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Towards quantitative measurements of relaxation times and other parameters in the brain

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Summary. The nature and physical significance of the relaxation times T1 and T2 and of proton density are described. Methods of measuring T1 and T2 are discussed with emphasis on the establishment of precision and the maintenance of accuracy. Reported standards of success are briefly reviewed. We expect sensitivities of the order of 1% to be achievable in serial studies. Although early hopes of disease diagnosis by tissue characterisation were not realised, strict scientific method and careful calibration have made it practicable to apply relaxation time measurement to research into disease process. Serial measurements in patients and correlation with similar studies in animal models, biopsy results and autopsy material taken together have provided new knowledge about cerebral oedema, water compartmentation, alcoholism and the natural history of multiple sclerosis. There are prospects of using measurement to monitor treatment in other diseases with diffuse brain abnormalities invisible on the usual images. Secondarily derived parameters and notably the quantification of blood-brain barrier defect after injection of Gadolinium-DTPA also offer prospects of valuable data.

Key words: Relaxation times – Quantification – Methodology – Tissue characterisation

Ever since it was discovered in 1971 that tumours have raised NMR relaxation times [1], the ideal of characterising biological tissue by its relaxation time has encouraged investigators to attempt measurements of relaxation times. The hope was that each tissue would have a distinct narrow range of relaxation times, and that reliable measurements of these times would enable an unambiguous identification of the tissue type to be made. The methodology for measuring the relaxation times of small samples had been established in vitro using NMR spectroscopy, and it was unclear whether such measurements could be made reliably in vivo, using MR imaging. Subsequently an enormous research effort has gone into developing and validating imaging methods of measurement, and into collecting values of relaxation times for a wide range of normal and pathological tissues over a range of magnetic fields. Improvements in our understanding of the instrumental effects mean that relaxation times can now be measured extremely accurately and precisely, but tissue characterisation has not followed, principally because of the large biological variation within tissues. However discrimination between a smaller number of tissues is often possible; subtle changes in white matter, of the order of 5%, can be seen between groups of patients. Because the normal variation is significant (also about 5%), the most sensitive measurements are serial, carried out on the same patient, when changes as low as 1–2% may be detectable. Although the development of quantitative techniques has focused on relaxation times, there is a treasure trove of other tissue parameters that can in principal be measured and which will provide extra independent information on the tissue state. These are summarised in Table 1, and are discussed below. Good descriptions of many aspects of imaging are given in the book by Foster and Hutchinson [2].

Significance of T1 and T2

MR images may show an almost infinite variety of tissue contrasts, depending upon how the timing parameters (TR, TI, TE) are set. The significance of T1, T2 and PD (proton density) is that they describe how a signal will vary (according to a simple model) with these timing parameters. After perturbation of the spin system by an applied radiofrequency field at the Larmor frequency, the longitudinal magnetisation recovers (relaxes) to its equilibrium (steady-state) value with time constant T1; transverse magnetisation decays away (relaxes) with time constant T2. The tissue may be described, or characterised, in terms of these three fundamental parameters, rather than its appearance in every conceivable pulse sequence that might be used. This model is known to be simplistic; however it is a useful conceptual tool. It assumes that within the voxel there is just one homogenous group of proton spins, relaxing with a single T1 and a single T2; and it assumes the

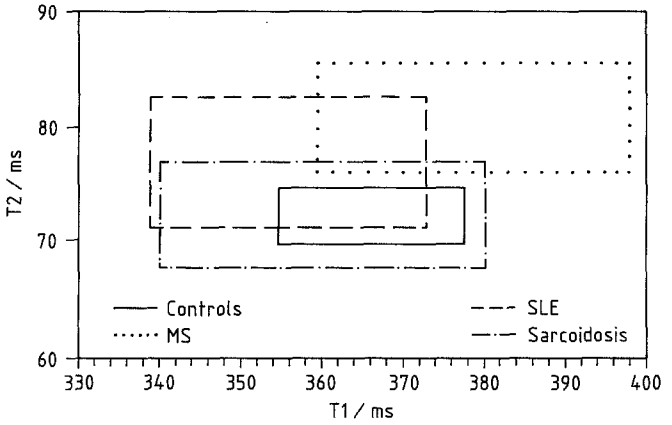

Fig. 1. Boxplot of T1 vs T2 measurements in patient groups and controls. Boxes represent ± one standard deviation. Multiple sclerosis (MS) had significantly raised T1 and T2 compared to normal. Systemic lupus erythematosis (SLE) had raised T2 only. MS T1 was significantly higher than SLE. (From Miller et al. [6])

tissue is static (i.e. there is no diffusion, flow or other movement).

The relationship between the NMR parameters (T1, T2 and PD) of a tissue, and its pathophysiological, biological state has been the subject of much study [3, 4], and it is still not completely understood. However a qualitative description can be given, which enables the observed phenomenon to be understood. Proton density, PD, describes the concentration of protons (hydrogen nuclei) available for observation by NMR. These occur mostly in water and in fat. To be "NMR-visible" they must have T2's longer than about 10 ms (otherwise the signal will have died away before data collection, which takes at least 10 ms in a conventional imaging sequence). There are small compartments of protons with shorter T2's which are "NMR-invisible" when imaging. Up to four water compartments can be seen using spectroscopy [5] with which signal can be observed from about 20 μs after excitation.

Relation to proton motion

Several descriptions of relaxation have been given [2–4]. A short intuitive picture is given here. The relaxation times depend on the amount of motion of the protons (mostly within water) within the tissue. Consider a water molecule immediately after excitation by a radiofrequency (RF) pulse. It is immersed in a sea of rapidly moving magnetic dipoles (i.e. other protons) which subject it to a fluctuating magnetic field that is in addition to the externally applied static field. For longitudinal (T1) relaxation to occur, the excited proton must lose energy to the surrounding magnetic field. This requires a fluctuation at the Larmor frequency (i.e. 20–60 MHz). The probability of this occurring, and hence the relaxation rate 1/T1, depends on how many moving protons there are, and also whether very rapid movement (in times of about the reciprocal of the Larmor frequency i.e. 10^{-8} s) is possible. As a water molecule becomes more free, (i.e. moves to a more "watery" environment), the movements due to Brownian motion occur in times much less than 10^{-8} s; the fluctuating field from the sea of dipoles partly time-averages to near zero in a time of 10^{-8} s, there are fewer fluctuations at the Larmor frequency, and the relaxation rate is reduced. High water content generally implies more mobile water protons and hence a longer T1.

For transverse (i.e. T2) relaxation to occur, either slow or fast field fluctuations are required (to dephase the magnetisation). Slow fluctuations occur more often in tissue (because of the existence of large slowly moving protein macromolecules), and therefore T2 is most influenced by the slow motions (taking approximately 10^{-4} to 1 s). An increase in free water will increase T2; in fact PD, T1 and T2 are positively correlated, in that they tend to increase together and measurements of all three parameters may not give increased tissue discrimination compared to using just one parameter. In most pathologies there is an increase in the amount of water that is free (i.e. not bound to other molecules) and therefore an increase in the relaxation times. T1 is field dependent (as it depends on the amount of motion at the Larmor frequency); white matter T1 increases from about 366 ms [6] at 0.5 T to 687 ms at 1.5 T [7]. T2 is almost independent of field, since it depends mostly on the low frequency motions; white matter T2 is 72 ms [6] at 0.5 T and 82 ms [7] at 1.5 T.

Methods of measuring relaxation times

Spectrometer method

NMR relaxation times have been reliably measured using spectrometers for several decades, and spectrometer methodology constitutes the "gold standard" by which imager methodology is assessed. In this context the essential qualities of a spectrometer are not that it can produce spectra, but the following:

(a) a single small uniform sample is used (hence there are no partial volume or multi-compartment effects),
(b) the magnetic field is uniform (with no application of gradients),
(c) the radiofrequency (RF) field is reasonably uniform, and powerful enough to avoid off-resonance effects and to allow the use of short pulses,
(d) the signal from the whole sample can be observed soon after an applied pulse (with no delay for imaging gradients),
(e) many measurements of signal can be made in a short time (since signal to noise ratio is good); hence the signal can be fitted to the model function for inversion recovery (IR) or spin echo (SE) signal. The recovery of longitudinal magnetisation can be followed over the whole range of inversion times (TI); the decay of transverse magnetisation in an SE sequence can be followed over a range of echo times (TE). These multipoint data usually fit the model functions well and relaxation times can be measured to within a few per cent.

The imager can be run in "spectrometer mode" i.e. with the gradients turned off, using a sample that is much smaller that the transmitter coil (to give a uniform RF field),

with full relaxation between repetitions, and with short non-selective pulses. The exact relaxation times of test objects can then be determined, with a view to measuring the imaging accuracy.

Imager methods

In an imaging sequence the signal from a voxel of uniform tissue with a single proton compartment will still follow the model functional expressions for IR and SE, provided that (a) the correct tip angle is used in the expression and (b) the imaging gradients are set up correctly. The tip angle may not be the intended 90° or 180°, for two reasons. The first, inhomogeneity in the applied RF field, arising from the use of a coil that is not much larger than the sample, means that the same flip angle cannot be applied to the whole sample. For this reason the use of a body coil for transmission is usually preferable to using the head coil, when making relaxation time measurements. (The head coil is used for reception, for optimum signal to noise ratio). Second, there is a variation of tip angle across the slice profile, from near its nominal value (e.g. 90°) at the slice centre, to 0° outside the slice. Near the slice edge the tip angle has some intermediate, usually unknown, value, and this is how many of the inaccuracies in measurements in relaxation times arise. A gaussian profile is the worst (since most of the slice is neither tipped 90° nor 0°); a rectangular profile is ideal (since within the slice the required angle is obtained, and outside it the tip angle is 0°, i.e. no signal is produced). The gradients can usually be set up accurately, provided there are no uncompensated eddy currents, and on a modern system this does not usually limit the accuracy of measurements.

Criteria for assessment of methods

In assessing methods of measuring relaxation times, the principle criteria are a) precision (i.e. how reproducible are the measurements on the same machine?) b) accuracy (how close is the measurement to the truth (measured using a spectrometer)) and c) examination time (long times reduce patient compliance, and may produce more movement artifacts). Precision reflects random errors; accuracy reflects systematic errors. Systematic errors may be acceptable provided they remain constant; the measurements will retain their sensitivity to tissue state even though systematic error is superimposed on them all, although comparison with other imagers at the same field will not be possible. If the systematic errors are of unknown origin they may change unpredictably (for example during an imager repair or upgrade) and decrease the sensitivity of tissue measurements. It has been suggested that the effect of systematic errors can be eliminated by calibration of the machine (plotting measured values verses true value for phantom solutions) and using this calibration to correct subsequently measured in vivo values; however if the systematic errors are unstable this procedure collapses. If the systematic errors are of known origin, it is often possible to alter the data collection technique to reduce or eliminate them, and this should be done where possible, as it will lead to more stable measurements (i.e. ones that do not vary artefactually with time). In conclusion, accuracy is as desirable as precision, since in accuracy lies stability. Examination time usually has to take third place to accuracy and precision; as our methodologies improve it may become possible to reduce examination time without compromising accuracy and precision.

Sequences

Early single-slice imaging measurements of T1 were made using the standard multi-point methods from spectroscopy [8]. Either an IR with a range of TI's, or saturation recovery (SR) with a range of TR's, was used to plot out a set of points on the magnetisation recovery curve. These multipoint methods are time consuming, and have generally lost popularity in favour of two point methods, where just two TI's or TR's are measured. These provide just sufficient information to calculate T1 (provided there is only one proton compartment). An SR sequence requires a $TR \leq T1$, in which case the slice profile becomes very distorted (since the tip angle, and hence saturation factor, depend on position in the slice profile) and accurate measurements of T1 are impossible [9]. For this reason IR's are generally preferred to SR's (they can be run at long TR's, so that the slice relaxes completely between inversion pulses. A modification of the SR, the total saturation recovery (TSR) [10], in which the magnetisation is completely destroyed (using a non-selective pulse) before being allowed to partly recover, circumvents the slice profile problem and can give accurate results [7]. In an attempt to speed up multi-point methods, low tip angle SR methods have been suggested [11]; however these are still prone to slice profile effects and accuracy is poor.

Early single slice imaging T2 measurements were made using spin echoes at varying echo times [8]. The multi-echo sequences (CPMG etc.) produced a considerable saving in time, and enabled a fairly complete magnetisation decay curve to be plotted, with at least 16 points. Multi-echo sequences run in multi-slice mode are inaccurate, and therefore current practice is to use either a 2 point (i.e. two echo) multislice sequence, if several slices are required, or else a multi-echo single slice sequence if a single slice is sufficient. The latter has the advantage of enabling multiple proton compartments to be identified, provided they have distinct T2's, since the decay curve can be decomposed into the sum of several exponentials.

When multislice imaging appeared, attempts were made to convert the methods described above to multislice. Two problems arose:

- There may be interference between adjacent slices; this may be minimised by using non-contiguous slices, such that the "tail" of one slice profile does not extend to the next slice profile. Spatially continuous coverage may be obtained using two (or more) interleaved sets, with a TR long enough to ensure that one set has relaxed before its neighbours are pulsed and examined.

• In all sequences producing echoes, at least two slice-selective pulses are used; these each define slices which must superimpose in space. In fact if the profile is non-rectangular, then even perfectly superimposed slices will not behave according to the model equations, and relaxation times will be inaccurate.

Attempts to run multi-point methods in multislice mode are attractive for their short imaging time, but generally suffer from two drawbacks:
1. Increased artifacts and loss of accuracy,
2. TR is usually too short to collect a complete set of slices at all points; a compromise must be made on either the number of slices or on the number of points.

Given these problems of making accurate measurements with selective pulses, it is worthwhile considering what sequences would be capable of giving no systematic errors. Slice profile errors can be avoided by using complete relaxation (long TR) or by complete saturation (non-selective 90° pulse). Slice superimposition errors can be avoided by using only one selective pulse (the remainder being broad-band non-selective pulses that affect the whole sample). Accurate IR and SE sequences could be built from selective 90° and non-selective 180° pulses. An accurate TSR would result from these pulses with an initial non-selective saturation 90° pulse. Making the 180° pulse selective, with a thicker slice than that selected by the 90° pulse, will probably preserve accurate performance, provided the tip angle is 180° over the width of the 90° slice, and this is probably how reliable multislice relaxation time measurements of the future will be made.

To make any measurements reliably needs constant attention to quality control [12–15], since the imagers are not generally designed with quantitative measurements in mind. Imager time must be made available to physicists for the implementation of quantitative sequences and for the regular testing of measurements on phantoms and control subjects. The stability of the imager may need to be controlled and measured over a long period of time if long term studies are to be carried out.

When making quantitative measurements the physicist can adopt the paradigm of the scientific instrument designer, who is presented with a sample (the patient) about which he or she wishes to make the most careful, detailed measurements possible, in a non-destructive way, using the infinitely adjustable instrument (the imager). The biological question to be answered and thus the bio-physical feature to be measured need very careful choice after discussion by all concerned. All must understand the reasoning if the collaboration is to end in success.

Results

Focal changes in relaxation times

Tissues with focal, grossly altered relaxation times have been visible since the beginning of magnetic resonance imaging, because it is these relaxation times that are responsible for image contrast. Many pathological tissues were found to have altered (usually raised) relaxation times, but the spread in measured values was so large that little tissue characterisation was possible [4]; all that could be concluded from an altered relaxation time was that the tissue was abnormal. It is still unclear how much of this overlap is genuine, biological variation, and how much is instrumental or methodological in origin.

The maturation of brain has been studied by several workers. Holland et al. [16] found T1 at 0.35 T decreasing from 1615 ms at birth to 487 ms (age 11–14) for white matter, and from 1590 to 805 ms (grey matter). T2 decreased from 91 to 49 ms (white matter) and 88 to 59 ms (grey matter). Baierl [17] found similar decreases. The relaxation times were presumably decreasing as an increasing proportion of the brain water became bound to myelin. Experimental oedema shows an increase in relaxation times [18]. Bell et al. [19] showed that T1 values were an accurate reflection of vasogenic oedema around tumours. MS lesions have been shown to have raised relaxation times [20]. Because these changes are localised they are clearly visible; however the region of abnormal tissue i.e. the "lesion", is heterogeneous and has no overall well defined relaxation time. This is one of the causes of lack of specificity, and also makes comparison between images difficult. Nevertheless large lesions can be examined to detect patterns and their evolution, an exercise in which region of interest quantification may play an important part. Improvement in spatial resolution and image processing increase the attraction of such methods as means of monitoring processes that are already partly understood, having a limited variety of tissue composition.

Diffuse changes

Even though the brain tissue is heterogeneous, and small diffusely scattered regions of abnormality are not individually detectable, the presence of diffuse abnormality may be established by measuring and averaging relaxation times over large regions. The pathophysiological explanations for the observed variations from the normal are usually complex, and may be pursued by further observation and experiment, including comparison with other diseases and combined physiological and NMR studies on animals. The study of subtle diffuse changes, principally in the normal appearing white matter (NAWM), requires considerable attention to the accuracy and precision of the imager, since the changes in relaxation time may be only a few per cent, and it is in this area that many of the challenges in quantitative methodology lie.

Accuracy

Several groups have measured the accuracy (i.e. deviation from the true value) of relaxation times measured using an imager, by examining solutions of paramagnetic salts. These solutions are calibrated by using the imager in "spectrometer mode" (see above), or by using a seperate spectrometer at the same field. Below we quote typical accuracies for the relaxation time values of white matter. Pykett et al. [21] measured T1 using an IR sequence at 0.15 T

within 2%. The 3D technique used no slice selective RF pulses. Bakker et al. [22] used multi-point IR and SE single slice sequences at 0.15 T to obtain accuracy of about 3% in T1, T2 and PD. Johnson et al. [23] measured accuracies at 0.5 T of about 1% with a single slice multi-point technique (IR and SE) for animal studies. A multi-slice two-point patient protocol gave accuracies of about 1% for T1 and 4% for T2. Condon et al. [24], using IR and SE sequences at 0.15 T measured errors of 10–20%. MacFall et al. [7] measured T1 at 1.5 T to within 3%, using a four point single slice total saturation recovery (TSR) sequence with broad band saturation and refocussing pulses; T2 accuracy, using a CPMG sequence, was bad (15%). Gowland et al. [25] used a hyperbolic secant slice selective inversion pulse to measure T1 within 2% at 1.5 T; although single slice, being selective it can probably be extended to multi-slice. The hyperbolic secant pulse was required because homogeneous excitation using the body coil was not available. From these studies we see that accuracies of 1–4% have been obtained by several groups over a range of fields, and that these good accuracies were not achieved by every group that measured them. In fact in a European Economic Community study of 15 imagers [26] a wide variety of accuracies were found (3–50%). This variety arises from methodological differences, principally concerned with control of RF amplitude and homogeneity, and slice profiles, as discussed above. Only EEC centres using two-point IR/SE techniques obtained good accuracy [27]. Good methodology has been described by several authors [6, 21, 23, 24]. With the identification of accurate techniques, and with the availability of appropriate stable imagers becoming widespread, we may look forward to these accuracies of 1–4% becoming the norm rather than the exception.

Normal variation of relaxation times in brain

When comparing the relaxation times of 2 (or more) groups of subjects, in order to investigate possible biological causes of changes in relaxation time, the relaxation times for each group are summarised by their mean and standard deviation. To detect a significant difference, the means must differ by a small multiple of the standard deviations, and therefore the standard deviation of relaxation time measurements in normal subjects is of great interest, and should be minimised if possible. The measured standard deviation will include.

a) instrumental imprecision (which could be measured by repeatedly scanning the same subject, and in principle can be reduced by improved methodology) and

b) normal biological variation between subjects (which cannot be altered until we understand its origin).

The ideal instrument will have instrumental imprecision that is negligible compared to the normal variation. Many groups have reported the standard deviation of their measurements of relaxation times in normal subjects. Kjos et al. [28] reported 4–8% for T1 and T2 at 0.35 T; Mander et al. [29] found 2.1% for T1 at 0.08 T (over only 5 controls); Smith et al. [30] suggested about 6% for T1 at 0.08 T. Holland et al. [16] reported 8% for T1 or T2 at 0.35 T although this included position dependence; Breger et al. [31] found 8% for T1, 5% for T2 at 1.5 T; Lacomis et al. [32] found 11% for T1 at 1.5 T; Besson et al. [33] suggested about 8% for T1 at 0.08 T. Ormerod et al. [20] reported 4% for T1 and 9% for T2 at 0.5 T; Johnson et al. [23] found 5% for T1 and 10% for T2 at 0.5 T. Larsson et al. [34] found 5% for T1, 6% for T2 at 1.5 T; Miller et al. [6] reported 3% for T1 and T2 at 0.5 T; Harvey et al. [35] found 4–6% (depending on position) for T1 at 0.5 T. These studies suggest firstly that inter-patient variability is close to 5% for both T1 and T2 from 0.08 T to 1.5 T, and secondly that several groups have measured erroneously high values by including other (methodological) sources of variation. The latter may be instrumental, of the kind discussed previously, or they may relate to how the image is analysed (and, in particular, variations in where the volume of interest is placed in the brain). It is also possible (though probably more rare) to measure an erroneously *low* value of standard deviation, by biasing the observation of mean value in a region of interest towards what the observer expects (i.e. excluding unexpected results). There is significant dependence on the position of the white matter chosen for analysis; the range of values is about 5–10% [20, 35, 36]. There may also be differences arising from sex and from physiological variations in water balance. Measurement of grey matter is more difficult, and produces larger standard deviations [28, 30] because the regions of interest are smaller, there is more chance of partial volume errors from neighbouring CSF, and the term "grey matter" covers a wide range cell mixtures. In conclusion, any reliable intergroup study must first demonstrate a normal variation of no more than about 5%.

Intergroup comparisons of normal appearing brain

Significantly raised relaxation times in the NAWM in several patient groups have been detected. In multiple sclerosis patients Ormerod et al. [37] found NAWM at 0.5 T raised by 9% (T1 and T2); Lacomis et al. [32] found 6–9% (T1) at 0.15 T; Larsson et al. [34] found grey matter raised 22% (T1 only) at 1.5 T and white matter raised 12% (T2 only); Miller et al. [6] found the NAWM raised at 0.5 T by 3% (T1) and 12% (T2); Haughton et al. [36] found 8% (T1) and 4% (T2) at 1.5 T; Brainin et al. [38] found T1 and T2 significantly raised at 0.5 T. In optic neuritis Ormerod et al. [37] found T1 and T2 raised by 13–14% at 0.5 T. In acute brain stem syndrome Ormerod et al. [37] found T1 and T2 raised by 5–7% at 0.5 T. In systemic lupus erythematosis Miller et al. [6] found T2 (but not T1) raised at 0.5 T by 6%. In alcoholics Smith et al. [30] found whole brain T1 of alcoholics raised by 3% at 0.08 T. In schizophrenia Besson et al. [33] found T1 raised by 12% at 0.08 T, although it was unclear whether this was the affect of the neuroleptic drug treatment. In 4 patients with near-terminal AIDS, Wetterberg et al. found significantly raised T1 (32%) and T2 (21%) at 0.02 T [39].

These higher relaxation times presumably indicate raised water content or mobility in the pathological con-

Table 1. NMR and physiological tissue parameters accessible by MRI. (Adapted from Tofts et al. [12])

Parameter	Type	Pathophysiology	How measured
Signal intensity	NMR	Depends on sequence	Customised
Relaxation times T1 T2	NMR	Water content oedema, scar tissue	IR, SE
Total water PD	Physiological	As T1 T2	IR, SE + NUC
ic $T2_{icw}$ ec $T2_{ecw}$	NMR	Unlikely to change Oedema + protein content	MDC
ic water PD_{icw} ec water PD_{ecw}	Physiological	Reduced in oedema Raised in oedema	MDC + NUC
BBB permeability DTPA leakage space	Physiological	Leaky BBB Probably ec space	Gd-DTPA + dynamic MRI
Perfusion, diffusion, flow	Physiological		Several sequences
Susceptibility	NMR	Iron content	Field map
Chemical shift image	Physiological	e.g. fat, NAA, PCr	Several sequences
Texture of image above parameters	Secondary	?	Computer algorithms
Volume of region of abnormal parameter value	Secondary	Size of lesion	Segmentation algorithms

ic = intracellular; *ec* = extracellular; *MDC* = magnetisation decay curve; *NUC* = non-uniformity correction; *BBB* = blood brain barrier

ditions studied. Lower relaxation times have not been recorded. The ability to separate two groups depends critically on the size of the methodological and instrumental variations, and the failure to detect a significant difference does not imply that one does not exist. This can be seen from the variety of results obtained by the five studies of multiple sclerosis described above. The relaxation times should be measured blind to avoid observer bias; and when reporting the absence of a significant difference, the smallest difference that would be detectable should be given. The measurements on normals and the patients should be interleaved in such a way as to avoid the possibility of artefact arising from imager drift during the study.

Serial measurements of normal appearing brain

A serial study of the effects of disease or therapy on a particular subject is not subject to all the normal variation discussed previously, and is therefore capable of greater precision and sensitivity. The instrumental reproducibility can be measured using repeat scans of phantoms or subjects (the latter is more realistic since it includes repositioning errors). Kjos et al. [28] reported 2–4% in humans at 0.35 T (T1 and T2); Breger et al. [31] using phantoms reported 6% (T1) and 2% (T2); Komiyama et al. [40] measured 1.3% (T1) and 1.7% (T2) on phantoms at 0.5 T; Harvey et al. [35] measured 2% in humans. The instrumental reproducibility sets the lower limit to the magnitude of serial change that can be detected. The intrinsic limitations are likely to be imager noise, variation in the position of the volume of interest (including variations in where the slice is positioned in the brain) and imager instability (i.e. variation in the imager accuracy). A careful study of the sources of variation [35] is likely to enable the major ones to be identified and possibly reduced. At 1.5 T precision of better than 1% may be possible with care. If the instrumental variation could be sufficiently reduced, we might expect to observe the natural biological variation with time for a single subject.

The few serial measurements reported have shown great sensitivity. Mander et al. [29] found a significant reduction in T1 of 1.1% at 0.08 T after the consumption of a large amount of alcohol. Smith [30] found significant reduction of T1 at 0.08 T in alcoholics as a result of abstinence, compared to their T1 at the time of admission. Fujimoto [41] found a rise in T1 of the striate boby of 5% at 0.1 T as a result of injection of the drug haloperidol (used to treat schizophrenia). In AIDS, the elevated T1 and T2 were reduced after treatment with the drug peptide T [39]. In diseases which do show an alteration in the relaxation times of NAWM, this may provide an objective way of assessing the progress of the disease and the effectiveness of therapy.

Other magnetic resonance and physiological tissue parameters

Although most quantitative work has concentrated on the measurement of two parameters (T1 and T2), there are many more available for tissue characterisation [12]. Some of these parameters (e.g. relaxation times) are NMR in origin (i.e. they describe NMR properties of tissue, rather than physiological properties); others are basic physiological parameters (e.g. flow or water content), independent of the measurement methodology, and in principle accessible by other (non-NMR) methods. They all give extra information that is usually independent of T1 and T2, and often more relevant. For example in active MS, in which there is Blood-Brain Barrier (BBB) breakdown, BBB membrane permeability measuring using Gd-DTPA is more relevant than T1 or T2 [42]. Table 1 summarises these parameters; they range from those studied in depth (e.g. T1, T2) to those on which work is only just starting (e.g. perfusion, texture).

Signal intensity from a single carefully controlled sequence can be a more time-efficient way of parameterising tissue than measuring the relaxation times (which require two or three sequences). For example a STIR sequence combines positive PD, T1 and T2 contrast, which may be desirable given that the three parameters are positively correlated, and may give just a good separation of lesion from normal tissue as would be obtained by calculating PD, T1 and T2 explicitly. Condon et al. [43] used an IRSE sequence to give a signal that almost exclusively arises from the CSF. The white matter is nulled by suitable choice of TI, and the CSF is enhanced by using a long echo time. The total volume of CSF is measured by summing the signal from all parts of the brain.

Total mobile water content can be derived from proton density (PD), since there is little fat in the brain. It has received little attention, since the images are relatively flat (a typical range is small; from 0.7 g/ml–1 g/ml). The sequences to measure T1 and T2 will provide PD as an extra "free of charge" parameter, with no extra scanning time required. Non-uniformity correction and calibration from an absolute concentration standard are required. PD may provide useful information, particularly as it has more obvious physiological significance than T1 and T2.

The multi-exponential decay of the magnetisation decay curve has been observed by many workers, using both spectroscopy [5], when up to 4 components may be seen, and imaging, when only the components with T2 greater than 10 ms are seen. The latter consist of intracellular mobile water (typical $T2_{icw} = 60$ ms), and extracellular water ($T2_{ecw} = 150$–500 ms). PD_{ecw} is normally about 0.2 g/ml; however in experimental oedema it can rise to 0.6 g/ml, and correlates with the electron microscopy measurements of extracellular space [18, 44]. $T2_{ecw}$ gives an indication of the protein content of the oedema [18]. The magnetisation decay curve for each pixel of a single slice multi-echo image set can be decomposed to give images of $T2_{icw}$, $T2_{ecw}$, PD_{icw} and PD_{ecw} [45, 46]. T1 relaxation curves are generally monoexponential, provided partial volume effects are not present [18, 47].

A method for the measurement of the permeability of leaky BBB membrane, using dynamic MRI scanning of Gd-DTPA, has been developed [48, 49]. This provides an objective index of disease activity in MS. The space into which Gd-DTPA leaks is also measured, and is probably the extracellular space.

Perfusion and flow characterise the random and directional movement of blood through tissue respectively. Flow measurements are well established [50]. Perfusion is harder principally because of measurement artefacts; it is reviewed in this issue [51]. The diffusion coefficient of water is a measure of its mobility, and can in principle be measured by applying gradients in a SE sequence [8]. Patient motion (including pulsatile brain and CSF movement) sets practical limits to this, although some reliable measurements have been made [52]. Le Bihan has proposed a method for measuring perfusion and diffusion independently [53].

Susceptibility images, or phase maps, are sensitive to iron-containing compounds (e.g. in haematomas) [54], and in principle could provide quantitative measurements of tissue magnetic susceptibility and possibly iron content.

Chemical shift imaging has a promise of providing quantitative concentration maps of compounds other than water. The non-water compounds in highest concentration are fats, and lipid images have the potential for studying demyelination products [55, 56]; some compounds at lower concentrations will probably also be able to be imaged, although only at low spatial resolution (e.g. N-acetyl aspartate, which appears to be a neuronal marker, and lactic acid and phosphocreatine, which give metabolic information).

Images of all of the 15 parameters listed in Table 1 can in principle be produced; from each of these could be derived secondary parameters by image analysis techniques, for example texture, or volume of abnormal tissue. In a study of T1 images of lumbar vertebrae, in osteoporosis and osteomalacia, Jenkins [57] has shown that although the 3 groups could not be separated using the mean T1 values, significant separation was possible using texture analysis, and that the texture measure correlated with the bone mineral density. Development of techniques for the calculation of secondary parameters is very much in its infancy, and we can expect considerable progress over the next decade.

With the advent of the possibility of having so many independent tissue characterising images on one patient, appropriate presentation methods will become vital. It may be required to superimpose many images in some way, so that the various attributes of a voxel of tissue can all be appreciated at the same time.

Conclusions

It is, at the moment, rare for an imaging unit to be used quantitatively to analyse tissue characteristics by measuring relaxation times, proton density, blood brain barrier defect, myelin breakdown and other factors that can be made to influence the MR signal, and it is almost unknown for this kind of work to form the main commitment of an MRI unit. A widespread loss of interest in such quantification followed the early enthusiasm, when the rather simplistic expectations of tissue "signatures" were seen to be unrealizable. Perhaps it was with some relief that the variability of T1 and T2 came to be appreciated by those who had begun to discover the unique and exciting diagnostic usefulness of MR images because, time-consuming though images were to achieve, serious work on relaxation time measurement took longer.

Looking back one can see that much of the disillusionment stemmed from failure to appreciate the demanding nature of experimental procedures using complex equipment. It is not surprising, then, that the physicist's term, "the NMR experiment" has survived from the days before in-vivo studies were possible, to be still applied by some to clinical diagnostic activities. Though it is unwise to perpetuate the phrase for fear of giving a patient or a patients' relatives the impression of inhumanity, it reminds one that quantitative imaging requires all the scientific rigour of the laboratory if it is to deliver the results of which it is

capable. Its capabilities are indeed great, many still only partly realised, to be deployed to help to answer carefully chosen problems for which the methodology is suitable.

In this chapter the physical basis, methodology, and the sources of inaccuracy and imprecision have been summarized and some of the findings have been mentioned. In particular, examples have been cited from work on the maturation of brain and the progress of myelination, the development of different forms of experimentally produced oedema, the separation of intra- from extracellular water compartments and the brain water in alcoholism and alcohol withdrawal. The nature of multiple sclerosis lesions, the quantitative estimation of blood brain barrier defect, the recognition of diffuse white matter abnormality in multiple sclerosis and in AIDS encephalitis at a stage when it was not suspected clinically have also been valuable fields of research.

The differential diagnosis of multiple sclerosis from systemic lupus erythematosis and cerebral sarcoidosis can be aided by such measurements when imaging fails to distinguish them, showing that, in the brain at least, primarily measured features and the parameters derived from them do, usefully, reflect differences in underlying pathology invisible in the usual images or very difficult to interpret. Work is soon to start on the measurement of brain relaxation times in HIV positive individuals as a means of early detection of encephalitis and of monitoring treatment. It has already been used to look for the physical response to steroid therapy of multiple sclerosis.

That which is now being actively pursued in the brain, to provide in vivo discrimination between the stages of pathological processes already recognized by pathologists in biopsy and autopsy material, must be extended to the spinal cord. Neither in the brain, nor under the more difficult conditions that apply to the cord, will progress be made without meticulous care. Quantification has a great deal to offer a really integrated team of mixed specialists prepared to investigate and utilize the possibilities of a well designed magnetic resonance imager.

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Note added in proof: The effect of temperature on T1 (–1–4%/°C) Should be born in mind when looking for small changes in T1 [58].

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