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Nuclear Magnetic Resonance (NMR): I. Imaging Biochemical Change

L. M. EASTWOOD, J. M. S. HUTCHISON and J. A. O. BESSON

Summary: Nuclear magnetic resonance (NMR) imaging of hydrogen in body water and fat is proving valuable in clinical investigation of the brain. An introduction to the technique and to the biological significance of the images is presented here. The 'multi-parameter' nature of these images is stressed, and the individual parameters described. NMR imaging may well be of value in investigating the pathology of organic and functional psychoses.

NMR proton imaging, first conceived only ten years ago (Damadian, 1974; Lauterbur, 1973), has developed quickly as a clinical tool; it uses radiofrequency (RF) radiation, in the presence of a magnetic field, to create cross-sectional images of the body. Superficially, these appear like X-ray computed tomography (CT) images, the most recent NMR images having achieved similar sub-millimetre resolution. There are, however, important differences. NMR imaging uses no ionising radiation, and is without known hazard (except to patients with cardiac pacemakers, who should not be imaged). The RF radiation penetrates bone without attenuation, thus avoiding some of the artefacts of X-ray CT. NMR imaging also offers the ability to select electronically the orientation and thickness of the image plane without moving the patient—a facility which has been used for direct creation of coronal and sagittal, as well as transaxial, images. The most important difference, however, lies in the information carried in the image, NMR being unusual in the 'multi-parameter' nature of the images created. An X-ray image reveals the distribution of electron density, but NMR images are sensitive to mobile protons (hydrogen nuclei) in water and lipids, and can reveal not only the distribution of those protons, but also parameters such as relaxation times T_1 and T_2, which carry information on their environment. The relative contributions of various parameters to an image depend critically on how the image was created, and the parameters themselves depend on the field strength of the magnet used. This, while introducing interpretation problems, gives the ability to obtain a wealth of new information. It is the capacity to image biochemical information which is the strength of NMR as a tool in clinical diagnosis and research.

Since the first studies on patients in 1980, NMR imaging has given particularly promising results in investigations of the brain (Bydder *et al*, 1982; Smith, 1983). The freedom from the 'bone attenuation' artefacts of X-ray CT has been of benefit in imaging the posterior fossa (Bydder *et al*, 1983). The 'triplanar' facility (creation of transaxial, sagittal, and coronal images) has been invaluable in the localisation of pathology and in studies of the brain midline and spinal cord. The biochemical information available, originally envisaged as of value in cancer detection (Damadian, 1974) has in practice proved far more sensitive, but less specific than this original concept predicted. If its full potential is to be realised, however, those who could benefit from using it must have some understanding both of the technique and of the physiological significance of the images created. This paper describes both the technique and its special significance, and presents the particular approach to NMR imaging taken in Aberdeen (Mallard *et al*, 1980).

Theory of NMR Imaging

Protons are spinning charged particles which behave as microscopic magnets, so that they tend to align when placed in the field of a magnet, giving overall magnetisation of the patient. This very small magnetisation can only be measured if it is tilted away from its alignment with the main field. The proton magnetisation possesses a characteristic frequency, which is controlled by the field strength of the main magnet; fields of 0.04 T and 0.08 T give frequencies of 1.7 MHz (MegaHertz) and 3.4 MHz respectively, both in the radiofrequency (RF) range. The proton magnetisation can be disturbed, and tipped away from its alignment with the static field, by applying a pulse of radiofrequency (RF) magnetic field perpendicularly to the static field, and rotating around it at the characteristic frequency. The angle of tip depends on the size and duration of this RF pulse, as shown in Figure 1. After the pulse, the magnetisation continues to precess round the main field direction (rather like

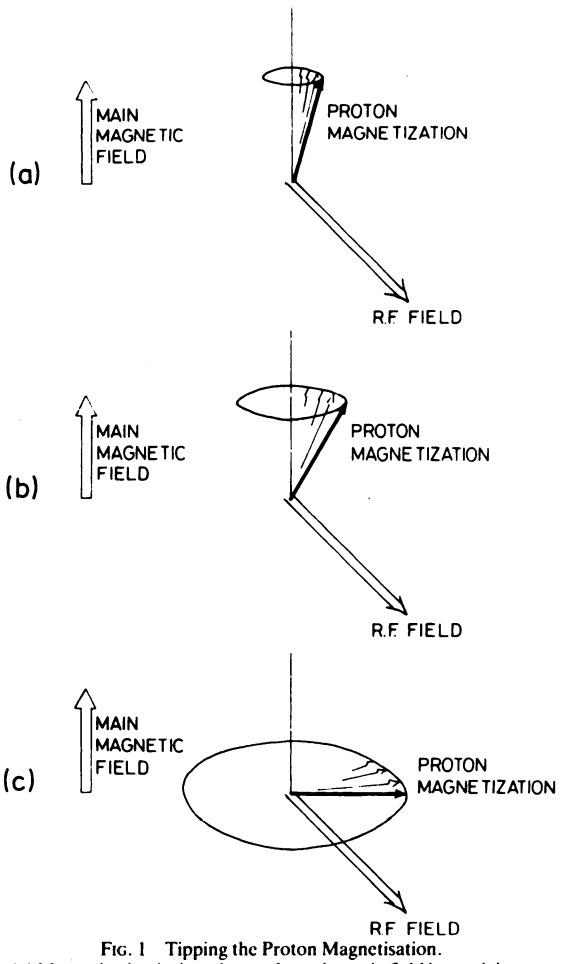

FIG. 1 Tipping the Proton Magnetisation.
(a) Magnetisation is tipped away from the main field by applying a radiofrequency (RF) pulse rotating synchronously with the precessing magnetisation.
(b) & (c) The longer, or larger, the RF pulse, the further the magnetisation tips. The usual RF 'readout' pulse gives 90° tip, into the plane perpendicular to the main field.

the axis of a child's spinning top precessing about the earth's gravitational field). Eventually, it regains equilibrium by re-aligning with the static field. The sequence of RF pulses which is used to create an image profoundly affects the information in that image, as will be discussed below. RF pulses are applied, and the signal due to precession of magnetization is detected, using a coil around the patient, the shape of the coil being arranged to give a homogeneous RF field.

The combination of magnet and RF coil can be used to obtain signals from protons in the body, but it gives no spatial discrimination. This is achieved by using magnetic field gradients, created by specially distributed sets of current-carrying windings. Because the characteristic precession-frequency of the protons depends on magnetic field strength, a field gradient can be used to map location to signal frequency. Many techniques of coding and de-coding are possible (Mansfield & Morris, 1982), the 'spin-warp' technique used in Aberdeen (Edelstein *et al*, 1980) being particularly insensitive to (inevitable) inhomogeneity in the magnetic field and to patient movement. Creating an NMR image generally requires that a large number of RF pulses are applied (typically N pulses to create an image of N×N pixels, or 'picture elements'), each coded with different field gradients. Diverse electronic equipment (computers, amplifiers, etc.) is used to drive and control the magnet, gradients, and RF coil, and to record and decode the NMR signals to create images.

The NMR Imager

From the point of view of the patient, NMR imaging is similar to X-ray CT, except that instead of the short cylinder access through the X-ray gantry, there is a much longer tube within the magnet, inside which the patient lies. For head imaging, a second smaller tube within the main access cylinder carries the RF receiver coil. The patient, on a couch with raised head extension, is slid into the imager until the head lies within the smaller coil. The increased possibility of claustrophobia in NMR imaging, as compared with, for instance, X-ray CT, is in part counteracted by the fact that because of the lack of hazard, medical personnel may stay with the patient throughout the examination.

The time required to create an image can vary considerably, depending on the method (the NMR 'pulse sequences') which is used. Patient movement during imaging should be avoided, although 'spin-warp' imaging is not seriously degraded by slight movement. The imaging pulse-sequence most commonly used in Aberdeen requires the patient to remain still for approximately four minutes, during which at least two different images of the same slice are created. Much shorter imaging times are possible, but with considerably reduced biochemical information in the images.

The equipment used to create an NMR image has been described elsewhere (Hutchison *et al*, 1980; Johnson *et al*, 1981; Redpath & Hutchison, 1982). As shown in Figure 2, the main components are a large magnet, a radio-frequency (RF) transmitting and receiving coil, and a set of field-gradient windings.

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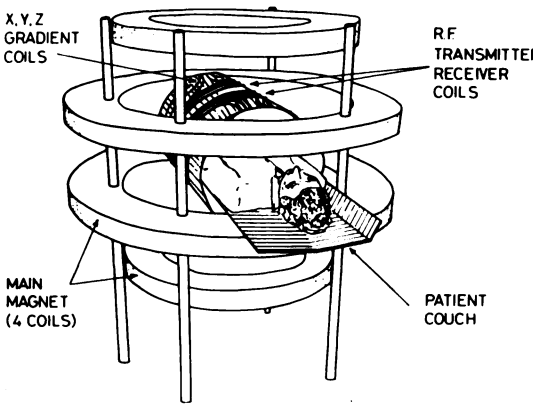

FIG. 2 The Aberdeen 0.04 T NMR Imager.

The magnet may be one of several types—resistive, superconducting, or permanent. For the clinician, its most important property is the field strength. An increase in magnetic field gives better signal-to-noise ratio for a given imaging time, but with an increase in capital cost and in installation costs and problems. The two NMR imagers designed and built at Aberdeen University use magnets with field strengths of 0.04 T (Telsa) and 0.08 T. (for comparison, the earth's magnetic field is about 50 μT.) They are resistive magnets, requiring cooling water and electrical power (about 10 and 25 kW respectively). Both are very low field systems (up to 1.5 T fields have now been used for imaging elsewhere), but they use side-access, vertical field magnets. This allows the use of efficient solenoidal RF coils which, at low field, give significant signal-to-noise ratio advantage over the 'saddle' RF coils of horizontal field systems (Hoult & Richards, 1976). Thus, although such parameters as T_1 are characteristic of 1.7 or 3.4 MHz systems, image signal-to-noise rato is that expected for a higher field.

Proton Density and Relaxation Times

NMR images may carry information on many parameters. These are: proton density, the spin-lattice relaxation time T_1 (describing the rate at which magnetisation re-aligns with the static field after disturbance), transverse relaxation time T_2 (describing the faster rate at which the spin-precession signal would disappear, given a perfectly homogeneous magnetic field), fluid flow, and molecular diffusion. The NMR pulse sequence generally used in Aberdeen is designed to bring out information on proton density and T_1, thus giving both anatomical and biochemical information. The imaging, and the biological interpretation, of these two parameters will be considered in more detail.

(a) *Proton density*

The interpretation of proton density images is not quite as obvious as it might seem, because the images show not all protons, but only fairly mobile ones. Protons—hydrogen nuclei—that are bound inside large molecules (such as proteins) have extremely short transverse (T_2) relaxation times. This means that the signals which they generate disappear very quickly, and are not detected. An NMR image of human tissues reveals protons in water and in free lipids, but not directly membrane lipids or proteins; the presence of these latter will be detected only indirectly via their influence on relaxation times. Proton density images do not give good soft tissue contrast, because water content of soft tissues does not vary greatly. If we assign a (nominal) value of 100 for water, then body fluids would give values approaching 100, while soft tissue values would lie in the range 70–80, and fat, with protons in mobile lipids, gives higher values. Good contrast is obtained only in regions of very low proton density, such as cortical bone, or gas in the gut, but this delineation may yield useful anatomical information.

To obtain the information to create a proton density image, RF pulses are applied to the patient which are just long enough to tilt the magnetisation through 90°, so that the precession, at right angles to the main field, gives the largest possible signal. Frequency-decoding is used to separate out the signals from different volume elements in the patient, giving the pixels of the image. The size of the signal from each should be directly proportional to local proton density, but unfortunately, this is only true if the time between each of the many RF pulses needed to create the image is long, compared with the T_1 (the spin-lattice relaxation time) of any of the tissues present. Otherwise, the magnetisation has not fully realigned with the main field before its next 90° tilt, and the signal recorded is reduced. Since the T_1 values of some body fluids may be well over one second, this could lead to very long imaging times. Instead, the inter-pulse period is kept long, when compared only with tissues whose proton density is to be measured. For brain tissue, T_1 values measured at 0.04 T (1.7 MHz) are in the region of 300 ms, and a pulse-period of one seond will give a reduction in signal size (and therefore apparent proton density) of less than 5%; if T_1 is known, the reduction is predictable and can be corrected.

'Proton density' images may also be affected by

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the transverse relaxation time T_2 (describing the 'inherent' rate of reduction of the NMR signal), if there is any delay between applying the 90° pulse and recording the signal. In spin-warp imaging, as used in Aberdeen, such a delay is obligatory, but a short time, typically 10 ms, is used, to minimise T_2 effects.

(b) *T_1, spin-lattice relaxation time*

After excitation of proton spins in the body, they lose their excess energy to their surroundings—the 'lattice'—at a characteristic rate. In soft tissues, time constants are in the order of hundreds of milliseconds; they have been measured for many soft tissues, both normal and pathological, *in-vivo* and *in-vitro* (Hazlewood, 1979; Ikehira & Smith, 1983). Some typical values at 0.04 T (1.7 MHz), corresponding to the first Aberdeen imager, are shown in Table I.

TABLE I

Typical proton spin-lattice relaxation times (T_1), in-vivo, at 1.7 MHz (0.04 T) (values in milliseconds)

Brain (white)	230–250
Brain (grey)	270–330
Fat	130–150
Liver	140–160
Muscle	160–200
Kidney	280–340
Cirrhosis	180–300
Hepatoma	200–400
Renal carcinoma	350–450

The energy exchange of spin-lattice relaxation is mediated by local fluctuations in magnetic field, due to the relative motions of many microscopic magnets. These magnets consist of spinning electrons and atomic nuclei, and they move in the rotational tumbling of molecules. Spin-lattice relaxation will be caused only by fluctuations at the characteristic frequency of the protons, and the probability that such fluctuations will occur depends on the chemical environment of the protons. Thus, the values of spin-lattice relaxation-time T_1 yield biochemical information. The probability of local field fluctuations at the characteristic frequency depend on that frequency. T_1 therefore depends on the magnetic field strength.

Protons in soft tissues will experience several different chemical environments. They may, for instance, be very mobile in 'free' water, or may be very tightly bound inside a protein molecule. In the latter case, as described earlier, their T_2 relaxation-times are so short that the resulting NMR signals are not seen. Measured tissue T_1 values indicate that water is observed in two states—one free water, the other a 'bound' state in a hydration sheath around a macromolecule of water interacting strongly with that molecule (Mathur-de-Vre, 1979). Protons exchange very quickly between the two states, so that the observed T_1 value is a simple weighted average of the T_1 values that would be expected for the states separately. The contrast in a T_1 image of soft tissues will depend on both the variation in the proportion of free to bound water, and on the difference between the T_1 values for free and bound water. When working at low field (low frequency), this difference is considerable, the T_1 of free water being much longer than that of bound, so that a change of only a few percent in free water content could give a 100% change in T_1. (The difference between T_1 values of free and bound water, and thus the available image contrast, is thought to decrease at high fields and frequencies—Diegel & Pintar, 1975). The ratio of free to bound water depends on water content, on the concentration of macromolecules, and on the ability of those macromolecules to bind water. Thus, the good contrast observed between grey and white matter in T_1 images of the brain is almost certainly due to the interaction between water and myelin in the white matter, leading to a reduction in T_1.

Water content and binding, as described above, seem to be the dominant influences on tissue T_1 values. Other factors can, however, be involved. Free lipids have short T_1 values so that their presence would reduce the measured T_1, and T_1 is also reduced by the presence of strongly magnetic molecules, such as free oxygen or copper ions. Temperature and possibly tissue pH may also matter. Direct interpretation of T_1 values is not always possible, but in clinical diagnosis they may still be indicative of pathology, and in research they will point to a limited number of biochemical 'scenarios' which may be worthy of further investigation.

It was shown in the previous section that proton density may, to good approximation, be determined from the size of a signal following a 90° readout pulse. T_1 values, however, can never be deduced from a single signal size. Instead, they must be calculated from the signals resulting from at least two different pulse sequences. If one of these is the single 90° pulse of the 'proton density' image, then the other may be a pair of pulses. The first, in effect a 180° pulse, completely inverts the proton magnetisation, then a delay allows partial return to equilibrium, after which a 90° pulse provides a readout of how far that return has progressed. The T_1 value may be calculated from the ratio between the signals resulting from the two pulse sequences,

90° and 180°-delay-90°. For a single tissue, with one T_1 value, this calculation can be very accurate (Redpath, 1982). If an image-pixel contains more than one tissue and relaxation time, the T_1 calculation will give some weighted average value. The calculated T_1 values can be used to create a pseudo-image—a map of tissue properties which may be interpreted in terms of tissue biochemistry.

The Benefits and Problems of NMR Imaging

From the point of view of the information obtained in NMR imaging, the important advantages lie in the provision of morphological detail, further enhanced by the triplanar sections and the low distortion effect of artefacts, such as those produced by the base of the skull in X-ray CT. In addition, because the data collected reflect aspects of the biochemical status of the tissues imaged, a new dimension of information, which is of value as a physiological and pathological parameter, is now available.

NMR imaging at magnetic fields currently applied is free from biological hazard, both from the point of view of the patient being imaged and from that of the operative, so that personnel are not required to be separated from the patient during imaging.

Some patients (about 2%) are unable to tolerate the enclosed positioning during imaging for the long periods required for detailed studies, and this does rarely present a problem. However, gross movement will distort the image, though minor degrees of movement are accommodated, and cardiac pacemakers are likely to malfunction if exposed to magnetic fields during imaging, so that the National Radiological Protection Board (1983) recommends that such patients should not be imaged.

Metallic implants and surgical clips may be displaced during imaging, but at low field strengths such as those used in the Aberdeen Imager, this is unlikely to occur.

Potential Value of NMR in Biological Psychiatry

NMR may prove to be of value in the investigation of organic and functional psychotic disorders. In assessing cerebral and cortical atrophy, morphological information can be obtained in the same manner as X-ray CT, viz—ventricular size, ventricular brain ratios, and sulcal widths. Furthermore, because the T_1 of grey matter is larger than that of white matter, contrast between these tissues is obtained on the T_1 images, and changes in thickness of the grey matter can be measured.

T_1 and PD can be measured in any area of brain tissue. These parameters may alter as a result of dynamic changes in distribution of brain water, as may occur in conditions which alter the level of hydration, increasing or reducing it. These hydration changes may be generalised, as in alterations in T_1 during alcohol withdrawal (Besson *et al*, 1981), or localised, e.g. as a result of vascular accidents.

NMR parameters may also alter in the face of structural pathological changes in cerebral tissues. This has been clearly shown to occur in tumours, infarcts (Bydder *et al*, 1982), and demyelinating diseases (Young *et al*, 1981).

In these situations, the pathology is gross and can be recognised visually on the images. It has furthermore been shown that measurable change in the parameters are present in more diffuse and subtle pathologies such as senile dementia of Alzheimer type (SDAT) and multi-infarct dementia (MID) (Besson *et al*, 1983), even when detectable change is not discernable visually on the images. This clearly provides scope for areas of investigation hitherto unavailable.

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Nuclear Magnetic Resonance (NMR)
II. Imaging in Dementia

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Summary: Proton NMR imaging of the brain is rapidly becoming established as a useful investigative tool in medicine. This paper examines the usefulness of the NMR parameters—spin-lattice relaxation time (T_1) and proton density (PD)—in differentiating groups of patients with senile dementia of Alzheimer type (SDAT) and multi-infarct dementia (MID) from each other, and from elderly controls. T_1 values increase with severity of dementia. NMR parameters may also be of use in localising regions of brain damage.

NMR imaging using the Aberdeen method measures two parameters—the proton density (PD) and the spin-lattice relaxation time (T_1); these parameters represent not all protons, but only fairly mobile ones. Protons, (hydrogen nuclei, that are bound inside large molecules such as proteins) generate signals that cannot be detected. Proton density data therefore refers to the protons in water and free lipids, and is a measure of the concentration of such protons. T_1 values represent the water as observed in two states, one 'free', the other a 'bound' state in a hydration sheath around a macromolecule, consisting of water interacting with that molecule. Protons exchange very quickly