

# IMPROVED DETECTION OF GADOLINIUM ENHANCEMENT USING MAGNETIZATION TRANSFER IMAGING

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Magnetization transfer (MT) imaging is a relatively new MR technique in which image contrast is modulated by selectively saturating a pool of tightly coupled protons in macromolecules and their associated "bound" water.<sup>1, 27</sup> Although many variations of this method exist,<sup>24</sup> the usual MT technique consists of applying a presaturation pulse with center frequency shifted from the water resonance by several hundred to several thousand Hertz. This off-resonance pulse has sufficient power to saturate protons in the macromolecular pool without directly affecting those in free water. After the MT saturation pulse has been applied, a routine MR imaging sequence (e.g., spin echo, gradient echo) can then be performed. MT saturation of the pool of macromolecular protons is transferred to nearby water molecules, presumably by means of dipolar cross-coupling and chemical exchange interactions. Through these complex interactions, tissue relaxation parameters are altered, and new image contrasts may be revealed.

MT imaging techniques have already proved useful in several neuroimaging applications: for improving the visualization of small vessels in time-of-flight MR arteriogra-

phy,<sup>7, 17</sup> for increasing tissue contrast in gradient-echo imaging,<sup>29</sup> for displaying the internal structure of the eye,<sup>4</sup> for assessing the integrity of myelin,<sup>6, 16</sup> for detecting cerebral infarction,<sup>20</sup> and for delineating a variety of intracranial mass lesions.<sup>15</sup> MT techniques have also been used in a variety of body imaging applications, including the knee,<sup>28</sup> heart,<sup>2</sup> liver,<sup>21</sup> and breast.<sup>22</sup>

In 1992, Tantu et al<sup>26</sup> demonstrated that at low fields synergistic enhancement could be obtained by the combined use of MT pulses and gadolinium. Over the last year, we have extended their work significantly, proving that the same effect can be obtained at high fields (using a different form of MT pulse) in conjunction with both low and high doses of gadolinium. This article reviews the theory of MT contrast and demonstrates its potential utility in gadolinium-enhanced cranial and spinal imaging.

## THEORY

MT imaging is a new MR technique in which image contrast is manipulated through

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the selective radiofrequency saturation of a pool of protons in macromolecules.<sup>1, 9, 27</sup> This macromolecular pool includes those hydrogen protons incorporated into cell membranes, phospholipids, proteins, and other bulky molecules as well as an inner sphere of tightly bound water protons that are in close thermal contact with the macromolecules.

The protons in the macromolecular pool have limited mobility and hence extremely short T2 values (measured in microseconds rather than milliseconds).<sup>3</sup> Because their magnetization decays so quickly, these protons have long been considered "invisible" during *clinical* MR imaging. Nevertheless, the macromolecular pool may contribute significantly to the overall MR signal in an *indirect* manner. Edzes and Samulski<sup>8</sup> first showed how protons in this macromolecular reservoir can modulate the MR signal from free water in tissue. Presumably this process occurs through dipolar cross-coupling and chemical exchange interactions.<sup>9</sup>

The extremely short T2 of the macromolecular pool also imparts to these protons a broad MR spectral density (line-width). By comparison, tissue water has a longer T2 and thus a narrow spectrum centered around a small range of resonant frequencies (Fig. 1). This inverse relationship between MR line-width and T2 is a fundamental property of Fourier spectra. For example, a slowly decaying sine wave (i.e., with a long decay time constant) has a narrow Fourier spectrum centered close to its principal frequency. A rapidly decaying sine wave (with a short decay time) contains numerous harmonics and therefore a broad frequency spectrum.

Tissue water, because of its narrow spectrum, can be stimulated only over a limited

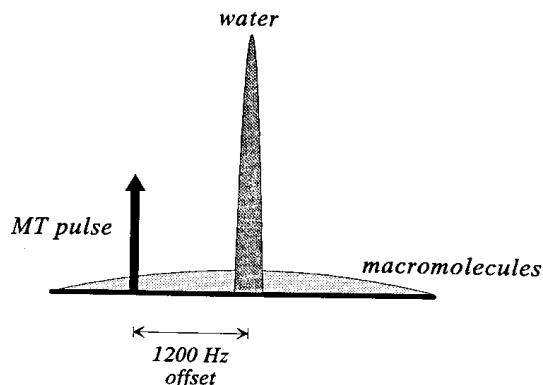
band of frequencies. Conversely, protons in the macromolecular reservoir may be stimulated over a large range of frequencies. Furthermore, the tight coupling among these spins allows rapid transfer of saturation effects among them. An RF pulse frequency-offset from the water resonance can thereby selectively saturate the macromolecular pool without directly stimulating the water protons. This macromolecular saturation may then be transferred to the water protons through dipolar interactions and modulate the observed MR signal.<sup>8, 13, 14</sup>

The magnetization transfer ratio (MTR) can be used to quantify the extent of saturation experienced by a given tissue during a MT experiment. This ratio is calculated by the formula:

$$MTR = \frac{SI_0 - SI_m}{SI_0} \times 100\%$$

where  $SI_0$  is the signal intensity of the tissue before the MT pulse and  $SI_m$  is the signal intensity after the MT pulse has been applied. The MTR indicates the percentage of signal loss occurring during the irradiation of the immobile pool of protons and consequently is proportional to Forsén and Hoffman's<sup>10</sup> pseudo-first-order rate constant for saturation transfer between two chemical species.

Although the exact mechanisms responsible for the generation of MT contrast remain unclear, a few simple concepts can reasonably explain many of the signal changes observed in routine cranial imaging. First, MT effects should be most noticeable in tissues (such as muscle and brain) where the interaction between water and macromolecules is the principal determinant of relaxation time.<sup>2, 6, 12, 28</sup>



**Figure 1.** The macromolecular pool, with its extremely short T2, has a broad MR spectrum. Tissue water, with its longer T2, has a narrow line-width. By applying an RF pulse offset from the water resonance by several hundred to one thousand Hertz, selective saturation of the macromolecular pool is possible.

Conversely, fluids (such as cerebrospinal fluid [CSF] and blood), which contain low concentrations of macromolecules, should experience little if any suppression of their signal when MT pulses are applied. Our measurements of MTR in various cranial tissues (Table 1) support this theoretical analysis.

The poor suppression of fat signal by MT pulses has also been noted in several previous studies,<sup>12, 17, 25, 28</sup> in which computed MTR values have not usually exceeded 5%. Adipose tissue contains large intracellular deposits of lipid stored principally as medium-chain and long-chain triglycerides. These triglycerides are of moderate size and mobility and hence have T2 relaxation times comparable to many other biologic tissues. Storage lipids can therefore not be considered *macromolecules* in the sense of those directly saturated by MT techniques. Furthermore, because they are hydrophobic and loculated into self-contained droplets within adipose cells, storage fats have few direct interactions with free water.

MT effects are also minimized whenever high concentrations of a paramagnetic substance are present within tissue.<sup>9, 12, 15, 26</sup> Contrast enhancement on MR is due to a direct water-gadolinium ion interaction, not macromolecular cross-relaxation.<sup>30</sup> MT pulses therefore preferentially suppress the signal from background tissues and render gadolinium-enhanced areas more conspicuous. This use of MT pulses has been exploited at low field to increase the conspicuity of various contrast-enhancing lesions.<sup>15, 26</sup> A similar phenomenon occurs in normal brain: The dural sinuses, pituitary gland, choroid plexus, and other normally enhancing tissues are rendered more intense than white matter on MT images.<sup>12</sup>

### DESIGN AND IMPLEMENTATION OF MAGNETIZATION TRANSFER PULSES

At the time of this writing, MT sequences are available to only a few research centers and clinical test sites. The hardware and software requirements for these pulses, however, are minimal; we anticipate a rapid dissemination of this technology to most centers throughout 1994. Additionally, many variations in pulse sequence design are possible. Ongoing research into MT pulse optimization will further complicate this rapidly expanding field. The reader should therefore keep in

**Table 1.** MAGNETIZATION TRANSFER RATIOS FOR VARIOUS CRANIAL TISSUES AT 1.5 T USING SE 3000/90 SEQUENCE WITH A 1200 Hz OFF-RESONANCE PULSE

Tissue	Magnetization Transfer Ratio (%)
Cerebrospinal fluid	0
Fat	3
Muscle	15
White matter	27
Gray matter	21

mind that all MT sequences are not necessarily equivalent.

Several methods of MT saturation have been used in clinical studies, including continuous wave irradiation and pulse techniques.<sup>24</sup> Because of specific absorption rate (SAR) constraints, continuous wave methods are largely limited to low-field systems.<sup>9, 19, 25</sup> Implementation of the MT technique at high fields has generally involved pulse MR methods. In these pulse methods, a MT saturation pulse of low power and short duration is applied offset from the water resonance by several hundred to several thousand Hertz. This off-resonance pulse is designed to have sufficient power to saturate protons in the immobile pool but with a frequency spectrum that will not directly stimulate protons in the free tissue water.

The MT sequences we have developed and used to generate the data in this article<sup>12, 18</sup> were all implemented on a clinical 1.5-T Signa unit (GE Medical Systems, Milwaukee, WI) operating in research mode. The MT pulse was produced by modifying in software the standard chemical-shift selective saturation pulse available on this system. Our resultant MT saturation pulse had a bandwidth of 250 Hz and an envelope composed of a 16-ms, apodized sinc function with two side lobes. The frequency offset of this pulse was set at 1200 Hz downfield from the water resonance. The pulse amplitude was maximized to produce a peak radiofrequency field flux density ( $B_1$ ) of 7.3  $\mu$ T. After each MT pulse, gradient homospoiling was performed by turning on the y-axis (phase-encoding) gradient to maximum amplitude for about 5 ms. (The purpose of this spoiling pulse was to prevent possible interference patterns with the next radiofrequency pulse.) Allowing for gradient ramp times, the interval between the end of the MT pulse and the beginning of the 90-degree

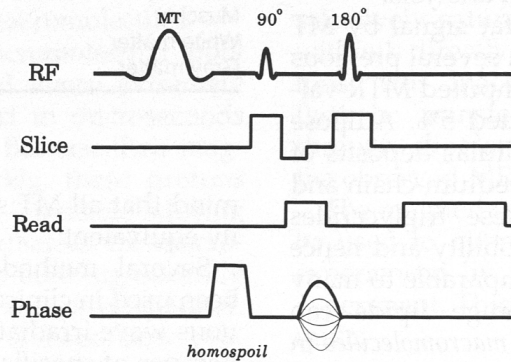


Figure 2. Schematic of the MT spin-echo pulse sequence.

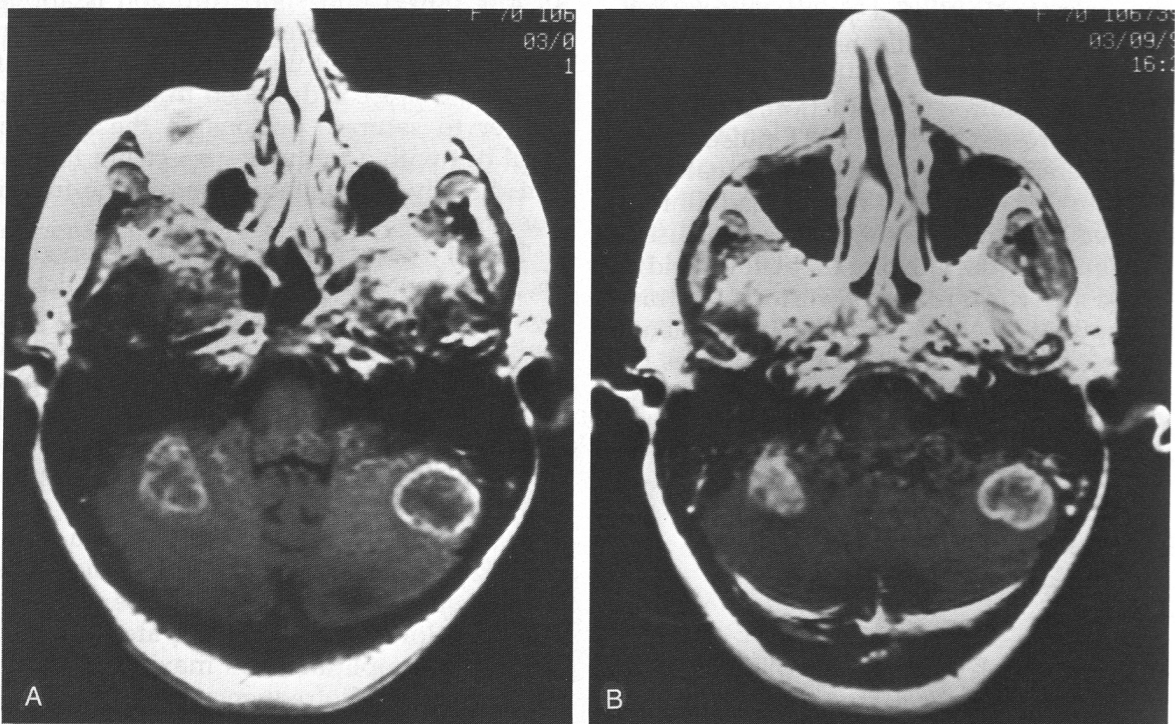
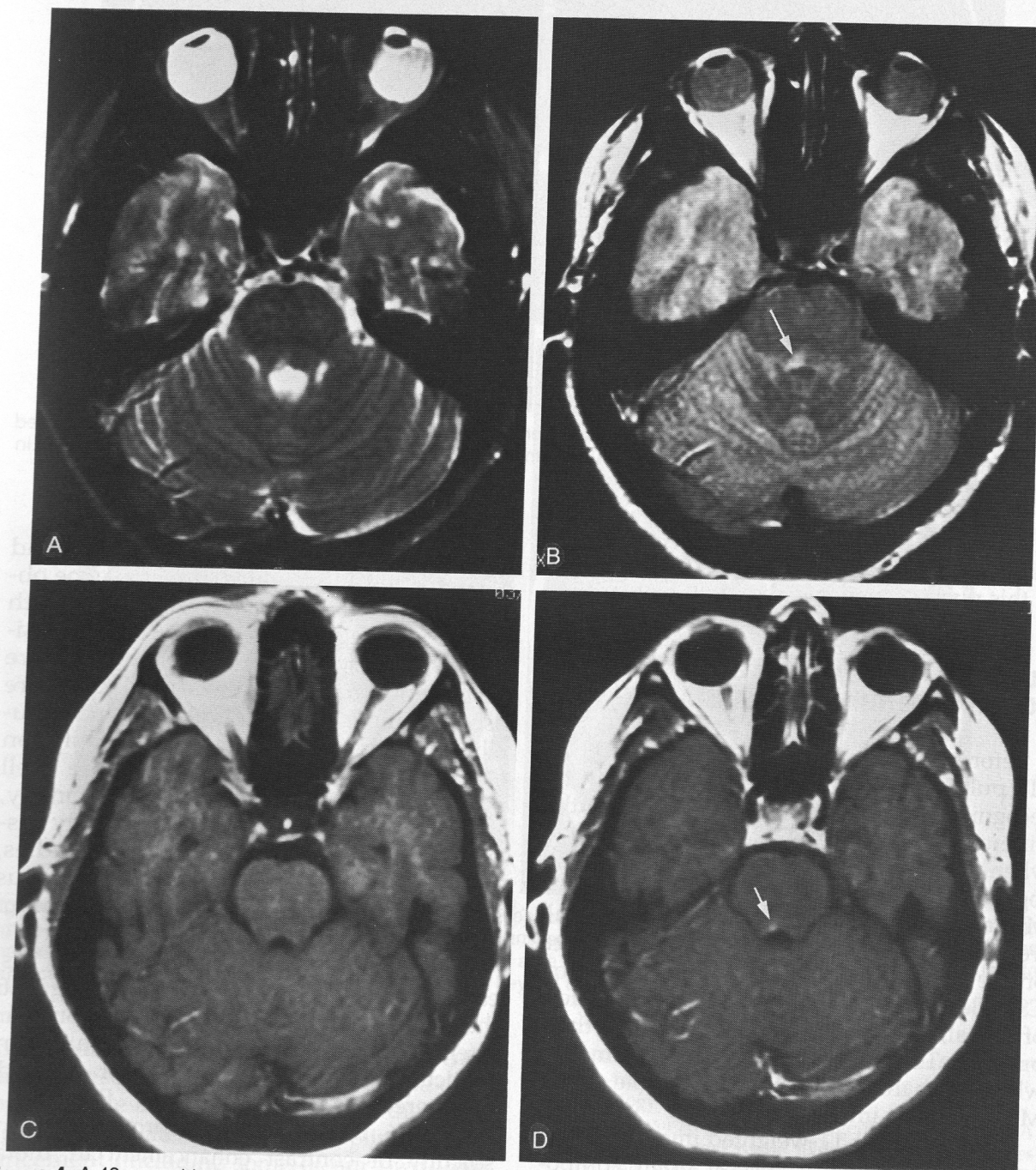
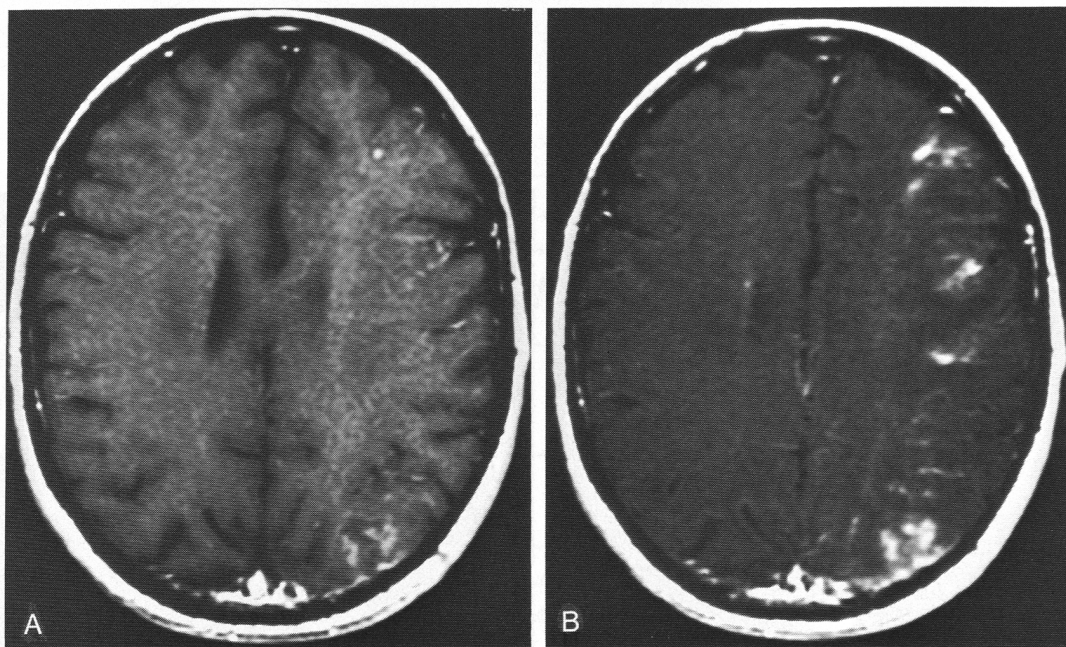


Figure 3. Metastases to the cerebellum in a 70-year-old woman showing increased enhancement with the MT technique. A, Conventional postcontrast, T1-weighted image. B, MT-enhanced postcontrast image shows significantly stronger enhancement.



**Figure 4.** A 43-year-old woman with multiple sclerosis and new onset internuclear ophthalmoplegia. *A*, T2-weighted and, *B*, spin-density-weighted images show a high-signal abnormality (*arrow*) in the region of the left abducens nucleus and medial longitudinal fasciculus. *C*, Conventional postcontrast, T1-weighted image fails to reveal enhancement. *D*, MT-enhanced image shows obvious contrast enhancement (*arrow*) in this acutely demyelinated lesion.



**Figure 5.** A 65-year-old man with a recent left hemisphere cerebral infarction. *A*, Conventional postcontrast, T1-weighted image reveals weak parenchymal enhancement. *B*, MT-enhanced image shows more extensive contrast enhancement in the same area.

pulse was approximately 6 ms. A schematic of this pulse sequence is shown in Figure 2.

#### CLINICAL APPLICATIONS OF CONTRAST-ENHANCED MT IMAGING

Before we discuss the synergistic effects of MT pulses and gadolinium, it is important to recognize that the normal brain has a slightly different appearance on spin echo imaging when MT pulses are used. We have catalogued some of these differences using our MT technique.<sup>12</sup> MT pulses reduce the signal from brain by 20% to 30% but have little effect on the signal from scalp fat, bone marrow, or CSF. Because of this differential suppression of signal, CSF and fat appear brighter than brain on T2-weighted MT-spin echo images when compared with conventional (i.e., non-MT) spin echo images.

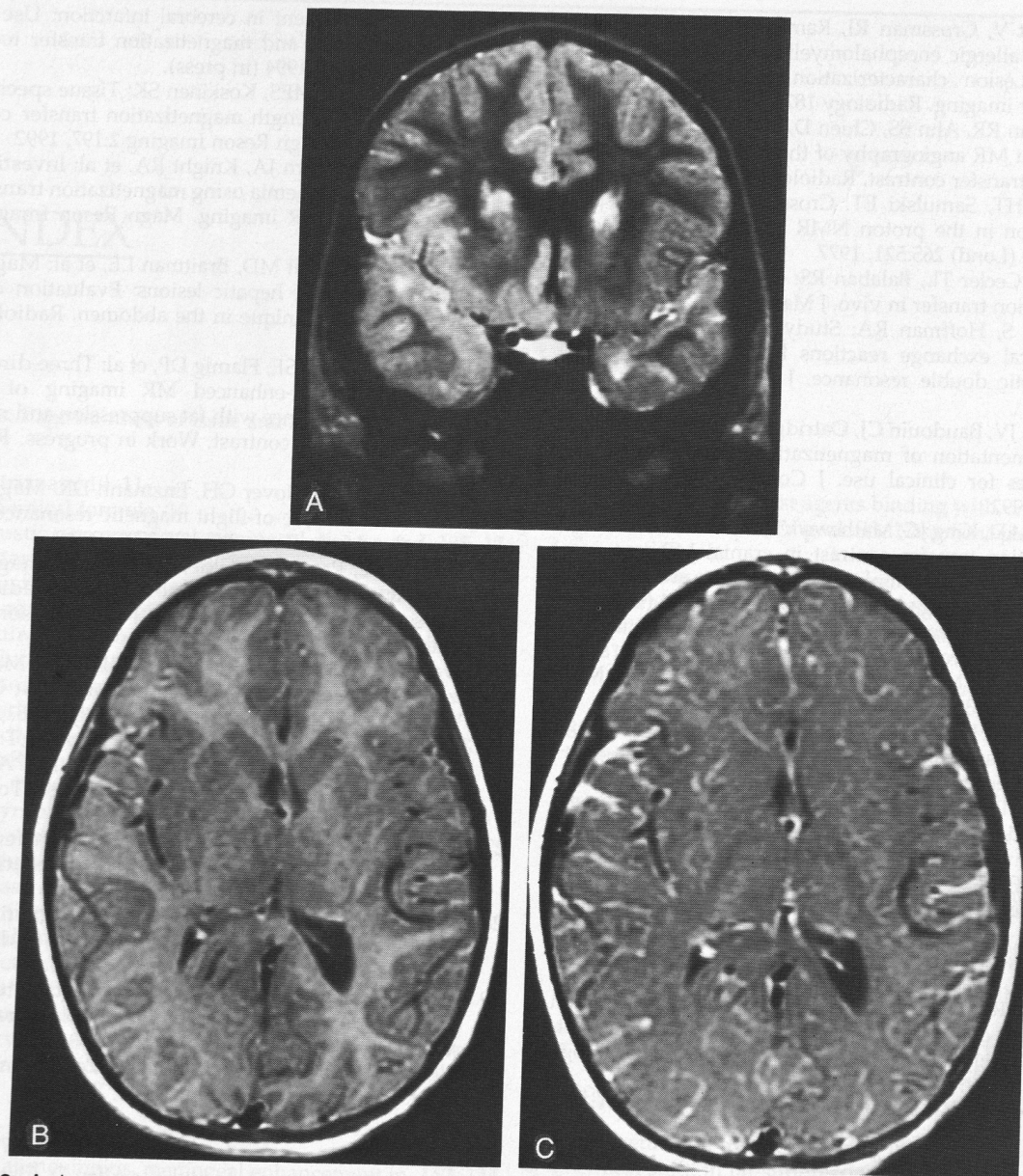
On precontrast T1-weighted images, differential suppression of several brain components takes place. As a result, several structures (gray matter along the central sulcus, globus pallidus, putamen, caudate, pulvinar, periaqueductal gray matter, and substantia nigra) are rendered significantly more conspicuous when MT pulses are used.

After administration of gadolinium, several

further differences between conventional and MT-saturated T1-weighted images may be observed. Structures normally enhancing with gadolinium (e.g., choroid plexus, dural sinuses, pituitary, pineal) are somewhat more conspicuous than normal when MT pulses are used. Multiple small cortical veins, not usually considered to enhance appreciably on conventional T1-weighted images, are well visualized on the MT images. Additionally, the body of the caudate nucleus typically displays vigorous enhancement on MT studies, an effect possibly related to the numerous subependymal vessels filled with gadolinium that lie in close apposition to this structure.

In the realm of central nervous system diseases, our preliminary experience suggests that MT techniques will one day become an integral part of the imaging armamentarium, particularly when gadolinium contrast is administered. As illustrated in Figures 3 through 6, MT saturation improves the conspicuity of contrast enhancement in metastatic disease, in demyelinating disease, in stroke, and in intracranial infections.

Our current hypothesis is that MT pulses result in images with increased contrast enhancement equivalent to that which could be obtained using double-dose or triple-dose gadolinium. This result has important eco-



**Figure 6.** A 4-year-old girl with biopsy-proved herpes encephalitis. *A*, T2-weighted coronal image demonstrates high signal in the right frontal and temporal region along the transverse fissure. *B*, Conventional postcontrast, T1-weighted image reveals only questionable enhancement in the same area. *C*, MT-enhanced, T1-weighted image reveals definite parenchymal and meningeal enhancement extending well beyond the T2 abnormality.

conomic ramifications because triple-dose contrast is three times as expensive as single-dose contrast. We anticipate that part of the existing medical literature on gadolinium enhancement (including some of our own) will have to be rewritten as MT techniques reveal the presence of enhancement in diseases where none was seen before.

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