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Technique for Measuring Hippocampal T2 Relaxation Time

John S. Duncan, Philippa Bartlett, and Gareth J. Barker

PURPOSE: To implement and validate methods for producing calculated coronal T2 maps with complete coverage of the hippocampus and the rest of the brain. **METHODS:** T2 relaxation times were estimated on three occasions for 12 quality assessment test objects with the use of fast spin-echo (FSE) and conventional spin-echo (CSE) sequences. Hippocampal T2 relaxation times were measured in 15 healthy subjects with FSE and CSE sequences. Ten of these subjects were scanned twice with CSE imaging. Twenty-two patients with temporal lobe epilepsy, in whom hippocampal T2 relaxation times were previously estimated by means of a multiecho sequence, were studied with CSE. **RESULTS:** CSE data were more reliable than FSE data. Reliability of hippocampal T2 measures on repeated acquisitions was superior for the CSE sequence with echo time 30,120 than for the 30,80 sequence (test-retest reliability, 4.0%; interrater reliability, 4.6%). CSE images were suitable for qualitative reporting, so additional T2-weighted sequences were not required. There was good correlation between these hippocampal T2 data and values obtained on a previously validated multiecho technique, with reliable identification of hippocampal sclerosis. **CONCLUSION:** T2 mapping with CSE 30/120 sequences may be readily applied, produces reliable T2 values in contiguous 5-mm sections, and may be useful in the assessment of the hippocampus and other cerebral structures.

Index terms: Brain, magnetic resonance; Brain, measurements; Hippocampus

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Increased signal on T2-weighted magnetic resonance (MR) images is a feature of hippocampal sclerosis (1–3). A previously developed technique for in vivo measurement of T2 relaxation time on a 1.5-T MR imager used a 16-echo sequence, and the measures have been shown to be useful in the assessment of hippocampal sclerosis, particularly if there are only subtle changes that may not be evident visually, in the evaluation of the contralateral hippocampus (4, 5), amygdala (6, 7), white matter and thalamus (8, 9), and in longitudinal studies of the development of cerebral abnormalities. In these human in vivo studies, data were acquired from a single section, or from three parallel 8-mm-thick sections, with an intersection gap of 24 mm. T2 maps were generated by fitting single exponentials to the image data of corresponding pixels from all 16 echoes, and the placement of regions of interest on T2 maps took only a few minutes. Limitations of the previous method have been the intersection interval that may make it difficult to compensate for a skewed head position in the scanner and that has effectively allowed only a T2 relaxation time measurement from a single position within the hippocampus. Further, because of its limited coverage of the brain, the T2 mapping sequence has had to be carried out in addition to the usual T1- and T2-weighted studies, resulting in prolongation of the total imaging time.

Accordingly, we sought to develop a robust technique for in vivo T2 relaxometry that could be readily implemented on commonly used MR scanners and that fulfilled the following requirements: sensitivity, specificity, and reliability that at least equal that obtained from the currently used method; complete coverage of the brain; and the ability to calculate T2 data from scan

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acquisition sequences that are used for routine imaging, without the need for further imaging time.

Materials and Methods

Studies on Test Objects

Twelve Eurospin II (Diagnostic Sonar, Livingstone, Scotland) MR quality assessment test objects with nominal T2 relaxation times in the range of 73 to 183 milliseconds (median, 136.5 milliseconds at 19°C) were studied on three separate occasions. The section thickness was 5 mm. Three sequences were evaluated: a fast spin-echo (FSE) sequence at 2000/34,84/1 (repetition time/echo time/excitations), with an echo train length of 8 and a 256 × 256 matrix; a conventional spin-echo (CSE) sequence at 2000/30,80/1 with a 256 × 256 matrix; and a CSE sequence at 2000/30,120/1 with a 256 × 256 matrix.

Image data were transferred from the scanner to a Sun Microsystems (Mountain View, Calif) workstation and converted to a variant of the University of North Carolina's "/usr/image" format. Pixel-by-pixel T2 maps were calculated from the images by using the expression $T2 = (TE_2 - TE_1)/[\ln(S_1/S_2)]$, where S_1 and S_2 are the signal intensity in the early- and late-echo images, with echo times TE_1 and TE_2, respectively.

Evaluation of Measures of Hippocampal T2 Relaxation Time in a Control Population

Fifteen healthy subjects with no history of neurologic disease were scanned. There were eight women and seven men ranging in age from 18 to 58 years (median, 28 years). Visual inspection of the MR images obtained in all subjects showed no indication of structural cerebral abnormalities; data were acquired from 30 hippocampi.

Four sequences were used, all with a 5-mm section thickness and no intersection gap, obtained by two interleaved acquisitions to cover the entire brain with a 24-cm field of view. Scans were orientated in the oblique coronal plane, in the same axis as the brain stem, orthogonal to the hippocampus and so minimizing partial volume effects (4).

Parameters for the FSE sequences were 2000/19,95/1 and 2000/19,133/1, an echo train length of 8, and a 256 × 256 matrix; parameters for the CSE sequence were 2000/30,80/1 and 2000/30,120/1, with a 192 × 256 matrix.

Flow-compensated gradients were used in the slice-select direction for the FSE sequence, and in all three directions for the CSE sequence. Scanning time was 5 minutes 12 seconds for the FSE sequences and 10 minutes 24 seconds for the CSE sequences.

A calculated T2 map, in the same orientation as the original scans, was obtained in the same manner as for the test object experiments. T2 maps were presented and regions of interest drawn using the Dispimage (University College, London, England) image display program (10). The section that included the anterior pons and medulla was used for hippocampal T2 measurements. Regions were placed separately by two observers to establish interrater reliability. Elliptical regions of interest were placed within the hippocampi, and were as large as they could be, typically 20 mm^2, while avoiding boundaries that would give rise to partial volume effects.

The same data set of T2 maps was remeasured in a blinded fashion by the same two observers after an interval of 4 to 6 weeks to assess the test-retest reliability of the analysis.

Ten control subjects were rescanned using the same imaging protocol after an interval of 2 to 10 weeks to assess the stability of the measurement in vivo.

Comparison of Hippocampal T2 Relaxation Times with Data Acquired Using the Previously Established 16-Echo Protocol

Twenty-two patients with temporal lobe epilepsy in whom hippocampal T2 relaxation times were measured by means of the previously established method with 16 echoes were studied by using the CSE sequences with echo times 30,80 and 30,120 as a further validatory step and to compare the normal and abnormal ranges for the methods. Seventeen of these patients had clearly defined hippocampal sclerosis by MR criteria (3, 4) and five had less clear-cut abnormalities; none had foreign-tissue lesions.

All subjects and patients gave informed consent, and these studies were approved by the Ethics Committee of the National Hospital for Neurology & Neurosurgery.

Statistics

Hippocampal T2 data were analyzed using Statworks and SPSS 6.1 (SPSS, Chicago, Ill) on a Macintosh PowerPC personal computer. Test-retest reliability and interrater reliability were assessed on 74 hippocampi (30 from healthy subjects and 44 from patients with temporal lobe epilepsy) by calculating the coefficient of reliability (11). The coefficient of reliability is a stringent test of repeatability and is calculated as 2 × standard deviation of the mean of the difference between two measures divided by the mean of both measures. Pearson's correlation coefficient was calculated for comparing the data obtained from test objects with their nominal T2 values, and for comparing data from the current sequences with the previously validated multiecho sequence.

Results

Studies on Test Objects

All three sequences used—FSE 2000/34,84/1, CSE 2000/30,80/1, and CSE 2000/30,120/1—produced measures of T2 that were lower than the reference values quoted by the manufacturer of the Eurospin II MR quality as-

TABLE 1: Estimation of T2 relaxation times in a series of 12 test objects scanned at 19°C

Sequence	Median (Range*), milliseconds	Test-Retest, mean (SD)	Coefficient of Reliability, %
FSE 34, 84	124 (67.1–158.5)	1.3 (1.0)	1.7
CSE 30,80	100 (57.8–129.5)	0.3 (0.6)	1.2
CSE 30,120	104 (58.1–132.4)	1.2 (1.0)	2.0

Note.—Correlation coefficient of measured values with nominal values as follows: FSE 34,84: $r = .99$, $P < .001$; CSE 30,80: $r = .99$, $P < .001$; CSE 30,120: $r = .99$, $P < .001$. FSE indicates fast spin-echo; CSE, conventional spin-echo.

* Denotes the range of calculated T2 values obtained from the series of Eurospin II MR quality assessment test objects that had nominal T2 values ranging from 73 to 183 milliseconds (median, 136.5).

sessment test objects (Table 1), and there was a linear relationship between the nominal and the measured values, with a high correlation coefficient ($r = .99$, $P < .001$). The test-retest reliability of all three sequences was satisfactory at 1.2% to 2.0%. Table 1 indicates the greatest variation detected between a pair of measurements. FSE and CSE sequences were then evaluated in vivo.

Evaluation of Measures of Hippocampal T2 Relaxation Times in a Control Population

Data were available from 30 hippocampi in 15 healthy subjects obtained with four acquisition sequences: FSE with echo times 19,95 and 19,133; and CSE 30,80 and 30,120. Hippocampal T2 relaxation times were obtained from a 5-mm section that was in the plane of the anterior brain stem. The hippocampal T2 relaxation times were distributed normally. Higher values were obtained with the FSE 19,133 sequence than with the other three sequences. The CSE sequences gave rise to a tighter normal range, with a coefficient of variation of 2.1% to 2.5%, compared with 6.5% to 7% for the FSE acquisitions (Table 2). The difference between the left and right hippocampi was less for the CSE sequence (maximum difference, 4.7 milliseconds) than for the FSE acquisitions (maximum difference, 23.0 milliseconds).

On the basis of these data we decided that the CSE acquisitions were preferable to the FSE acquisitions, because of the smaller range of normal data, smaller coefficient of variation, and smaller difference between left and right hippocampi in healthy subjects. The upper limits of normal for hippocampal T2 relaxation times using the CSE 30,80 sequence were 84.1 milliseconds (+2 SD) and 86.1 milliseconds (+3 SD); for the CSE 30,120 sequence, the upper limits were 89.2 milliseconds (+2 SD) and 91.0 milliseconds (+3 SD).

TABLE 2: Hippocampal T2 relaxation times, ms, in 30 normal hippocampi obtained with four different acquisition sequences

Sequence	Range	Mean (SD)	Coefficient of variation, %
FSE 19,95	74.8–93.5	81.3 (5.7)	7.0
FSE 19,133	99.0–135.0	110.4 (7.1)	6.5
CSE 30,80	75.8–85.6	80.1 (2.0)	2.5
CSE 30,120	81.6–89.1	85.6 (1.8)	2.1

Difference in relaxation times, ms, between left and right hippocampi in 15 healthy subjects

Sequence	Range	Mean (SD)
FSE 19,95	−4.5 + 14.8	1.5 (4.7)
FSE 19,133	−11.0 + 23.0	1.6 (7.1)
CSE 30,80	−4.7 + 3.8	0.7 (2.4)
CSE 30,120	−3.5 + 3.7	0.4 (1.9)

Note.—FSE indicates fast spin-echo; CSE, conventional spin-echo.

Test-Retest and Interrater Repeatability Measures of Hippocampal T2 Relaxation Times Obtained with CSE Sequences in Patients with Temporal Lobe Epilepsy

Data were available from 74 hippocampi, comprising left and right hippocampi from 15 healthy subjects and from 22 patients with temporal lobe epilepsy, of whom 17 had clear evidence of hippocampal sclerosis, with prolongation of hippocampal T2 previously demonstrated on the multiecho sequence (4). For test-retest reliability, the coefficient of reliability was superior for the CSE 30,120 sequence than for the CSE 30,80 sequence, being 4.0% for the former and 7.1% for the latter (Table 3A). The coefficient of reliability for interrater repeatability was 6.4% for the 30,80 sequence and 4.6% for the 30,120 sequence (Table 3B).

Stability of Hippocampal T2 Measurements on Repeated Data Acquisition with CSE in Healthy Subjects

In 10 healthy subjects (20 normal hippocampi), data were acquired twice, an average of 4 weeks apart (range, 2 to 10 weeks). The two

TABLE 3A: Test-retest reliability of analysis of one data set of hippocampal T2 relaxation times, ms, acquired with CSE 30,80 and 30,120

CSE 30,80 (n = 74)
Mean (SD) measure 1: 84.0 (7.0)
Mean (SD) measure 2: 84.1 (6.1)
Mean (SD) difference: −0.1 (3.0) Coefficient of reliability = 7.1%
CSE 30,120 (n = 74)
Mean (SD) measure 1: 90.3 (7.2)
Mean (SD) measure 2: 90.5 (7.1)
Mean (SD) difference: −0.3 (1.8) Coefficient of reliability = 4.0%

TABLE 3B: Interrater reliability of analysis of one data set of hippocampal T2 relaxation times, ms, acquired with CSE 30,80 and 30,120

CSE 30,80 (n = 74)
Mean (SD) measure 1: 84.0 (7.0)
Mean (SD) measure 2: 84.1 (6.5)
Mean (SD) difference: 0.06 (2.7) Coefficient of reliability = 6.4%
CSE 30,120 (n = 74)
Mean (SD) measure 1: 90.3 (7.2)
Mean (SD) measure 2: 90.7 (7.0)
Mean (SD) difference: −0.3 (2.1) Coefficient of reliability = 4.6%

Note.—CSE indicates conventional spin-echo.

TABLE 4: Test-retest reliability of analysis of two data set acquisitions of hippocampal T2 relaxation times, ms, acquired with CSE 30,80 and 30,120

CSE 30,80 (n = 20)
Mean (SD) measure 1: 79.8 (2.3)
Mean (SD) measure 2: 80.0 (2.2)
Mean (SD) difference: −0.2 (2.6) Coefficient of reliability = 6.5%
CSE 30,120 (n = 20)
Mean (SD) measure 1: 85.3 (1.8)
Mean (SD) measure 2: 86.2 (1.9)
Mean (SD) difference: −0.9 (2.0) Coefficient of reliability = 4.6%

Note.—CSE indicates conventional spin-echo.

data sets were analyzed on separate occasions. The coefficient of reliability was superior for the CSE 30,120 sequence at 4.6% as compared with 6.5% for the CSE 30,80 sequence (Table 4).

Comparison of CSE Hippocampal T2 Relaxation Time Measurements with Data Acquired Using a 16-Echo Sequence

In 22 patients (44 hippocampi), 17 of whom had clear-cut hippocampal sclerosis, hippocampal T2 relaxation time data were available from the 16-echo sequence used previously and from both of the CSE dual-echo sequences. Normative data for the 16-echo sequence were as follows: mean, 102.4; SD, 2.8; range, 93 to 108 (mean + 2 SD = 108.0; mean + 3 SD = 110.8) (12). The normal ranges for the different sequences were clearly different. The CSE 30,120 T2 data were strongly correlated with the multiecho sequence data ($r = .91$, $P < .001$) (Fig 1). The CSE 30,80 T2 data were also well correlated with the multiecho data, albeit less strongly ($r = .61$, $P < .001$).

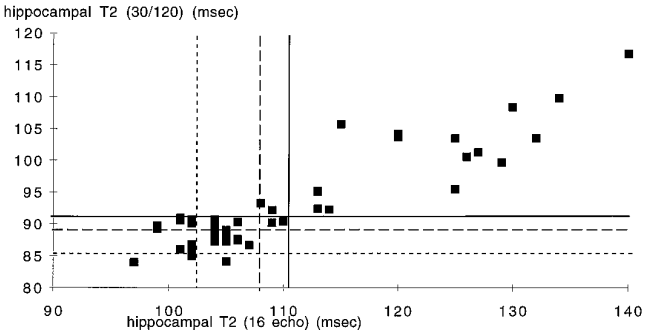

Fig 1. Hippocampal T2 relaxation times (in milliseconds) obtained with CSE 30,120 dual-echo sequence plotted against data obtained with a 16-echo sequence in 22 patients with temporal lobe epilepsy, 17 of whom had clear-cut hippocampal sclerosis. *Dotted line* indicates mean control values for the 30,120 sequence (85.6 milliseconds) and the multiecho sequence (102.4 milliseconds). *Hatched line* indicates 2 SD above mean control values for the 30,120 sequence (89.2 milliseconds) and the multiecho sequence (108 milliseconds). *Solid line* indicates 3 SD above mean control values for the 30,120 sequence (91 milliseconds) and the multiecho sequence (110.8 milliseconds).

There was also good agreement between the normal and abnormal data for the multiecho and CSE 30,120 dual-echo sequences. If the multiecho hippocampal T2 relaxation times were abnormal (>108 milliseconds), the 30,120 hippocampal T2 relaxation times were always abnormal (>89 milliseconds). Values for seven hippocampi from patients with temporal lobe epilepsy were in the normal range for the multiecho T2 data and were mildly elevated on the 30,120 sequence: six were between 90 and 91 milliseconds, and one was 93.3 milliseconds (91 milliseconds is 3 SD above the mean value of hippocampal T2 relaxation time obtained with the 30,120 sequence).

Agreement between the normal and abnormal data for the multiecho and CSE 30,80 dual-echo sequences was not as good. Values for five hippocampi from patients with temporal lobe epilepsy were in the normal range for the multiecho T2 data and were mildly elevated on the 30,80 sequence, in the range of 86 to 93 milliseconds (84.1 milliseconds is 2 SD above, and 86.1 milliseconds is 3 SD above the mean value of normal hippocampal T2 relaxation time using the 30,80 sequence). Three hippocampi

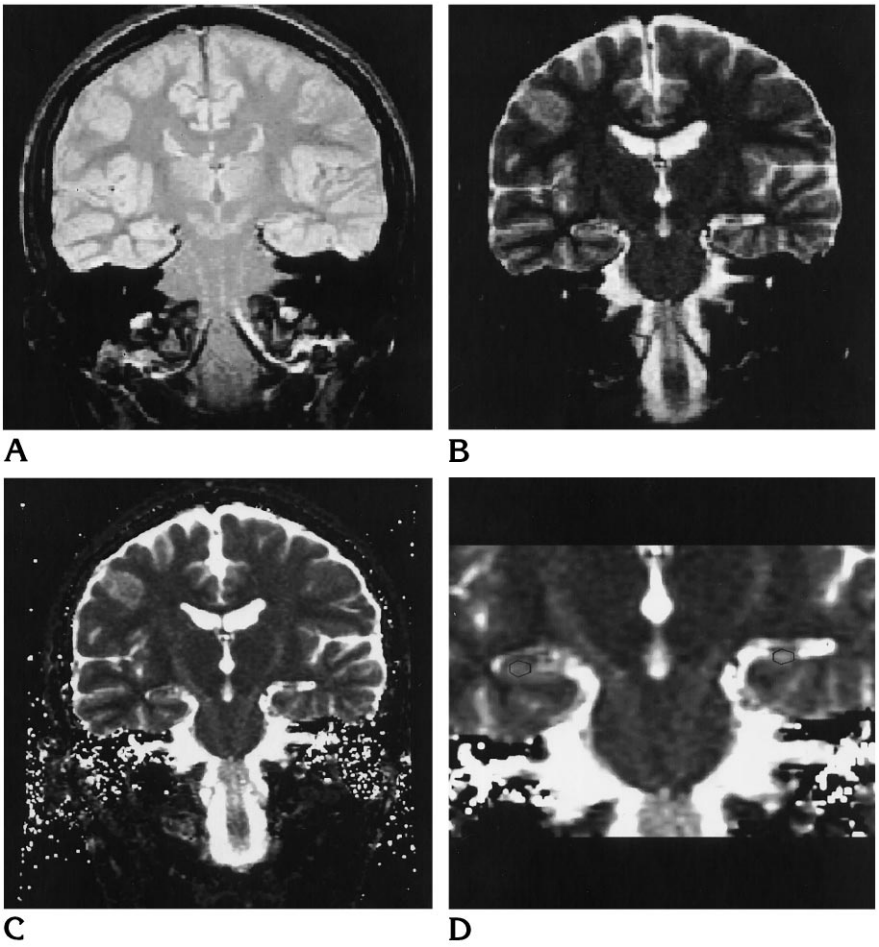

Fig 2. Oblique coronal CSE images through the body of the hippocampus. The left side of the brain is on the right of the image.

A, Echo time of 30; *B*, echo time of 120; *C*, T2 map calculated from these images; *D*, magnified T2 map showing placement of regions (20 mm^2) used to determine hippocampal T2 relaxation times. T2 relaxation times are 100 and 91 milliseconds for left and right hippocampi, respectively.

were abnormal on the multiecho sequence, in the range of 110 to 114 milliseconds, but had hippocampal T2 relaxation times that were in the normal range for the CSE 30,80 sequence, in the range 82 to 84 milliseconds.

The CSE 30,120 sequences took 10 minutes 24 seconds to acquire and produced sets of images that were eminently suitable for qualitative reporting by a neuroradiologist, so that additional T2-weighted sequences were not required (Fig 2).

Discussion

In this study, the absolute accuracy of T2 measures was not a prime consideration; this was considered to be much less important than the production of reliable and reproducible data that differentiated normal from abnormal hippocampi.

We were able to implement and validate a method for obtaining reliable quantitative T2 data by using a dual-echo CSE sequence on a standard General Electric (Milwaukee, Wis) Signa MR scanner. Initial studies on standard test objects gave reasonable results for both CSE and FSE acquisition sequences. Studies in healthy volunteers, however, showed that the normal range and coefficient of variation of hippocampal T2 relaxation time were much greater with the FSE sequences than with the CSE sequences. We discarded the FSE sequences from further consideration at this point, since a major reason for quantifying hippocampal T2 relaxation times is to discriminate normal from abnormal hippocampi and to identify subtle and bilateral abnormalities that may not be evident at visual inspection.

As with the multiecho technique, the dual-echo sequences may be placed in any orientation as well as orthogonal to the hippocampus from a sagittal scout image. The 30,120 dual-echo sequence appeared to have advantages over the 30,80 sequence. Principally, there was

superior test-retest and interrater reliability on assessments of a single data set and on repeated acquisitions from a subject.

As expected, lower estimates of T2 were obtained from studies of test objects and in vivo measurements of hippocampal T2 relaxation times using the dual-echo CSE sequences rather than the 16-echo sequence with a fitted curve. This was not a concern, as the clinical requirement was to be able to distinguish normal from abnormal hippocampal T2 relaxation times reliably, and accurate absolute quantitation was not an issue.

The CSE dual-echo sequence has several advantages over the previously used 16-echo sequence. The images obtained (echo times of 30 and 120) were highly satisfactory to neuroimaging specialists for the purposes of qualitative reporting and could be incorporated into a standard imaging protocol without the need for additional sequences. Further, 5-mm-thick sections have produced reliable data, minimizing partial volume effects; with the multiecho sequence, 8-mm-thick sections were found to give optimal quantitation of hippocampal T2 relaxation times. Additionally, by using the CSE dual-echo sequences, it is possible to get complete coverage of the hippocampus and brain with contiguous 5-mm-thick sections collected in two interleaved acquisitions. In contrast, the multiecho sequence gave only a single hippocampal section. Complete coverage in 5-mm-thick sections allows for correction of misalignment of the patient in the scanner and also permits the construction of a profile of T2 values throughout the length of the hippocampus, analogous to the profiles of cross-sectional areas that may be derived from volumetric data. We are in the process of conducting a comparative study of these profiles to define better the spectrum of hippocampal sclerosis.

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