Chapter

17 It's Not Just Squiggles: In Vivo Spectroscopy

17.1 Introduction

By now you are familiar with the chemical shift between fat and water in the human body, which can cause artefacts. It occurs because protons in different environments experience shielding of the magnetic field by the electron clouds of neighbouring atoms. Chemists use magnetic resonance to investigate the structure of molecules by measuring very precisely the position of peaks in a spectrum (they still call it 'nuclear magnetic resonance'). The area of each peak is a measure of the relative number of protons in that particular position. In the chemical soup of the human body, the number of water and fat protons is several thousand times higher than the number of protons on other molecules so we can't usually distinguish other metabolites. In vivo spectroscopy uses gradients to selectively excite a volume of tissue, from which the **F**ree **I**nduction **D**ecay (FID) is recorded and, after Fourier transformations, produces a spectrum from the nuclei within that voxel. For many years this technique was technically difficult and results were not diagnostically helpful, but it has become much more reliable and is now considered by many to be an essential part of a brain MR examination.

In this chapter we will explain the following:

- the main features of a proton spectrum for normal brain include metabolite peaks for N-acetyl aspartate, creatine and choline;
- either PRESS or STEAM sequences can be used for single-voxel spectroscopy – PRESS is more common in clinical practice;
- combining spectroscopy with phase-encoding gradients in two or three directions allows us to create chemical shift images or 'maps'.

An MRS Dictionary

MR spectroscopy has its own language too, which will be unfamiliar to users who have only done MR imaging. For a start, it is frequently abbreviated as MRS, distinct from MRI.

Peaks on the spectrum are also called *resonances*. Some metabolites do not have simple resonances, but may be split into two (called a *doublet*), three (*triplet*) or even more sub-peaks. Effective *water suppression* is essential to allow the metabolite peaks to be detected.

Shimming refers to the process of adjusting field gradients to optimize the magnetic field homogeneity over the voxel, and is usually performed automatically. The uniformity of the magnetic field over the voxel is usually expressed as the *linewidth* (the full-width at half-height) of the water resonance and may be quoted in Hz or ppm. Anything which reduces the homogeneity is described as causing *line broadening*, i.e. increasing the linewidth of the peaks.

The FID is detected in *quadrature* and produces a spectrum with both *real* and *imaginary* components. The phase-corrected real spectrum is known as the *absorption* spectrum and contains all the useful information; the imaginary part is called the *dispersion* spectrum and is not used in clinical MR spectroscopy. Processing of the FID usually includes *zero-filling* to improve the spectral resolution and *apodization* to improve the signal-to-noise ratio. *Phase correction* is necessary to remove *baseline roll* from the spectrum, and the *residual water peak* can also be removed using specialist algorithms.

17.2 Some Basic Chemistry

A proton spectrum is shown in Figure 17.1a from a specialist spectroscopy phantom designed to mimic the in vivo brain metabolites. The water peak has been suppressed so that the lower-concentration metabolites can be seen. In all spectra the reference frequency (zero ppm) is set according to the chemical shift of a standard compound, tetramethylsilane $Si\text{-}(CH_3)_4$, which has a single proton resonance because it is a completely symmetrical molecule. When $Si\text{-}(CH_3)_4$ is

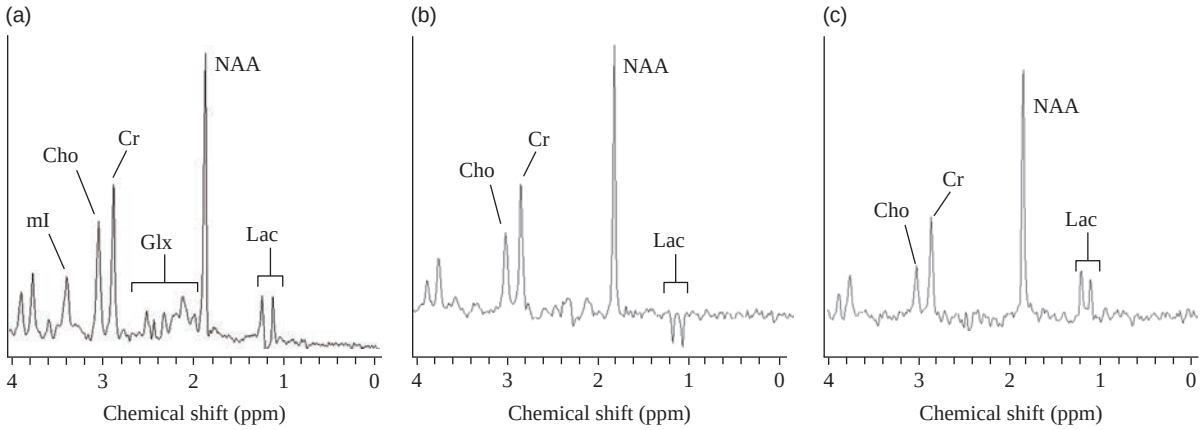

Figure 17.1 (a) A spectrum (TE = 30 ms) from an MR spectroscopy phantom containing the main brain metabolites in normal concentrations, plus lactate. Echo times of (b) 135 ms and (c) 270 ms produce spectra with different appearances. (All spectra are 0.1 ppm lower than in vivo spectra due to the temperature difference.) Cho denotes choline; Cr, creatine; Glx, glutamine and glutamate complex; Lac, lactate; ml, myo-inositol; NAA, N-acetyl aspartate.

at zero ppm, water at 37 °C is at 4.65 ppm. Since we don't have Si-$(CH_3)_4$ in the human body, we can just set the water resonance to be 4.65 ppm, and everything else is relative to that. Notice that the zero frequency is on the right-hand side of the spectrum, and it is usual to 'read' a spectrum from right to left. All other metabolites have a unique pattern of peaks at specific chemical shifts, and the presence and concentration of these chemicals can be found by detecting peaks at the appropriate ppm. Above 4 ppm the spectrum becomes unreliable, since the suppression of the water peak at 4.65 ppm tends to corrupt the neighbouring portions of the spectrum too. (Note that the phantom temperature is considerably lower than human body temperature, which causes a shift in the spectrum of about –0.1 ppm, i.e. to the right.) The most important peaks are as follows:

- 1.3 ppm: **Lac**tate (Lac) is a doublet and a very specific marker of cell death and tissue necrosis. If both peaks of the doublet can be seen, it is a good indication that the resonance is indeed lactate and not lipid contamination. Lipids have very broad resonances at 0.9 and 1.4 ppm (not seen in the phantom spectrum). On in vivo spectra it's often hard to distinguish lipid from lactate.
- 2.0 ppm: **N**-**A**cetyl **A**spartate (NAA) is regarded as a marker of neuronal integrity and will be reduced if neurons are being destroyed by a disease process.
- 2.1–2.5 ppm: **Gl**utamine and **Gl**utamate complex (Glx) is a mixture of peaks that may be elevated or decreased in conditions related to liver function.
- 3.0 ppm: **Cr**eatine (Cr) is the total peak from phosphocreatine and creatine and is often taken as a reference level, as it is relatively constant throughout the brain and it tends not to change significantly in disease processes. However, there is evidence that it can change particularly in malignant tumours.
- 3.2 ppm: **Cho**line (Cho) is considered to be an indicator of membrane activity since phosphocholines are released during myelin breakdown, and it is often elevated if malignant processes are present.
- 3.6 ppm: **m**yo-**I**nositol (mI) is a sugar alcohol which is thought to be a product of myelin breakdown and its peak is often higher in conditions such as Alzheimer's disease and malignant tumours.

Just as image contrast is highly dependent on the sequence chosen and the timing parameters, so the height of peaks depends on the MR spectroscopy sequence and on the TE and TR used. Each metabolite has T_1 and T_2 relaxation times which, for brain spectra, are reasonably independent of the tissue in which they are present. In spectroscopy we are only interested in maximizing the signal-to-noise ratio of the spectrum peaks, so we need to avoid signal loss due to T_1 relaxation and T_2 decay. Ideally TR should be at least 2000 ms and certainly no less than 1500 ms. TE should be short, usually 30 ms, but for historical reasons TEs of 135–144 ms and 270–288 ms are also used (see Section 17.3.2). Figures 17.1b,c show spectra

from the same phantom at these TEs; in both spectra the NAA, Cr and Cho peaks are still visible, and you can see that the signal-to-noise ratio is reduced (look at the baseline between 0 and 1 ppm). A spectrum at TE = 144 ms is particularly useful to separate lactate from lipid contamination: not only is the lipid signal lost because it has a short T_2, but the lactate peak is inverted, making it easily identifiable.

Currently the main clinical applications for in vivo spectroscopy are stroke, dementia, tumours and multiple sclerosis. Epilepsy shows marked changes in proton spectra, but consistently acquiring high-quality spectra is difficult because the epileptic focus is often in the temporal lobe (see Box 'Technical Challenges of Proton Spectroscopy'). The MRS changes seen in pathology are rather generic, and MRS tends to be sensitive but not specific for a particular disease. This means that MRS results must be used together with MRI or other tests to reach a diagnosis for an individual patient. Clinical boxes in this chapter will describe the most common applications in use today.

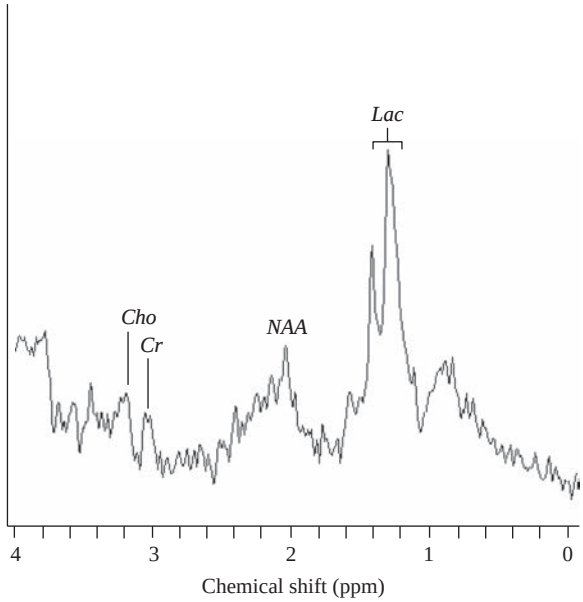

Figure 17.2 Typical spectrum from a patient with stroke.

Clinical Application: Stroke

Current clinical guidelines for acute stroke advise a very rapid imaging assessment to rule out haemorrhagic stroke, followed by 'clot buster' drugs or removal of the thrombus. CT is still much faster and more widely available than MR, so MR – imaging or spectroscopy – remains a research application for stroke. The ischaemic infarct rapidly shows signs of cell death and MRS in this area demonstrates the characteristic lactate peak, often with a broad lipid peak (Figure 17.2 shows lipids at 0.9 and 1.4 ppm, with the lactate doublet overlying the latter). Lactate may also be present in smaller concentrations in the ischaemic penumbra, the region around the core which, if reperfused sufficiently quickly, may recover its function. In sub-acute or late stages of stroke, reduced NAA and Cr peaks and elevated Cho are present (the latter feature is not shown in Figure 17.2). Chemical shift imaging (CSI, see below) is probably the best way of getting metabolite information about the penumbra, but due to the longer scan times CSI is even more challenging in the acute phase of stroke.

Technical Challenges of Proton Spectroscopy

The frequency separation of peaks in the spectrum depends on the field strength and on the magnetic field homogeneity. At low fields or with a poor shim the peaks tend to overlap and that causes difficulty in interpretation and in measuring peak heights. It is generally thought that a field strength of 1.5 T is the minimum necessary for in vivo spectroscopy. However, it is not obvious that the highest field strengths will give much better results, as at 3 T and above patient susceptibility becomes the dominant source of non-uniformity and thus spectral resolution may be degraded unless there is good local shimming, probably involving higher-order shim coils.

Regardless of the pulse sequence used for proton spectroscopy, effective water suppression and high magnetic field homogeneity are essential to produce a good spectrum. The water peak is at a much higher concentration than the peaks of all the other metabolites, and without suppression those peaks cannot be seen. Typically a very narrow bandwidth frequency-selective pulse, often called a **CHE**mical **S**hift **S**elective (CHESS) pulse, is applied at exactly the Larmor frequency of water using a low-power Gaussian pulse to give a 90° pulse, followed by gradient pulses to spoil any transverse magnetization. Optimization of the strength and central frequency of the water suppression is essential, as inaccurate CHESS pulses can leave too much water (Figure 17.3) and suppress neighbouring metabolite peaks.

To be clinically useful the automated shimming performed by the scanner must give reproducible

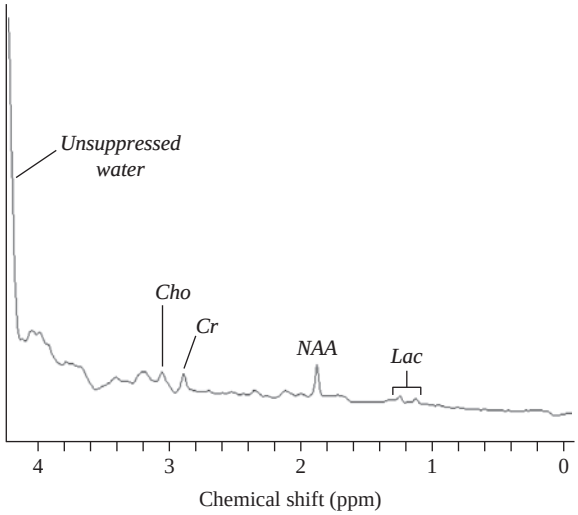

Figure 17.3 The effects of inaccurate water suppression. The large residual water peak at the left of the spectrum dominates the signal and none of the metabolite peaks can be reliably detected.

results. Manual shimming (where the operator adjusts the currents for the linear and higher-order shim coils while observing the FID or the water linewidth) is a tricky technique to perform well and adds a significant time penalty to the scan time. Research studies, however, may require skilled operators to check the automated shimming and adjust it manually if necessary.

17.3 Single-Voxel Spectroscopy

17.3.1 Steam

STEAM stands for **ST**imulated **E**cho **A**cquisition **M**ode and uses three selective 90° pulses, applied in succession on orthogonal gradients to excite a single voxel (Figure 17.4). A total of four echoes is produced from this set of pulses (or five if the first two RF pulses are closer together than the second and third), one of which is a stimulated echo, and this is the signal that is acquired for spectroscopy. For many years STEAM was the only sequence capable of short echo times (down to 30 ms), which show the Glx and mI peaks, and so it has been used for many research studies. Because there is such a large body of literature about a range of conditions, it is still popular with many researchers, especially those with long-term studies. However, it has a lower signal-to-noise ratio than PRESS (Section 17.3.2) and does not show the useful Lac inversion at TE = 144 ms.

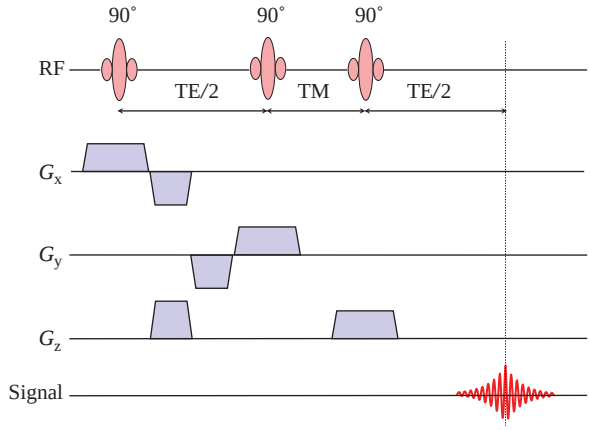

Figure 17.4 The STEAM pulse sequence. TM denotes the mixing time – see Box 'Stimulated Echoes'.

17.3.2 Press

PRESS stands for **P**oint-**RES**olved **S**pectroscopy and is based on the spin-echo sequence. A 90° pulse is followed by two 180° pulses so that the primary spin echo is refocused again by the third pulse. Each pulse has a slice-selective gradient applied along one of the three principle axes (Figure 17.5a), so that protons within the voxel are the only ones to experience all three RF pulses.

The signal intensity depends on the pulse spacing and relaxation times, and is intrinsically twice as high as STEAM, so spectra can be acquired with good signal-to-noise ratio (SNR) in a relatively short time.

When PRESS was first developed on clinical scanners, its minimum TE was rather long and often only NAA, Cr and Cho could be reliably detected. At an echo time of 144 ms, lactate is completely out-of-phase with the rest of the spectrum and appears as an inverted peak (refer to Figure 17.1b). Since TE was long anyway with PRESS, it made sense to choose a TE of 144 ms for their studies. At 288 ms TE Lac is back in phase again (although SNR is even lower), and the acquisition of two spectra could be used to confirm the presence of Lac (Figure 17.1c). Modern scanners are able to produce short-echo-time PRESS with a 30 ms TE, and since the SNR is twice as high, PRESS is taking over from STEAM for almost all MRS studies (Figure 17.5b).

Stimulated Echoes

Stimulated echoes were first described in 1950 in an important paper by Hahn, which also contributed greatly to the understanding of spin echoes. To

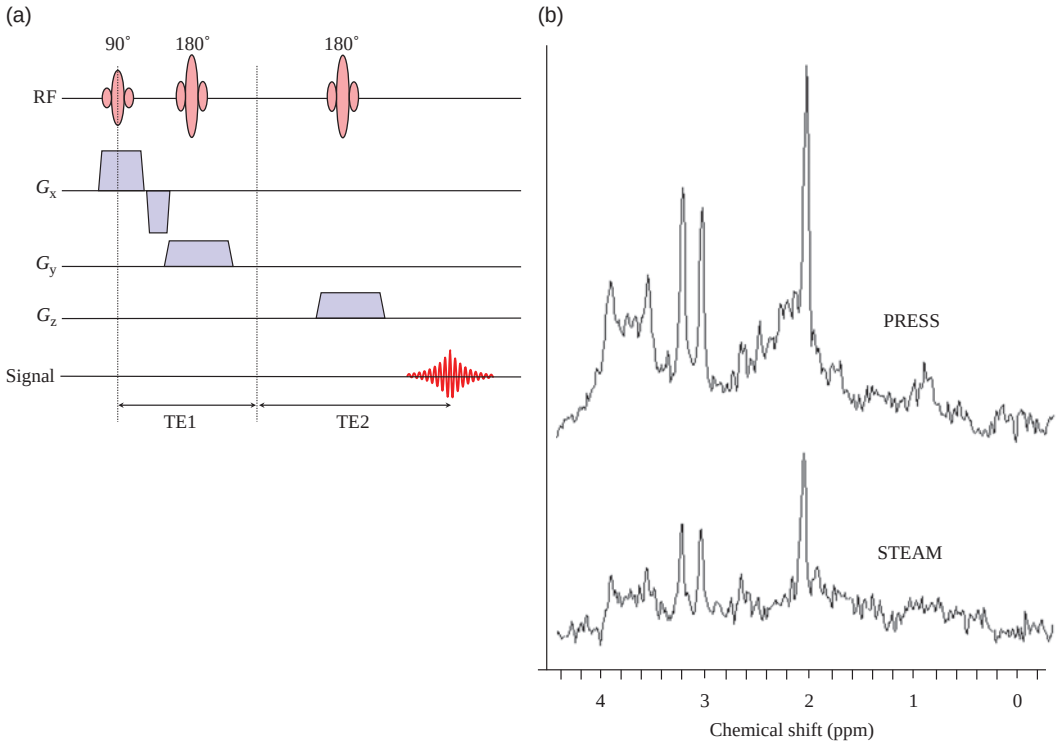

Figure 17.5 (a) The PRESS pulse sequence. (b) In vivo spectra acquired with PRESS and STEAM with the same timing parameters are only subtly different, mainly around the Glx complex.

understand how they are produced, consider a series of three 90° pulses with unequal spacing (Figure 17.6). Some dephasing occurs after the first pulse, and the fan of protons is turned through 90° by the second pulse, leaving some components in the transverse plane, which refocus to produce the first spin echo. Other components are put into the longitudinal direction, where they relax with T_1 only, until the third RF pulse is applied. These components are turned into the transverse plane again, where they refocus to produce a stimulated echo. The maximum height of the stimulated echo can be calculated from the expression

$$S \propto \frac{M_0}{2} \cdot \sin\alpha_1 \cdot \sin\alpha_2 \cdot \sin\alpha_3 \cdot \exp\left(\frac{-\mathrm{TE}}{T_2}\right) \cdot \exp\left(\frac{-\mathrm{TM}}{T_1}\right)$$

i.e. it is affected by both T_2 relaxation during the first inter-pulse period and T_1 relaxation between the second and third pulses (known as the mixing time, TM). If we assume that TE and TM are both short compared with the relaxation times and provided each pulse is a perfect 90°, the maximum possible signal is 50% of M_0. To use stimulated echoes for spectroscopy, it is only necessary to add slice-selective gradients to each axis so that only protons within the required voxel experience all three RF pulses.

In order to understand the formation of echoes with multiple RF pulses of an arbitrary flip angle it is helpful to use coherence pathway diagrams, as described in Chapter 13. Note that if TE/2 $>$ TM, four echoes will be produced in total, whereas if TE/2 $<$ TM there will be five, the extra one being the second refocusing of the spin echo due to RF pulses 1 and 2.

17.3.3 Voxel Positioning

The choice of voxel position is critical to achieving a good-quality diagnostic spectrum. Obviously it is important to put the voxel in an appropriate place to detect the pathology under investigation. For example, within a focal brain lesion there may be necrosis, active tumour and oedema. Appropriate contrast images are needed for planning the voxel.

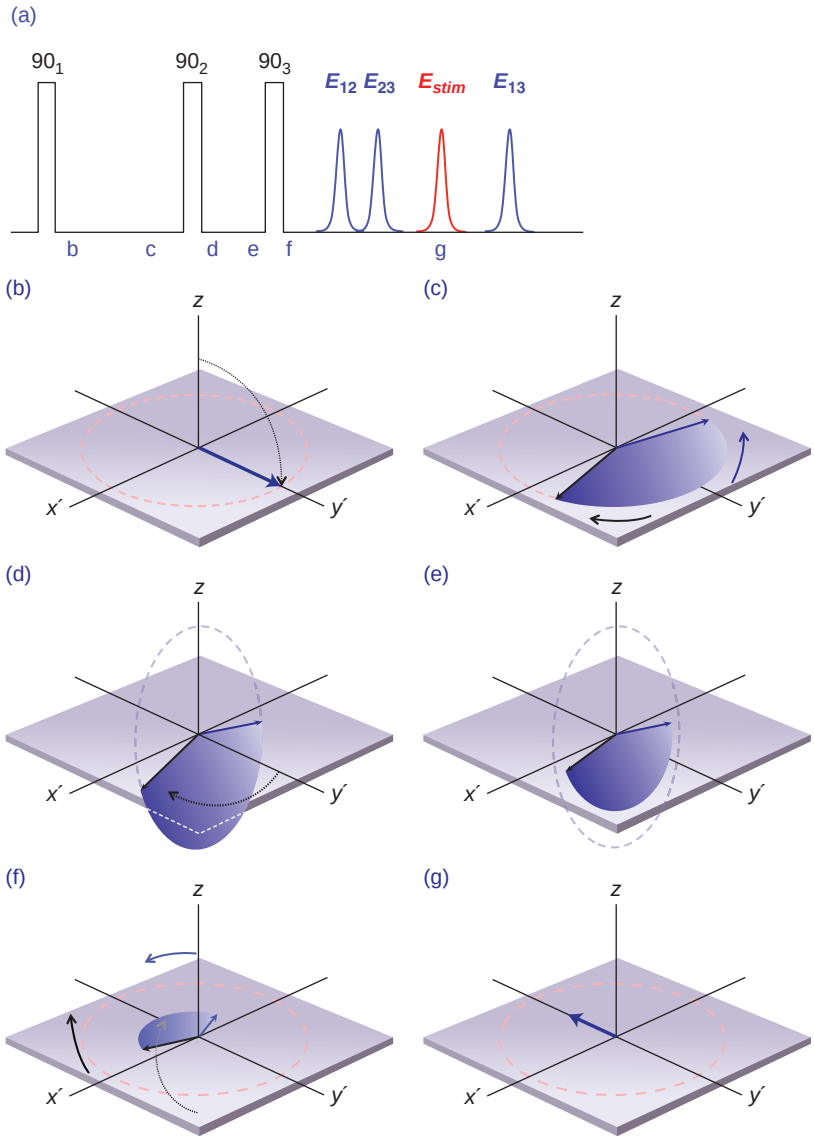

Figure 17.6 (a) Three RF pulses at uneven spacing produce three primary spin echoes and one stimulated echo. (b) The components which form the stimulated echo are flipped first into the transverse plane where they dephase with T_2 relaxation (c), then into the longitudinal plane (d) where dephasing stops and T_1 relaxation occurs (e), then finally flipped back into the transverse plane (f) where they rephase and form an echo (g).

In order to grade a tumour, the voxel should be in the active tissue, but it can be difficult to distinguish these regions on standard T_1-weighted or T_2-weighted scans. It has been shown that gadolinium has only a small effect (causing a small amount of line broadening), so post-contrast T_1w scans can be useful for positioning the voxel. However, this is only true if the concentration of gadolinium within the voxel is relatively low: at higher concentrations the T_1 and T_2 shortening effects must be considered. The question of whether to perform MR spectroscopy before or after gadolinium administration is a controversial one and there are strong opinions both ways.

Clinical Application: Dementia

Diagnosis of dementia is primarily based on clinical signs, although both PET and MRI show promise in this area. MRI is mainly used to measure volumes of the hippocampus or temporal lobe. Spectroscopy has a role to distinguish Alzheimer's disease from other dementias. Proton spectra show decreased NAA and

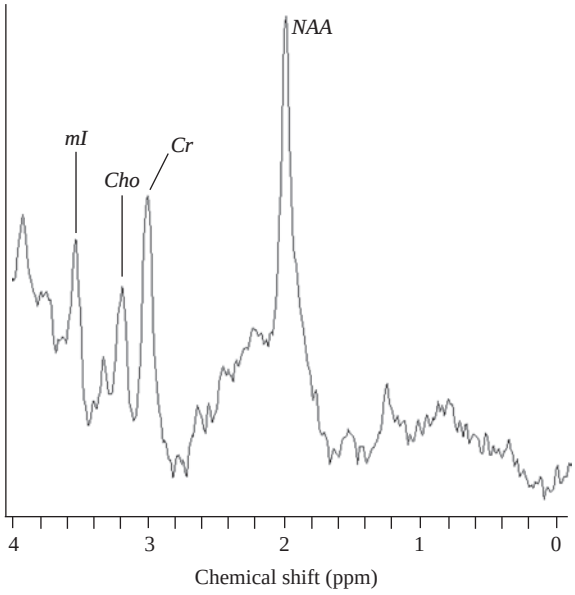

Figure 17.7 Typical spectrum from a patient with Alzheimer's disease.

elevated mI and Cho, although Cho also tends to increase with age so this must be interpreted with care. A short TE is needed to see the mI peak. Figure 17.7 shows an example from a patient in the early stages of disease, where the main diagnostic feature is the increased mI. There are metabolite variations between different parts of the brain, and in the future CSI is a promising technique for dementia.

A good shim over the voxel is absolutely essential to produce a readable spectrum, and a linewidth of less than 0.08 ppm (5 Hz at 1.5 T) is ideal. Voxels in inhomogeneous regions of the brain are always difficult to shim, in particular the temporal lobes, the base of the brain and the cortex near the skull. For non-focal diseases a good choice would be the occipital grey matter or white matter (Figure 17.8). Obviously lesions and stroke infarcts do not always place themselves in positions that are easy to shim, and we just have to live with that. If the prescan results in a higher linewidth, a repeat prescan can sometimes bring it down as the automated shimming technique improves on its starting point. Spectra with linewidths of 0.15 ppm (9 Hz at 1.5 T) or higher are probably not worth acquiring, as the resulting spectrum will be poor quality (Figure 17.9) and unlikely to help a diagnosis. In general smaller voxels are easier to shim

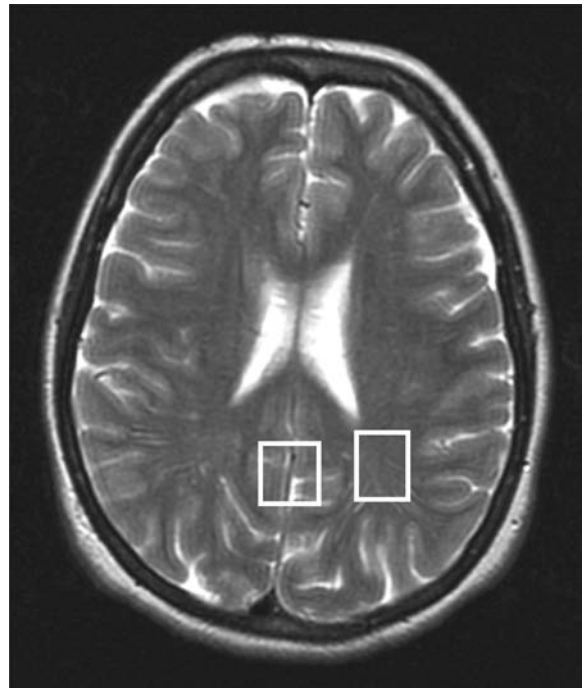

Figure 17.8 Axial image of the brain showing suggested voxel locations for grey matter (occipital mid-line) and white matter (parietal).

than larger ones, but the SNR also depends on volume, so a voxel with 1 cm sides is often considered the practical minimum size to achieve a reasonable SNR. If the volume of the voxel is further reduced in order to help the shim, then the number of signal averages recorded (also known as transients in MRS) should be increased.

Whatever criteria are chosen for positioning MR spectroscopy voxels, consistency is the key to obtaining reliable spectra. Don't be tempted to change the timing parameters, as the resulting spectrum will not be comparable with a normal reference spectrum. The only exception to this rule is the number of signal averages, which may be increased to improve SNR in small voxels. Short echo times are preferred because the improved SNR allows more peaks to be seen, and a second spectrum with long echo time (144 ms) may be used to confirm the presence of Lac if necessary. Alternatively a second short TE spectrum could be acquired from a contralateral site to provide a 'normal' reference, although this really only works if lesions are truly focal (even a stroke may cause changes on the contralateral side if the blood supply is altered).

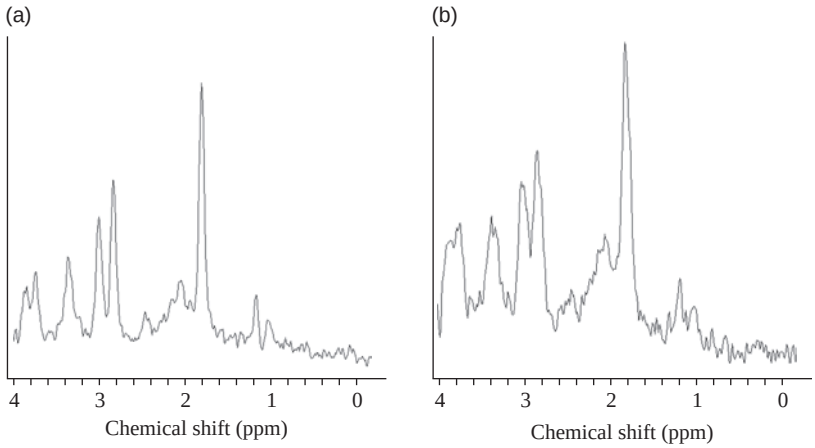

Figure 17.9 The effects of shimming on a phantom spectrum: (a) well shimmed and (b) badly shimmed.

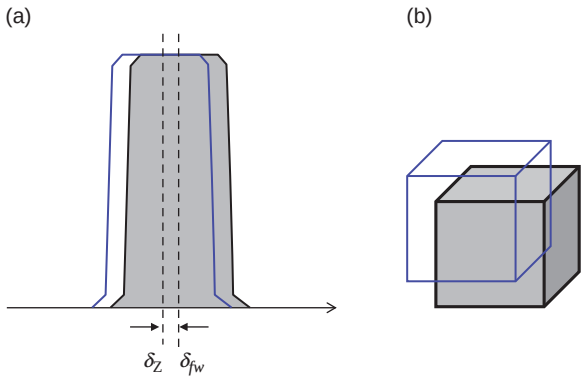

Figure 17.10 (a) The chemical shift effect causes fat and water to have slightly offset slice locations. (b) In three dimensions and with a small voxel size, the offset may be significant.

Chemical Shift Effect in Excitation

A significant problem in exciting the tissue within a MRS voxel is sharpness of the voxel edges. Taking water and fat as a simple example, a frequency-selective pulse (Figure 17.10a) will excite slices of water and fat at slightly different physical locations due to the chemical shift of 3.5 ppm. In three dimensions, the fat voxel will be offset with respect to the water voxel (Figure 17.10b). With the added complication of the excitation profile caused by imperfect selective pulses, you can see that the edges of the voxel become rather poorly defined. This is sometimes known as 'voxel bleed', and if the voxel is positioned close to the scalp it can lead to contamination of the spectrum with lipid signals. In this situation, it can help to rotate the voxel so that a corner is pointing towards the scalp, rather than having an edge parallel to the scalp. Adding spatial saturation bands on all six sides (right, left, superior, inferior, anterior and posterior) can improve the voxel profiles.

A voxel which overlaps the ventricles will have reduced SNR because the cerebrospinal fluid (CSF) contains almost no metabolites, but contributes to the water peak. Partial volume effect is impossible to avoid with MRS, and it is really a matter of experience and careful positioning to get the best results.

Clinical Application: Brain Lesions

The most widespread use of MR spectroscopy currently is in the differential diagnosis between various brain lesions. Low-grade lesions and meningiomas show reduced NAA and elevated Cho (Figure 17.11a), features that progress in more malignant tumours (Figure 17.11b) where Lac may also be present. Many researchers have found a correlation between the levels of NAA and Cho with the tumour grading, and lipids are also found in necrotic tissue or cysts. Metastatic lesions may be distinguished from gliomas by taking a voxel just outside the enhancing rim of the lesion. Gliomas will show the typical pattern of lower NAA and higher Cho, while metastases show a normal brain spectrum. Alanine, a metabolite seen at ~1.5 ppm, is considered specific for meningiomas. Abscesses may also show alanine, but always show lactate and lipids at 1.1–1.4 ppm, and an absence of NAA.

17.4 Processing of Single-Voxel Spectra

Several specialized processing steps are performed on the acquired FID to produce a high-quality spectrum. Whether they are done in the time domain or the

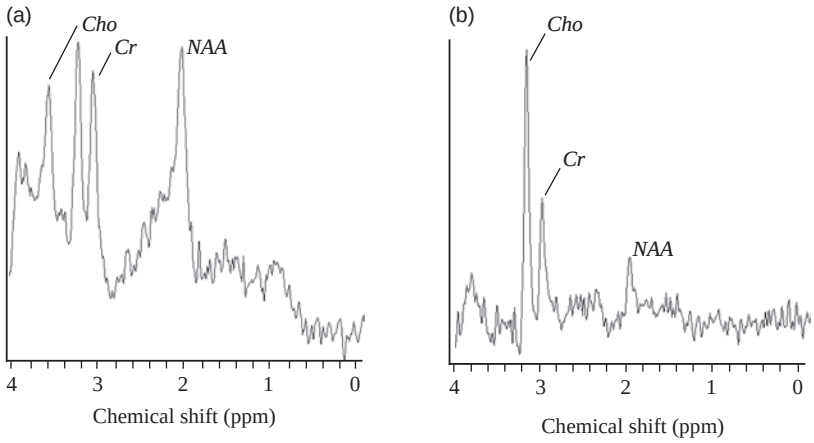

Figure 17.11 Typical spectra from a patient with (a) low-grade glioma and (b) grade III astrocytoma.

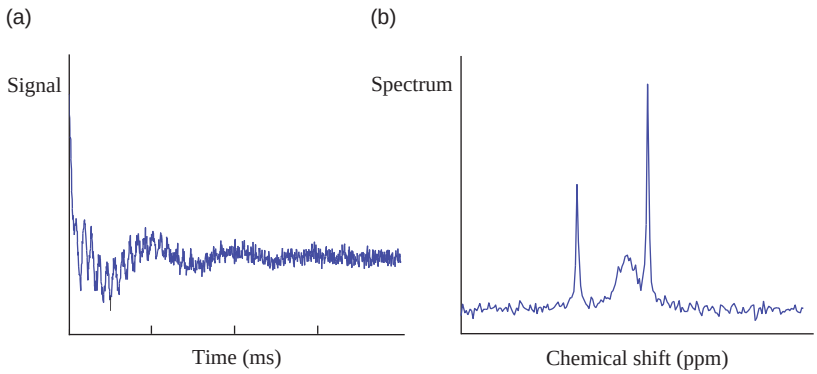

Figure 17.12 The raw FID (a) and spectrum (b) from simulated data (PRESS, 30 ms TE).

frequency domain, i.e. before or after the Fourier transform, depends on which is computationally easier. All the figures in this section are from a simulated acquisition of a spectrum with two narrow resonances and one broader peak: the raw 'FID' and its spectrum are shown in Figure 17.12.

The FID is usually digitized for only a few tens of milliseconds. Extending the digitization time would just increase the noise level in the spectrum, since the FID will have decayed away. It is common to zero-fill the data at this stage, i.e. extra data points all set to zero are added to the end of the acquired data (Figure 17.13). This corresponds to interpolating between data points in the frequency domain, giving a smoother-looking spectrum, and is much easier to do before the Fourier transform. Apodization is also applied before Fourier transform of the FID. This means multiplying the acquired FID by a smoothly varying function such as an exponential decay or a Gaussian function (Figure 17.13). Apodizing has the effect of suppressing the noisier tail-end of the FID, which therefore improves the SNR. However, it also makes the peaks slightly broader in the frequency domain, and so is also often called line-broadening. It corresponds to convolving the frequency spectrum with a Lorentzian or Gaussian function, which is computationally far more difficult than apodization in the time domain.

After Fourier transformation, the spectrum needs to be phase-corrected. A zeroth-order phase correction compensates for any mismatch between the quadrature receive channels and the excitation channels (Figure 17.14) to produce the pure absorption spectrum. This is usually done using the residual water peak, which is still the largest peak in the spectrum. The need for localizing gradients means that there is always a delay between excitation and turning on the receivers. During this delay the nuclei will dephase by an angle that is proportional to their frequency, which then needs to be corrected by a first-order phase correction (i.e. a linear phase shift across the spectrum, Figure 17.14). Unfortunately the first-order phase

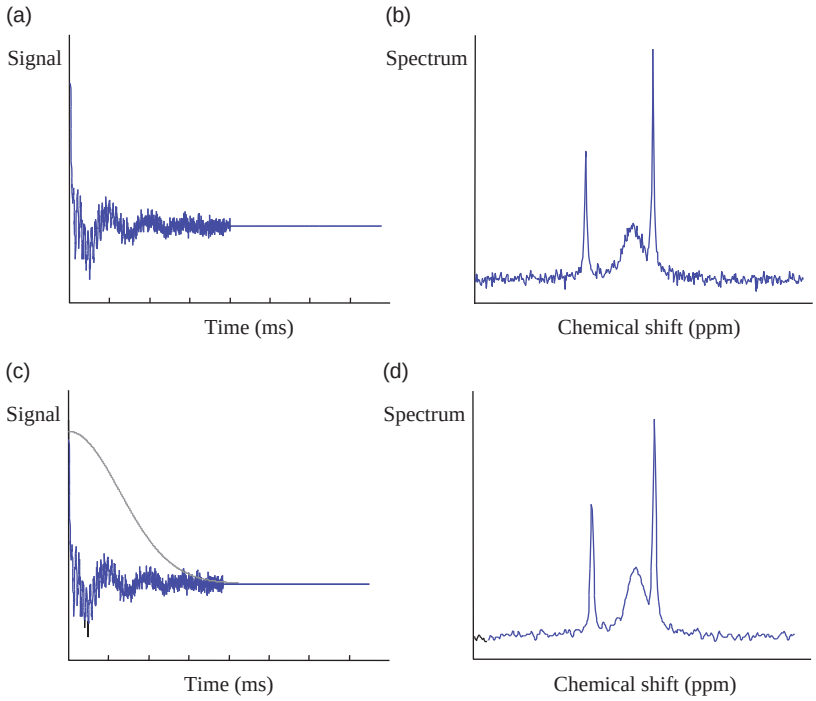

Figure 17.13 (a) Zero-filling the FID is equivalent to (b) interpolating between points in the frequency spectrum. (c) Apodization (multiplication of the FID by a special function) improves SNR (d) at the expense of a little line-broadening.

correction introduces another feature, a slowly varying baseline known as baseline roll. This can be corrected by fitting a spline or polynomial function to the spectrum between the metabolite peaks and then subtracting the resulting function (Figure 17.14).

At this stage the spectrum is presented to the user and is ready for qualitative interpretation. Quantitatively, simple ratios are calculated by finding the area under the spectrum between defined ppm limits for the main metabolites, and these are also presented on the screen. Further quantification is usually done by moving the raw data offline onto an independent workstation. For example, to measure absolute concentrations of the metabolites a model of their known resonances can be fitted to the data using a specialist software package. As with the other processing steps, fitting can be done either in the time domain or the frequency domain.

Clinical Application: Liver and Breast

The primary application of MRS in liver is to assess the fat content in diffuse liver disease. Steatosis is characteristic of non-alcoholic fatty liver disease which is linked with obesity and can lead to cirrhosis. Since liver biopsy is the gold standard method to assess steatosis, MRS is an attractive non-invasive alternative. Fat and water suppression are not needed and a large voxel can be used, as the goal is simply to assess the ratio of fat to water. However, it is still difficult to obtain a high-SNR spectrum within one breath-hold, so the results are often contaminated by motion (Figure 17.15a). Recently, imaging methods, using Dixon techniques, have started to replace MRS for liver fat assessment.

In breast cancer there can be many suspicious bright spots in the MR scans, and MRS may be used to distinguish benign lesions from malignant cancers. Normal breast tissue or benign tumours have almost no Cho signal, while malignant tumours have elevated Cho (Figure 17.15b). Breast spectroscopy is made difficult by respiratory motion and by the presence of large lipid signals. Fat suppression can be achieved by increasing the echo time (the fat signal is lost due to the short T_2 of fat) or using a fat suppression pulse.

17.5 Chemical Shift Imaging

Chemical **S**hift **I**maging (CSI) uses phase-encoding techniques to acquire spectra from a matrix of voxels. Each slice-selective gradient is replaced with a phase-encoding gradient, which works in the same way as

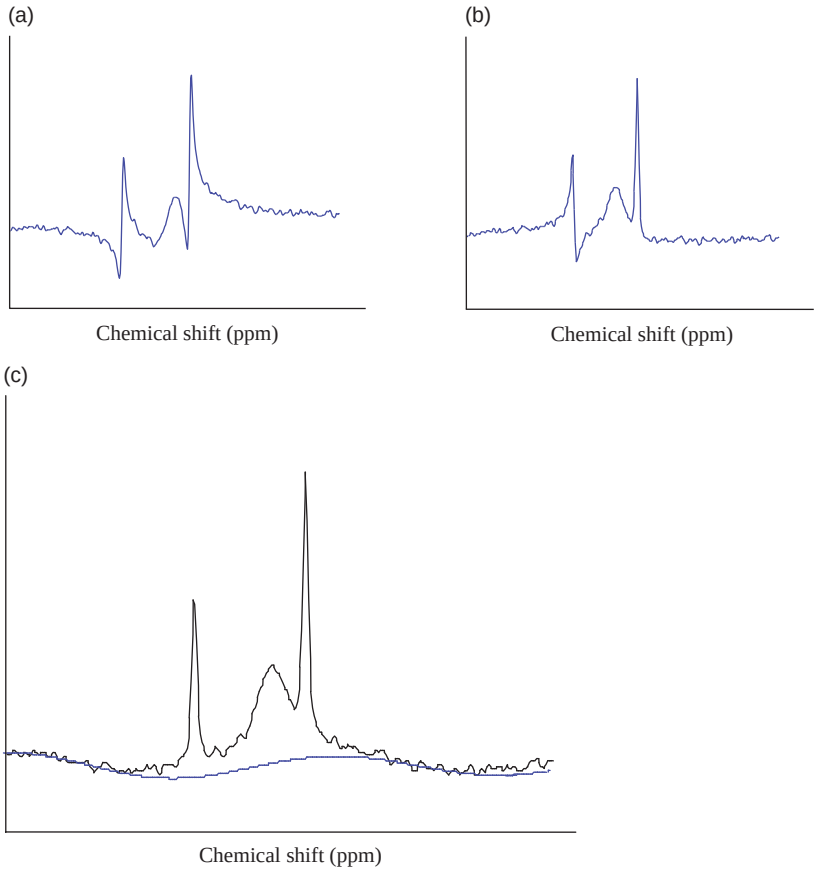

Figure 17.14 (a) A real spectrum may not be correctly phased immediately after Fourier transform (FT). (b) Zeroth-order phase correction has correctly phased the right-most peak, but first-order phase correction is now necessary to correct for hardware delays. (c) Baseline correction is achieved by fitting a spline function (a smoothly varying polynomial function) to the portions of the spectrum known to contain only noise, then subtracting that function.

the slab-select gradient in 3D imaging sequences (see Section 8.8). In principle this can be done for all three directions, but it is more usual to leave one direction as a straightforward slice select, i.e. to perform 2D single-slice CSI.

CSI is normally performed with PRESS. Instead of producing an echo from a small voxel, the 'voxel' is now a chunky slab. The phase-encoding gradients sub-divide the slab into a grid of voxels of the required size. The first phase-encoding gradient must step through all its values for each value of the second phase-encode gradient, so the acquisition time will be $TR \times N_{PE1} \times N_{PE2} \times NSA$. If $15 \times 15 \times 15$ mm^3 voxels are required with a head-sized field of view (FOV) of 24 cm, the matrix required is 16×16. Since TR should be at least 1500 ms to avoid T_1 effects in the spectra, the minimum scan time is thus 6 min 24 s. The good news is that although the voxel size is rather small, the SNR is similar to the equivalent single voxel acquisition thanks to the repeated excitations (in this case $16 \times 16 = 256$). Multi-slice CSI can be done in an interleaved fashion by changing the frequency of the slice-select RF pulse (just as 2D multi-slice images can be produced). Alternatively Hadamard encoding can be used, which offers improved slice profiles and further improves the SNR of the whole acquisition. This is preferable to phase encoding in the third direction, which would push up the scan time to 25 min for just four slices.

Significant time savings in CSI can be made by using a few tricks from normal MR imaging. A simple example is to use a rectangular FOV and reduce the number of phase encodes accordingly. For a typical axial brain CSI, this can reduce the scan time by 20–25%. It is also possible to use a RARE-like echo train with different phase encoding for each echo, known as Turbo CSI. The acquisition time for a PRESS echo is a lot longer than for imaging, typically 200 ms, so the turbo factor is only 2–4 in order to avoid T_2 blurring. Even a small turbo factor allows

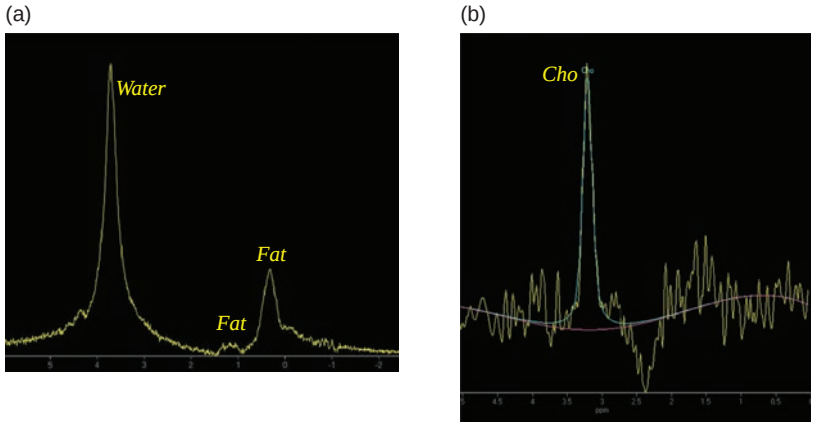

Figure 17.15 Typical spectra from a patient with (a) fatty liver disease and (b) malignant breast cancer.

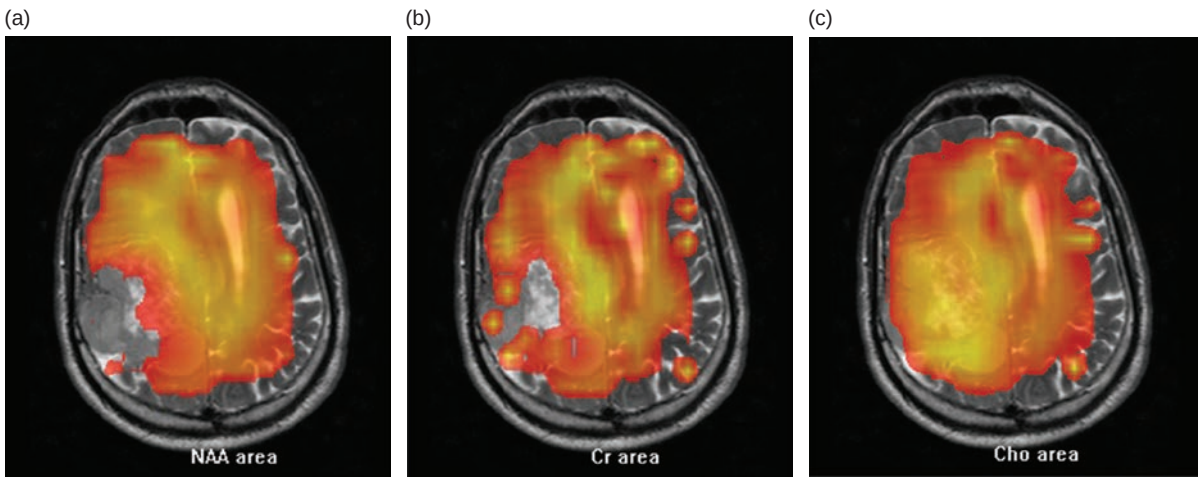

Figure 17.16 CSI metabolite maps from a patient with a brain tumour. (a) NAA, (b) Cho, (c) Cr.

significantly higher matrix sizes within a reasonable scan time, for example a 24 × 24 matrix with a turbo factor of 4 and TR of 2500 ms takes 6 m and offers significantly improved voxel resolution of 10 mm × 10 mm.

New parallel imaging techniques (such as SENSE and GRAPPA) offer further time savings with multi-element receive coils by using coil sensitivities to reduce the number of phase-encoding steps required. Both Turbo CSI and parallel imaging have disadvantages of course: they both involve a reduced spectral resolution because the echo has to be acquired more quickly, and parallel imaging reduces SNR in the final images.

Having produced a matrix of spectra, the usual way to display the data is as a series of maps, usually of the main metabolite peaks NAA, Cr and Cho, or other important metabolites (Figure 17.16). In these maps the intensity of the voxel depends on the area of the relevant peak in that position's spectrum. Software is available which allows the user to define a chemical shift range from which to produce a map; for example, a 'lactate' map could be created from the range 1.2–1.4 ppm. As a colour scale is often used for these maps they need careful interpretation as even small changes in peak area can produce dramatic colour changes.

Clinical Application: Prostate

MR imaging is widely used to assess prostate cancer and chemical shift imaging is a useful part of this examination. A normal prostate spectrum contains Cr and Cho, with a high level of citrate (Cit). The Cit peak

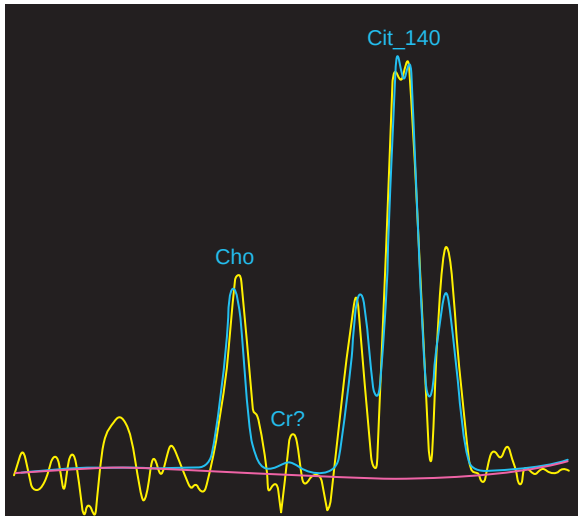

Figure 17.17 Typical spectrum from a patient with normal prostate.

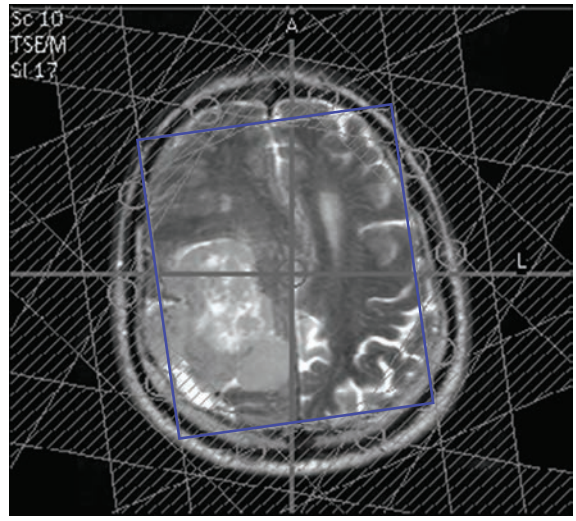

Figure 17.18 When planning CSI, a sub-volume is defined for shimming (blue box). Multiple saturation bands (hatched white bands) are placed over the scalp and skull bone marrow to reduce lipid contamination.

has complex *J*-coupling and, like lactate, its appearance changes with echo time. It has been shown that an optimal echo time is 120 ms at 1.5 T, or 100 ms at 3 T. At this TE, the two outer peaks almost disappear and Cit appears as a doublet (Figure 17.17), upright at 1.5 T and inverted at 3 T. In cancer, Cho levels are elevated and Cit is reduced. It is therefore possible to measure the ratio of Cho to Cit, which should be <1 in normal tissue and increased in cancer. Lipids frequently interfere with the spectrum, so fat suppression is used as well as water suppression. Haemorrhagic breakdown products can linger for days or weeks after biopsy and can also make the spectrum unreadable, so it is recommended to avoid MRS during this period.

Technical Difficulties in CSI

CSI has all the technical problems of single-voxel spectroscopy and a few more of its own! A major problem is the difficulty of shimming an entire slice to the level necessary for good spectra from every voxel in the matrix. In fact this is so difficult that it is usual to define a sub-region within the brain which is used for shimming (Figure 17.18). Outside of this region the shim is allowed to remain poor and spectra in these voxels will be very low quality. When setting up a CSI scan, the edges of the region of interest should lie well within the skull to avoid the susceptibility changes associated with bone.

Since the 'imaging' matrix is so small (usually only 16×16), the Fourier transform produces large ringing (Gibbs') artefacts across the field of view and smoothing is usually applied in an effort to reduce this. However, the smoothing introduces smearing across the voxels, making the voxel bleed much worse than in single-voxel MRS. The resolution of CSI is therefore not just the size of the pixels as in normal MRI, but is always worse. It is now measured using the point-spread function (PSF), which can be calculated if you know the k-space sampling and post-processing filters. Absolute quantification of metabolite concentration is difficult and relative quantification is more useful, not least because there are so many voxels in a single CS image.

Residual field non-uniformities across the field of view may cause incorrect water suppression, as the suppression pulses are applied to the wrong part of the spectrum. Phase errors in the selective RF pulses are significant over the larger volume in CSI, and vary from voxel to voxel across the field of view. Baseline correction is often compromised and spectra will rarely be as high a quality as those obtained from single-voxel techniques. This makes it particularly difficult to produce reliable metabolite maps from short echo time CSI, where the baseline is also compromised by short-T_2 macromolecules. Interpretation of CSI maps should include inspection of the underlying spectra to decide whether or not a 'deficit' or 'elevation' is actually present.

Phosphorus Spectroscopy

After protons, phosphorus is the second most studied nucleus for in vivo spectroscopy. Phosphorus spectro packages are available commercially from the main vendors, typically on 3 T platforms. Phosphorus (^{31}P) has a lower Larmor frequency than hydrogen, which means that a higher field strength is necessary to achieve good spectral resolution. Phosphorus is also much less abundant than protons, with a whole-body concentration 1000 times smaller, and so SNR is relatively poor. Since phosphorus is a major component in adenosine triphosphate (ATP), consumed and renewed during the conversion of sugars to energy, ^{31}P spectra are typically used to study muscle metabolism.

In vivo ^{31}P has much shorter T_2 than protons and a rather long T_1. Echo-based sequences such as PRESS, even at short echo times, are unsuitable; instead, sequences are used that acquire the FID immediately after excitation. ISIS (**I**mage **S**elective **I**n vivo **S**pectroscopy) is a subtractive technique that uses ±180° selective pulses in all possible combinations on the three axes, such that the final signal is only from the required voxel. Although it is a good voxel-selective technique, eight TRs are required for each signal acquisition. A normal ^{31}P spectrum from muscle is shown in Figure 17.19. Notice that the spectral width is nearly 20 ppm, in contrast with that of proton spectra, which is only about 5 ppm. Reading from right to left, ATP has three main resonances at about –15 ppm, –8 ppm and –4 ppm labelled β-ATP, α-ATP and γ-ATP respectively, one for each phosphorus atom in the molecule. Phosphocreatine (PCr) is used as the reference chemical shift at 0 ppm. The other main peaks are phosphodiesters (PDE) at 3 ppm and inorganic phosphates (Pi) at 5 ppm.

During and after exercise, ^{31}P spectra show changes reflecting the initial decrease in ATP then its recovery during aerobic exercise. The main changes during aerobic exercise are a reduction in the PCr peak accompanied by an increase in the Pi peak, which returns to normal gradually when exercise ceases. In diseases such as muscular dystrophy ^{31}P spectra show a high Pi:PCr ratio at rest, and during exercise abnormal patterns are seen. ^{31}P spectroscopy is also used to investigate the liver, where the main difference in the appearance of the spectrum is that PCr is not present in the liver; a PCr peak in such a spectrum indicates contamination with overlying muscle. Repeated ^{31}P spectra can be acquired to study the metabolism of the liver, in the normal state and in hepatitis and cirrhosis, and to monitor the response of malignant lesions to therapies.

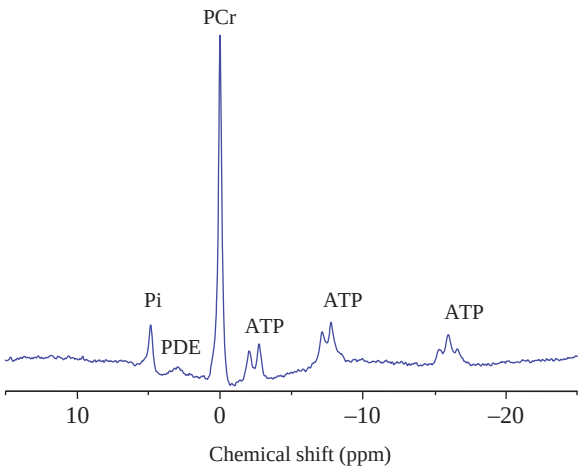

Figure 17.19 Phosphorus spectrum from normal muscle showing the main metabolite peaks. PDE denotes phosphodiesters; Pi inorganic phosphate and PCr phosphocreatine. Courtesy of Dr F. Howe, St George's Hospital Medical School, London.

Other Nuclei

Other nuclei are used by research groups, but these have not yet made it to routine clinical applications.

Our bodies contain plenty of carbon, but unfortunately only the ^{13}C isotope is MR-visible and this isotope only comprises about 1% naturally. Most studies rely on adding ^{13}C to a compound which is either injected or ingested. For example, ^{13}C–glucose can be used to examine glucose metabolism in the brain, where studies of stroke patients have shown that lactate turnover is higher in the ischaemic penumbra compared with the infarct core.

Fluorine is another nucleus which is present in high concentrations in the bones and teeth, but is not MR-detectable because it has an extremely short T_2. Like carbon spectro, pharmaceuticals can be labelled with ^{19}F (an MR-active isotope), and then used to investigate pharmacokinetics. For example, ^{19}F-CSI of the brain is possible using ^{19}F-tagged deoxyglucose ([^{19}F]DG), which is taken up by tissues from the blood supply in the same

way as glucose. The more common form of FDG using ^{18}F is regularly used in PET imaging to study brain perfusion. So MR studies of [^{19}F]DG have the potential to provide the same information without the radiation dose associated with PET.

Finally, ^{23}Na is MR visible, but is present at very low concentrations in vivo. Like ^{19}F and ^{31}P, it has very short T_2 and requires an FID acquisition method.

There is interest in ^{23}Na imaging for stroke, where it is shown to be sensitive for changes in the intra- and extracellular concentration of sodium ions.

See also:

- Slice-selective RF pulses: Section 8.4.1
- 3D phase encoding: Section 8.8

Further Reading

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