radiation and a high signal in unmyelinated white matter. In many of the images there were strong similarities to the distribution of high signal within white matter seen with pulsed gradient spin echo sequences (TE 130 ms) designed to demonstrate effects due to anisotropic diffusion. Arguments are advanced to support the view that the high signal intensity in white matter tracts is due to one or more long T2 components that may be associated with unmyelinated or sparsely myelinated fibres within white matter. The resemblance to diffusion weighted images may reflect the fact that both employ long TEs and both produce a low signal from CSF. If myelin possessed a different susceptibility from axoplasm so that magnetic field gradients were generated around nerve fibres when their orientation was not parallel to B_0, diffusion of water might then produce the observed dependence on fibre direction. The high signal regions in white matter are a potential source of confusion in image interpretation, and measurements of T2 in white matter need to be made with these regional variations in mind. The concept of normal appearing white matter also needs to be applied with a knowledge of these differences. The IR sequences used in this study provide a very high T2 dependence with a low signal from CSF and may be useful for detecting disease in the CNS of adults and children. **Index Terms:** Magnetic resonance imaging, techniques—Inversion recovery—Brain, white matter—Brain, myelination—Diffusion.

From Picker International, Wembley, Middlesex (J. V. Hajnal and I. R. Young); and the Departments of Radiology (B. De Coene, C. J. Baudouin, J. M. Pennock, and G. M. Bydder), Histopathology (P. D. Lewis), and Pediatrics (F. M. Cowan), Hammersmith Hospital, Royal Postgraduate Medical School, London, U.K. Address correspondence and reprint requests to Dr. G. M. Bydder at NMR Unit, Hammersmith Hospital, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS, U.K.

The degree to which MR images of the brain may be usefully T2 weighted is limited by the fact that the brain signal decays much more rapidly than that of CSF and that motion of high signal CSF creates artefacts that degrade the resultant images. To avoid this problem we have used an inversion recovery (IR) sequence with an inversion time (TI) of ~2,100 ms at 1.0 T to greatly reduce or null the

signal from CSF. This was combined with an echo time (TE) of 240 ms to produce very heavily T2-weighted pulse sequences.

Using these sequences, we have observed high signal regions in various normal white matter regions consistent with the presence of long T2 components within them. We have also observed changes of signal intensity within white matter which show a strong similarity to those found using heavily diffusion weighted pulsed gradient spin echo (PGSE) sequences (1–3).

In this paper we describe the technique used, illustrate the results, and present arguments in support of the view that the high signal in white matter may arise from unmyelinated or sparsely myelinated nerve fibres. We also note that the resemblance of these highly T2-weighted images to diffusion weighted PGSE images may reflect the fact that both employ long TE values and give a low signal from CSF. In addition, if there was a difference in susceptibility between myelin and axoplasm so that internal magnetic field gradients were created when myelinated nerve fibres were not parallel to B_0, diffusion of water within this inhomogeneous field might then produce differences in signal intensity that correlated with fibre orientation.

MATERIALS AND METHODS

With the permission of the Research Ethics Committee of the Royal Postgraduate Medical School, two normal adult volunteers (32 and 47 years old), one 34-year-old man with an intrinsic brain tumor, and one 3-month-old infant with a cerebral infarct were examined on a Picker 1.0 T HPQ MR imaging system.

A long TR IR sequence, in which a nonselective 180° pulse was followed by a succession of slice selective 90 and 180° pulses, resulted in a set of TE 16 ms IR images with progressively increasing values of TI. This was used to determine the null point for CSF which was ~2,100 ms. Useful attenuation of the CSF signal was also achieved using images with TI values up to ~600 ms on either side of this figure. Within this range of TI values gray and white matter display little T1 weighting, having recovered much of their equilibrium longitudinal magnetisation. The same IR sequence was then used with a TE of 240 ms for examination of the brain using a slice thickness of 8 mm. For comparison, images produced by conventional multislice SE sequences (TE = 80 ms) and diffusion weighted PGSE sequences from normal volunteers were available.

RESULTS

Images from the first normal volunteer (32-year-old man) are shown in Fig. 1. The transverse IR 8,050/240/2,120 image (Fig. 1a) displays a high signal intensity in the posterior internal capsule particularly in the region of the parietopontile tract. Relatively increased signal intensity areas are also seen in the occipitothalamic tract and medial to the occipital horns of the lateral ventricles. High signal regions are seen in relation to the anterior horns of the lateral ventricles. The transverse IR 8,050/240/2,400 image (Fig. 1b) displays relatively high signal

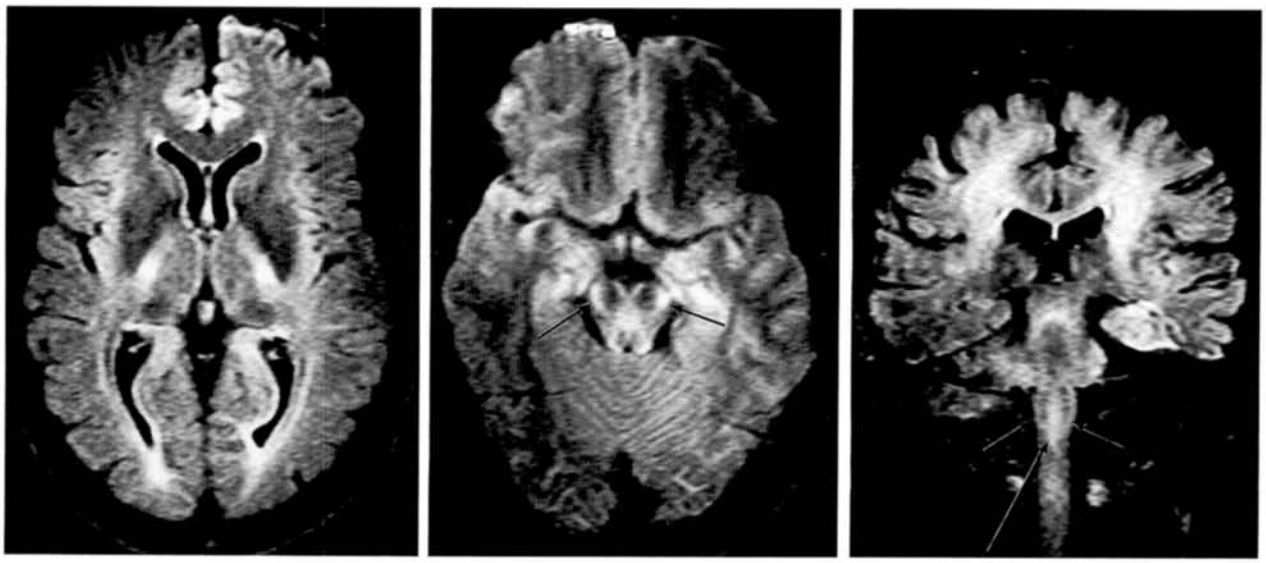


FIG. 1. Normal 32-year-old man: IR 8,050/240/2,120 **(a),** IR 8,050/240/2,400 **(b),** and coronal IR 8,050/240/1,840 **(c)** images. The posterior internal capsule, parietopontile tracts, and occipitothalamic tracts are highlighted in (a). High signal regions are present in the medial and lateral (arrows) parts of the midbrain (b). The white matter signal is elevated in the centrum semiovale and brain stem as well as in the lateral (small arrows) and medial (long arrows) medulla (c).

laterally in the midbrain (arrows). The medial aspect of the cerebral peduncles also has a high signal and so do aspects of the central and posterior regions of the midbrain. The coronal IR 8,050/240/1,840 image (Fig. 1c) displays relatively high signal regions in the centrum semiovale, corpus callosum, and midbrain. There are also linear high signal areas in the lateral medulla (short arrows) as well as in the central medulla (long arrows).

Figure 2a (IR 8,050/240/1,560) from the second volunteer displays high signal regions posteriorly in the centrum semiovale. The low ventricular image (Fig. 2b, IR 8,050/240/1,840) shows high signal intensity areas in the posterior internal capsule including the parietopontile tract (arrows), the posterior corpus callosum, and the occipitothalamic radiation. At a slightly lower level (Fig. 2c) the posterior internal capsule and occipitothalamic radiation are again highlighted. The sagittal image (Fig. 2d, IR 8,050/240/1,800) displays high signal regions in the inferior and posterior aspects of the corpus callosum. High signal areas are seen posteriorly in the pons, and a high signal region is seen traversing it (arrow). This is from the corticospinal tract.

The patient with an intrinsic tumor of the brain displayed regions of high signal in the left parietal region on the SE 2,500/80 sequence in the region of the tumor (Fig. 3a). This region has a generally high signal in Fig. 3b (IR 8,720/240/1,560) with low signal components within it. The opposite centrum semiovale has a high signal intensity (arrows).

At another level the IR 8,050/240/2,120 image (Fig. 3c) displays the tumor as well as high signal regions in the posterior internal capsule and occipitothalamic radiation. The coronal image (IR 8,720/240/2,120, Fig. 3d) again displays the tumor. The parietopontile tract on the right (arrow) has a high signal intensity.

Images from the 3-month-old infant are shown in Fig. 4. Figure 4a is an IR 3,400/30/800 image, which shows a low signal area in the right frontotemporal region consistent with infarction. There is evidence of myelination (short T1) in the posterior internal capsule and part of the occipitothalamic radiation as is usually found at this age. The IR 8,060/240/2,240 image (Fig. 4b) shows that the area of infarction has a low signal intensity. The myelinated region in the posterior internal capsule is of low signal intensity

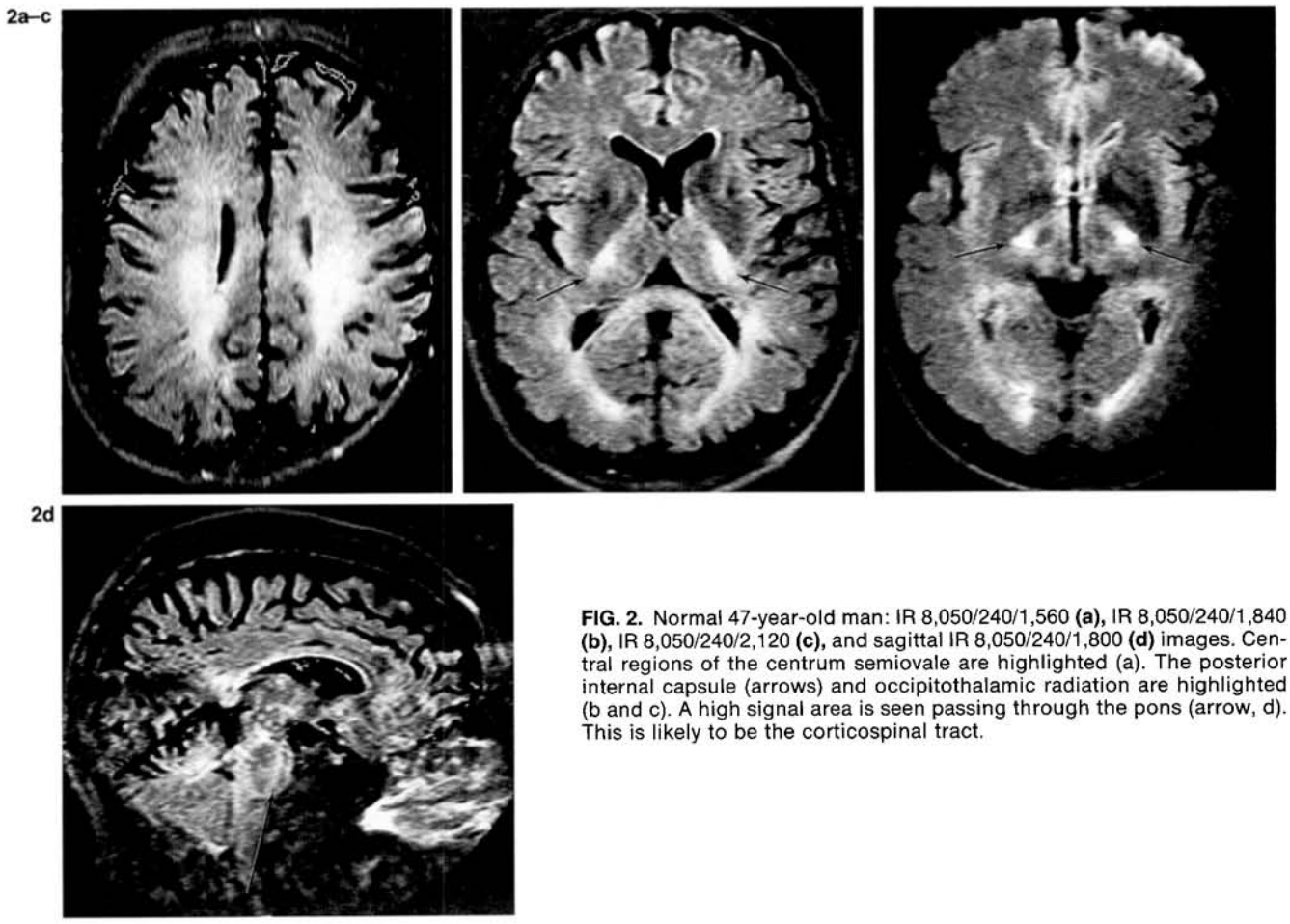
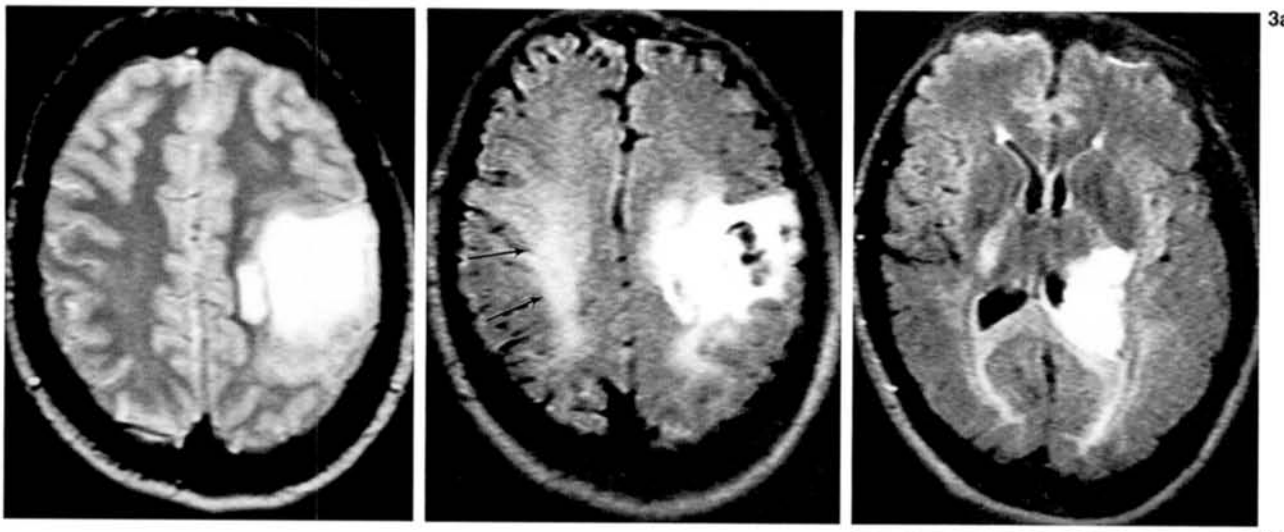


FIG. 2. Normal 47-year-old man: IR 8,050/240/1,560 **(a),** IR 8,050/240/1,840 **(b),** IR 8,050/240/2,120 **(c),** and sagittal IR 8,050/240/1,800 **(d)** images. Central regions of the centrum semiovale are highlighted (a). The posterior internal capsule (arrows) and occipitothalamic radiation are highlighted (b and c). A high signal area is seen passing through the pons (arrow, d). This is likely to be the corticospinal tract.



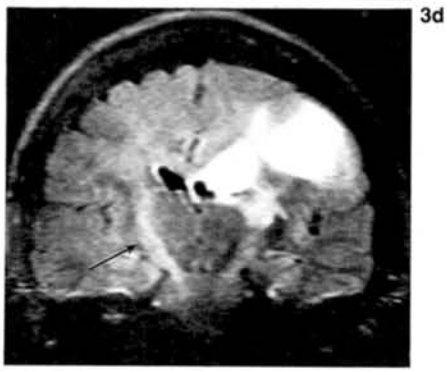


FIG. 3. Intrinsic tumor of the brain in a 34-year-old man: SE 2,500/80 **(a),** IR 8,720/240/1,560 **(b),** IR 8,050/240/2,120 **(c),** and coronal IR 8,720/240/2,120 **(d)** images. The tumor is highlighted in (a), (b), and (c), but low signal regions are seen in (b). These hypointense foci remain unexplained; possibly they are caused by minimal bleeding, calcification, or hypercellular regions. Part of the centrum semiovale is highlighted on the right (arrows, b). The right parietopontile tract is highlighted (c and d) (arrow).

but the unmyelinated white matter is generally of high signal intensity. The appearances of myelinated and unmyelinated white matter are reciprocally related to those in Fig. 4a.

Reference diffusion weighted PGSE sequences (TR/TE/direction of gradient/diffusion time/sensitivity) of a normal 31-year-old man in the coronal plane Fig. 5a (SE 2,070/130/Y/44/550) and Fig. 5b (SE 2,070/130/X/44/550) as well as the sagittal plane Fig. 5c (SE 2,050/130/X/44/550) are shown. The corpus callosum and parietopontile tract are highlighted in Fig. 5a. There is a close resemblance to the right side of Fig. 3d. The pons is generally of low signal intensity in Fig. 5c apart from a high

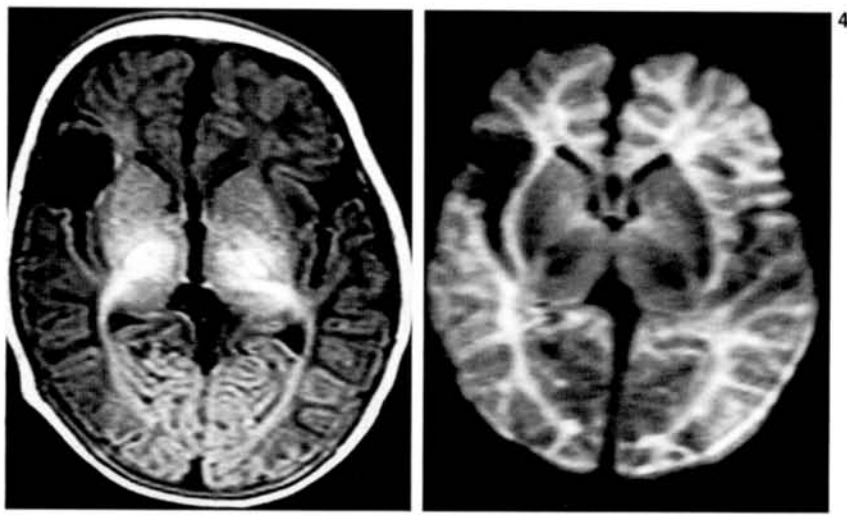


FIG. 4. Cerebral infarction in a 3-month-old infant girl: IR 3,400/30/800 **(a)** and IR 8,060/240/2,240 **(b)** scans taken at similar levels. The right presylvian infarct is of low signal intensity on (a) and (b). Myelinated areas in the posterior internal capsule are highlighted in (a) and appear dark in (b). Unmyelinated white matter is highlighted in many areas in (b).

5a–c

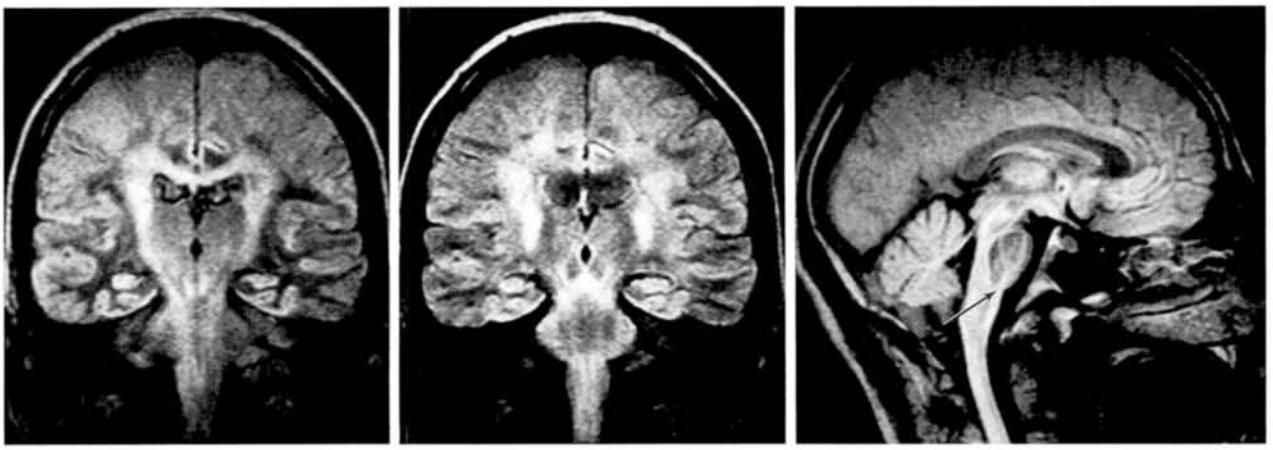


FIG. 5. Normal 31-year-old man. Reference diffusion weighted coronal SE 2,070/130/Y/44/550 **(a)** and SE 2,070/130/X/44/550 **(b)** and sagittal SE 2,050/130/X/44/550 **(c)** images of the brain. In (a) white matter in centrum semiovale and corpus callosum is highlighted. The parietopontile tract is well shown in (b). The pons has a low signal intensity with a highlighted region passing through it (arrow, c). This is probably the corticospinal tract.

signal region (arrow), which is from the corticospinal tract. There is a strong similarity to Fig. 2d.

Correspondence was also seen between the appearance of the parietopontile tract in Figs. 1a and 2b and the appearances found with diffusion weighted PGSE imaging and previously published by us (3) as Figs. 16a and 17. Highlighting of projection fibres in the coronal plane was also illustrated in that paper in Figs. 7c, 16b, and 21d,e (3).

DISCUSSION

Use of very heavy T2-weighted IR sequences in this study produced two major findings: (a) regions of white matter in the centrum semiovale, posterior internal capsule, parietopontile tract, occipitothalamic radiation, brain stem, and cerebellum displayed greater signal intensity than surrounding gray or white matter; and (b) many of the images bear a strong resemblance to those produced by the application of heavily diffusion weighted PGSE sequences. An explanation for both of these observations is required.

The increased signal intensity in the subependymal region may be due to the presence of long T2 components in white matter from transudation of CSF. The very high T2 weighting may increase the conspicuity of these. The fact that the CSF also has a low signal intensity means that these changes are not obscured by partial volume effects between CSF and white matter as may be the case with conventional T2-weighted SE sequences.

The high signal observed in white matter remote from the ventricular system is not accounted for by this explanation. It is possible that these regions of high signal, in which there is presumably one or more long T2 components, may come predominantly from unmyelinated or sparsely myelinated fibres in all or part of the relevant white matter tract (including compact tracts). The arguments in favor of this are as follows: (a) Unmyelinated white matter in infancy gives a high signal with heavily T2-weighted SE sequences but myelinated white matter gives a lower signal as illustrated in Fig. 4. (b) The fact that the parietopontile tract gives a high signal with heavily T2-weighted sequences (TE 80) has been described previously by Mirowitz et al. (4). Histological staining for myelin and axonal fibres from two normal brains studied by these authors revealed lightly staining areas in the region of the parietopontile tract, consistent with the presence of relatively lightly myelinated fibres. In our own study using very heavily T2-weighted sequences (TE 240) the parietopontile tract was one of the most striking features observed and was readily identified in all three adults who were studied. (c) Curnes et al. (5) have pointed out that a decreased signal intensity is seen in many heavily myelinated compact fibre pathways of the brain using heavily T2-weighted (TR 2,500, TE 80) SE sequences. These authors also found that the myelin fibre density was reduced in the posterior internal capsule and suggested that this was the best explanation for the increased signal intensity that they observed in this region with their T2-weighted (TE 80) images. (d) Quantitative histological studies have shown that not all the fibres within the white matter are myelinated. According to Lassek, ~60% of all pyramidal tract fibres are myelinated in humans (6); DeMeyer found ~94% were myelinated (7). Both references are cited in Blinkov and Glezer (8) and Brodal (9). (e) It is also possible to argue that the long T2 components observed in white matter are unlikely to be due to presence of blood within capillaries. The regional cerebral blood volume of

gray matter is much greater than that of white matter. This would tend to produce a high signal in gray matter and a low signal in white matter which is the reverse of the observed effect. The presence of capillary blood would not easily account for the striking difference between structures such as the anterior and posterior limb of the internal capsule where measurements of regional cerebral blood volume by other techniques such as positron emission tomography show little or no difference.

The similarities between very heavily T2-weighted SE sequences and highly diffusion weighted PGSE sequences, as exemplified by selective highlighting of the corticospinal tracts within the pons (Figs. 2c and 5c), are striking. This differentiation of neighbouring tracts with similar degrees of myelination but quite different orientation requires another explanation.

Diffusion weighted sequences utilise externally applied gradients to produce an irreversible dephasing of signal from spins that are free to diffuse in the direction of the field gradient. The spins in myelinated nerve fibres that are parallel to the gradient can move further in that direction than those in fibres that are perpendicular to the gradient. As a result the former suffer more dispersion and produce a lower net signal than the latter. The signal from gray matter is attenuated by the externally applied gradients to an intermediate degree (3). Thus with diffusion weighted imaging the subset of fibres that is perpendicular to the applied gradient appears bright. The sensitivity to diffusion depends on the magnitude, duration, and spacing of the gradient pulses and is specified by a composite parameter b (1). Typical values of b used for in vivo imaging range from 100 to 1,000 s/mm^2.

In the present case the diffusion weighting of the TE 240 sequence is small ($b < 35$ s/mm^2) and insufficient to explain the contrast seen. For the sagittal image shown in Fig. 2d the dominant sensitisation is from superior to inferior, which would be expected to make the corticospinal tract appear dark rather than bright.

The observed appearance may be explained in part if the signals from some tracts are attenuated as a result of diffusion of water through internal gradients around the nerve fibres. Even quite modest gradients could produce substantial attenuation if they are constantly present over the extended TE used in these studies. Such gradients might be produced if there was a susceptibility difference between tissue water and myelin.

To estimate the magnitude of these gradients and the attenuation they might produce, we note that during in vivo spectroscopy the water resonance of localised areas of the brain can be shimmed to a line width of ~0.1 ppm. The local field inhomogeneity in the B_0 field (ΔB_0) is then approximately given by

$$\Delta B_0 \simeq 10^{-7} B_0 \quad (1)$$

Supposing half of this is produced by a susceptibility difference between water and myelin, the average local gradient, G_0, produced by an axon of radius r would be approximately given by

$$G_0 \simeq \frac{\Delta B_0}{r} \quad (2)$$

Taking the value of r to be ~5 μm, we obtain for B_0 = 1T, $G_0 \simeq 10$ mT/m. These gradients are in a direction transverse to the axis of the fibres.

The diffusion related attenuation, R, produced by such a gradient, if it were applied uniformly across a fluid sample is given by

$$R = \exp\left[-\left[\frac{\gamma^2 G_0^2 (TE)^3}{12}\right] D^*\right] = \exp - bD^* \quad (3)$$

where b is the diffusion sensitivity parameter, D* is the apparent self diffusion coefficient of the fluid (3), and γ is the gyromagnetic ratio.

For TE 240 ms, Eq. 3 gives b = 8,200 s/mm^2. Using a mean value for D* of $\sim 0.5 \times 10^{-3}$ mm^2/s, which is appropriate for white matter when measuring diffusion perpendicular to the direction of the fibres [see references cited in (3)], results in a value for $R \simeq 0.02$. Thus, given the same values of T2, under the conditions used for this study, myelinated fibres might yield a signal as low as one-fiftieth that of unmyelinated or sparsely myelinated fibres. This simple argument probably overestimates the effects of such gradients but serves to indicate that they may be significant.

Returning to the observation that the corticospinal tract is highlighted in the pons we note that these fibres are basically running parallel with the B_0 field, whereas most other fibres in the region are transverse or oblique to the direction of B_0. This parallel orientation places the surfaces of the myelin sheath parallel to the main magnetic field. In this orientation no susceptibility induced gradients are produced adjacent to the myelin, and the water signal will be less attenuated than in other orientations.

There is a further ramification to this argument. With a cylindrical geometry, susceptibility differences produce field gradients outside the cylinders but not inside. Thus the fibre orientation effects we have observed may indicate that the long T2 components are extraaxonal.

Susceptibility induced effects may in fact be relevant to our first observation that some of the highlighted tracts are sparsely myelinated. It may be

6a,b

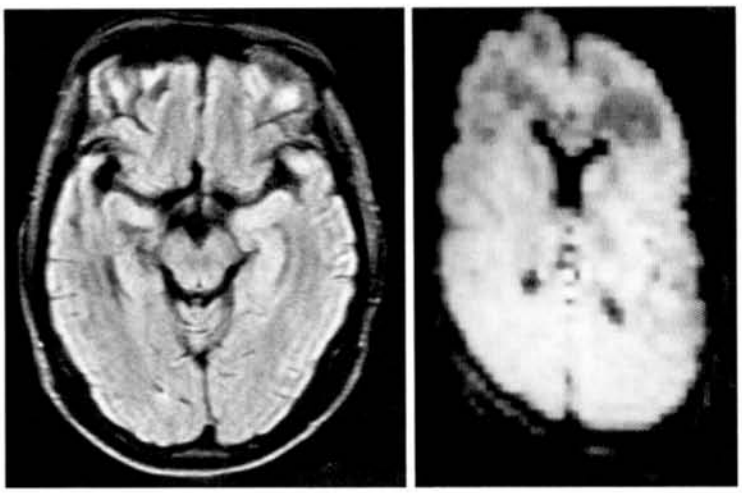


FIG. 6. Preinversion multiecho IR 6,050/45/2,160 image with 256 × 256 resolution using three echoes per excitation **(a)** and PIETIR EPI IR 4,000/120/2,500 sequence with 64 × 128 resolution **(b).** The CSF is nulled in both cases.

that this highlighting is not so much due to the presence of longer T2 components than in heavily myelinated fibres, but that the signals from these components are less attenuated because of the lower intrinsic gradients around sparsely myelinated fibres.

A number of consequences follow from the observation of high signal regions within white matter. Although these have previously been recognised in the posterior internal capsule their occurrence in the cerebrum semiovale, brain stem, and cerebellum is a potential source of confusion since heavily T2-weighted sequences are the most commonly used technique for disease detection with MR of the brain, and high signal areas are frequently taken as an indication of pathology.

The observations are also important in determining values of T2 in white matter. The T2 of normal white matter has been described as monoexponential (10), biexponential (11,12), and triexponential (13). There are likely to be significant differences in the measured values of T2 depending on the region that is sampled and the values of TE that are used. Artefacts produced by CSF may mask longer T2 components, which only show up using extended values of TE.

Likewise the concept of normal appearing white matter needs to be used with a knowledge of the normal appearances of the brain at different values of TE and with a knowledge of the normal values of T2 (or its components) in different regions of the brain.

Prolonged inversion and echo time IR (PIETIR) sequences may provide high sensitivity for disease detection without artefact or partial volume effects from CSF. Such sequences are well suited to the application of gradient moment nulling (14) by virtue of their long TE. Although the PIETIR sequence is easy to implement, it is slow. Use of a preinversion multiecho form based on the RARE sequence (15) is a way to reduce this problem as shown in Fig. 6a. Echo planer imaging (EPI) is another solution (Fig. 6b).

Much of the basic information necessary to correlate myelination, T2 values, susceptibility effects, and diffusion is not yet available, but it could prove to be a rewarding area for further research and may provide basic insights into the structure and function of the brain.

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