Magnetic resonance spectroscopy and cognitive function in healthy elderly men

Karen J. Ferguson,1,5 Alasdair M. J. MacLullich,2,3 Ian Marshall,1 Ian J. Deary,4 John M. Starr,3 Jonathan R. Seckl2 and Joanna M. Wardlaw1,5

1Brain Imaging Research Centre for Scotland, 2Molecular Medicine Centre, 3Geriatric Medicine Unit, Western General Hospital and Departments of 4Psychology and 5Clinical Neurosciences, University of Edinburgh, Edinburgh, UK

Correspondence to: A. MacLullich, Geriatric Medicine Unit, University of Edinburgh, Western General Hospital, 21 Chalmers Street, Edinburgh EH3 9EW, UK
E-mail: a.maclullich@ed.ac.uk

Summary
Subtle cognitive decrements in older people are important in terms of the associated morbidity and as a risk factor for dementia. However, their pathophysiological basis is poorly understood. Proton magnetic resonance spectroscopy (1H-MRS) may provide the means to investigate early changes in brain metabolite concentrations. We examined the relationships between N-acetylaspartate (NAA), choline (Cho) and creatine (Cr) metabolite ratios in a voxel in the parietal cortex and cognitive function in 88 healthy, non-demented, unmedicated men aged 65–70 years. We also used linear regression to give a value for each metabolite adjusted for the levels of the other two metabolites. Both NAA/Cr and Cho/Cr ratios correlated positively with tests of verbal memory and a verbal memory factor (e.g. NAA/Cr and Logical Memory: r = 0.24, P < 0.05). Cho/Cr ratios also correlated positively with tests of visual memory (e.g. visual reproduction: r = 0.21, P < 0.05). Adjusted Cr levels correlated negatively and significantly with tests of verbal memory and the Verbal Memory Factor. The regression analysis suggested that Cr levels better explained the correlations between NAA/Cr and Cho/Cr ratios and cognitive variables than NAA or Cho levels. These results suggest that in healthy men aged 65–70 years, metabolite levels relate to cognitive performance. Rising Cr levels may be an early marker of cognitive decline.

Keywords: cognition; creatine; 1H-MRS; memory; spectroscopy

Abbreviations: Cho = choline; Cr = creatine; 1H-MRS = proton magnetic resonance spectroscopy; NAA = N-acetylaspartate; PCr = phosphocreatine; VOI = volume of interest

Introduction
Deficits in cognitive function become more common with ageing. Alzheimer’s disease and other dementias are at the severe end of the spectrum, but milder deficits in cognitive function are also important in terms of the associated morbidity and also because milder deficits are a risk factor for the development of dementia (Petersen et al., 1999). The mechanisms underlying these changes are poorly understood. Pathological studies demonstrate that neuronal loss does occur in dementias such as Alzheimer’s disease, but there may be very little neuronal loss in the absence of such disease processes (West et al., 1994), suggesting that changes in the function of neurones might play an important role in cognitive ageing.

Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive technique that can measure levels of certain metabolites in the brain in vivo. Commonly identified metabolites are N-acetylaspartate (NAA), choline-containing compounds (Cho) and total creatine (Cr). NAA is neuron-specific (Simmons et al., 1991) and is considered to be a marker of normal functioning neurones. Cho levels reflect the quantities of Cho-containing compounds, which are involved in both the synthesis and breakdown of phospholipid membranes. Increased Cho may reflect increased membrane synthesis (e.g. in gliosis) or breakdown (e.g. necrosis) (Pettegrew et al., 1997). Creatine levels reflect the quantity of phosphocreatine (PCr) and Cr involved in energy metabolism in neurones and glial cells.

1H-MRS is increasingly used in the study of neurodegenerative diseases. For example, decreased levels of NAA have been found in pathological states in which there is known to be neuronal loss, such as Alzheimer’s disease (Schuff et al., 1998; Pfefferbaum et al., 1999a), epilepsy (Breiter
et al., 1994; Aasly et al., 1999), Huntington’s disease (Sanchez-Pernaute et al., 1999) and schizophrenia (Lim et al., 1998; Deicken et al., 1999). However, there are very few studies of metabolite changes in mild cognitive impairment. In a study of otherwise healthy people aged >70 years, Catani and colleagues reported higher myo-inositol/Cr ratios in 11 persons with mild cognitive impairment compared with 11 healthy controls (Catani et al., 2001). Pfefferbaum and colleagues reported a positive correlation between NAA levels and a face recognition task in 13 healthy elderly subjects (Pfefferbaum et al., 1999b). Even fewer studies have been published in young, healthy adults. One group reported a positive association between absolute NAA concentrations and performance on cognitive tests in 40 subjects (Jung et al., 1999). Overall, the literature to date does not allow firm conclusions to be drawn concerning changes in brain metabolites with ageing.

We explored relationships between tests of cognitive function and metabolite levels using H1-MRS in a large sample of healthy elderly men. We are performing a longitudinal study in this cohort and in the present paper report the baseline findings in subjects aged 65–70 years.

**Methods**

**Subjects**

Subjects were healthy male volunteers aged 65–70 years who were living in Edinburgh, UK. They were recruited through an invitation letter and interview. All were recruited with the assistance of their local General Practitioners. Each subject was interviewed by a physician (A.M.) to screen for symptoms suggestive of significant illness, including dementia, cerebrovascular disease, ischaemic heart disease and depressive illness. Those with symptoms were excluded. Subjects with past history of cancer, heart disease, respiratory disease, diabetes, neurological disease and other significant disease were excluded. Venous blood was analysed for urea and electrolytes, calcium, liver function tests, thyroid function tests, glucose, glycosylated haemoglobin, haemoglobin, white cell count, platelet count, B12 and folate levels, and any subject with abnormalities according to standard clinical criteria was excluded. No subject was on regular medication at the time of cognitive testing or imaging. One hundred subjects were entered into the study following the screening process.

**Cognitive testing**

Subjects underwent a battery of tests designed to assess several domains of cognitive functioning; memory was tested in detail. All testing was carried out in the morning by the same tester (A.M.) who was blind to the results of brain imaging. The order of tests was the same for each subject and frequent breaks were provided to reduce the effects of fatigue. Fluid, non-verbal intelligence was evaluated with Raven’s Standard Progressive Matrices (Raven et al., 1977) using the number correct in 20 min. Verbal memory was evaluated with the Logical Memory (immediate and 30 min-delayed) subtest of the Wechsler Memory Scale (Wechsler, 1981) and the Rey Auditory–Verbal Learning Test (Lezak, 1995). Testing of delayed paragraph recall, in which subjects returned for retesting (Logical Memory 24 h-delayed), was performed in 58 subjects. Visuospatial memory was evaluated with the Visual Reproduction (immediate and 30 min-delayed) subtest of the Wechsler Memory Scale (Wechsler, 1987) and Administration A of the Benton Visual Retention Test (Sivan, 1992). As the immediate and delayed components of both Logical Memory and Visual Reproduction are highly correlated (r = 0.83 and r = 0.75, respectively), the summed standardized scores from each component were entered into the analysis. Verbal fluency was assessed with the Controlled Word Association Test using the letters C, F and S (Lezak, 1995). Attention and processing speed were evaluated with the Digit-Symbol Substitution Test from the Wechsler Adult Intelligence Scale (Wechsler, 1981). Pre-morbid IQ (intelligence quotient) was assessed with the National Adult Reading Test (Nelson and Willison, 1991). Performance on the National Adult Reading Test tends not to show decrements early in the process of ageing-related cognitive impairment, whereas performance on tests of short-term memory and fluid intelligence does show decline with ageing (Parkin and Java, 1999).

**MRI scanning**

All MRI scanning was performed on an Elscint Prestige scanner operating at 1.9 T (Elscint, now GE Medical, Israel). Spectroscopy was carried out following detailed structural imaging, the results of which are published elsewhere (MacLullich et al., 2002). Placement of the volume of interest (VOI) for spectroscopy was carried out using the structural images acquired for volumetric analysis in the coronal plane. The VOI (15 × 15 × 15 mm) was placed over the parietal lobe and included mainly white matter with some grey, but avoided any contamination from non-cerebral tissue (Fig. 1). Following shimming on the VOI, water-suppressed, PRESS-localized 1H signals [TR (repetition time)/TE (echo time) = 1500/145 ms] were acquired with 200 repetitions [number of excitations (NEX)]. Phase reference signals (eight NEX) were acquired from the same VOIs without water suppression. The time domain signals sampled the second half of the PRESS echo and consisted of 1024 complex data points sampled at 1 ms intervals.

**Spectral quantification**

Spectroscopic data were transferred to a network of Sun workstations (Sun Microsystems, Mountain View, CA, USA). The water reference signals were used for time domain correction of eddy current effects (Ordridge and Cresshull, 1986), and the residual water signal removed by
Hankel-Lanczos Singular Value Decomposition identification of water components (van den Boogaart et al., 1994). Signals were then transformed to the frequency domain. Spectral peak areas corresponding to the metabolites Cho, Cr and NAA were quantified in the frequency domain, fitting for frequencies, areas and line widths with a Gaussian lineshape using in-house software (Marshall et al., 2000). A sample spectrum is shown in Fig. 2. No attempt was made to relate fitted peak areas with absolute metabolic concentrations.

Statistical analysis
We wished to avoid making assumptions about whether any particular metabolite levels remained relatively constant, and therefore did not rely solely on the use of ratios as the main comparator. As an alternative method we regressed each metabolite value against the remaining two and saved the standardized residual values. This method is similar in aim to the use of ratios but has the advantage of not assuming that Cr levels are an appropriate internal control. In the present paper these derived values are termed ‘adjusted metabolite levels’. As scores in diverse cognitive tests are substantially positively intercorrelated (Carroll, 1993), the cognitive test data were subjected to principal components analysis, excluding the National Adult Reading Test because it is a measure of pre-morbid IQ, and Logical Memory 24 h-delayed because the number of subjects was substantially less than for the other tests. Individual cognitive test results and factor scores derived from principal components analysis were correlated with metabolite ratios and with the adjusted metabolite levels derived as described above.

Results
Of the 100 participants scanned, three were excluded when unexpected pathology was discovered on structural MRI: two because of congenital arachnoid cysts, and one because of a pituitary adenoma (non-secretory). Of the remaining 97 subjects, 88 spectra were suitable for metabolite quantification analysis as determined by evaluation of the appearance of the spectra by a neuroradiologist and assessment of the quality of curve fitting during analysis of spectra by a research fellow. Data from two further spectra were excluded as the standardized residual values in the linear regression analysis were >3 standard deviations (SD) from the mean.

Principal components analysis of the cognitive tests revealed two factors with eigenvalues >1, explaining a total of 66% of the variance. The data were subjected to Direct Oblimin rotation. The two factors were designated General Cognitive Factor and Verbal Memory Factor. Loadings are shown in Table 1. These factor loadings were entered into the correlational analysis in addition to the raw cognitive test scores with the metabolite ratios and the adjusted metabolite levels.

For the correlational analyses, there were 86 subjects for all comparisons except: Raven’s Matrices (n = 84), where two subjects were excluded because of incorrect completion of the answer sheets; Logical Memory (n = 85), where one subject’s score was invalid in this test because of interruption of the testing session; and Visual Reproduction (n = 85), where a further subject also had the test session interrupted. Listwise deletion meant that factor scores from 82 subjects were available. For Logical Memory 24 h-delayed, 58 subjects returned for retesting, of which 50 had spectra suitable for inclusion.

Age did not correlate with any of the metabolite ratios or adjusted metabolite levels. Correlations between ratios of metabolite levels and cognitive test results are shown in Table 2. NAA/Cr ratios were correlated positively with...
Logical Memory ($r = 0.25, P < 0.05$), Logical Memory 24 h-delayed ($r = 0.43, P < 0.01$) and the Verbal Memory Factor ($r = 0.25, P < 0.05$). Cho/Cr ratios were positively correlated with the Benton Visual Retention Test, Visual Reproduction, the Auditory–Verbal Learning Test, Logical Memory, Logical Memory 24 h-delayed, and the Verbal Memory Factor ($r$ values 0.21 to 0.38, $P < 0.05$). NAA/Cho ratios did not correlate significantly with any test scores.

The correlations between the adjusted metabolite levels and cognitive test results are shown in Table 3. Adjusted Cr levels were significantly negatively correlated with Logical Memory ($r = -0.26, P < 0.05$), Logical Memory 24 h-delayed ($r = -0.39, P < 0.01$) and the Verbal Memory Factor ($r = -0.26, P < 0.05$). There were trends in the same negative direction with Raven’s Standard Progressive Matrices, Visual Reproduction and the Auditory–Verbal Learning Test. Adjusted Cho levels and adjusted NAA levels did not correlate significantly with any of the cognitive test scores.

### Discussion

The main findings in this study are that higher NAA/Cr and Cho/Cr ratios are associated with better performance on several cognitive tests. Both ratios correlated positively with Logical Memory, Logical Memory 24 h-delayed and a

---

### Table 1  Factor loadings for cognitive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>General cognitive factor</th>
<th>Verbal memory factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency</td>
<td>0.57</td>
<td>-0.10</td>
</tr>
<tr>
<td>Digit-Symbol Substitution Test</td>
<td>0.76</td>
<td>-0.08</td>
</tr>
<tr>
<td>Auditory–Verbal Learning Test</td>
<td>0.61</td>
<td>0.64</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>0.74</td>
<td>-0.40</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>0.63</td>
<td>0.62</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>0.81</td>
<td>-0.18</td>
</tr>
<tr>
<td>Raven’s Matrices</td>
<td>0.81</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

### Table 2  Correlations between metabolite ratios and cognitive test results

<table>
<thead>
<tr>
<th>Test</th>
<th>NAA/Cho</th>
<th>NAA/Cr</th>
<th>Cho/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Adult Reading Test</td>
<td>-0.17</td>
<td>0.13</td>
<td>0.20</td>
</tr>
<tr>
<td>Raven’s Standard Progressive Matrices</td>
<td>-0.00</td>
<td>0.19</td>
<td>0.15</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>-0.15</td>
<td>0.17</td>
<td>0.25*</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>-0.05</td>
<td>0.21</td>
<td>0.21*</td>
</tr>
<tr>
<td>Digit-Symbol Substitution Test</td>
<td>-0.06</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Auditory–Verbal Learning Test</td>
<td>-0.08</td>
<td>0.21</td>
<td>0.22*</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>-0.10</td>
<td>0.24**</td>
<td>0.25*</td>
</tr>
<tr>
<td>Logical Memory (24 h-delayed)</td>
<td>-0.07</td>
<td>0.43**</td>
<td>0.38**</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-0.18</td>
<td>-0.01</td>
<td>0.11</td>
</tr>
<tr>
<td>General Cognitive Factor</td>
<td>-0.09</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Verbal Memory Factor</td>
<td>-0.09</td>
<td>0.25*</td>
<td>0.25*</td>
</tr>
</tbody>
</table>

*Correlation is significant at the $P = 0.05$ level (two-tailed); **Correlation is significant at the $P = 0.01$ level (two-tailed). $n = 86$ for all tests except Raven’s Standard Progressive Matrices ($n = 84$), Logical Memory ($n = 85$), Visual Reproduction ($n = 85$) and Logical Memory (24 h-delayed; $n = 50$) and the General Cognitive and Verbal Memory Factors ($n = 82$).

### Table 3  Correlations between adjusted metabolite levels and cognitive test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Adjusted Cr</th>
<th>Adjusted Cho</th>
<th>Adjusted NAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Adult Reading Test</td>
<td>-0.20</td>
<td>-0.19</td>
<td>-0.08</td>
</tr>
<tr>
<td>Raven’s Standard Progressive Matrices</td>
<td>-0.18</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td>-0.12</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>Visual Reproduction</td>
<td>-0.17</td>
<td>0.13</td>
<td>0.21</td>
</tr>
<tr>
<td>Digit-Symbol Substitution Test</td>
<td>-0.05</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Auditory–Verbal Learning Test</td>
<td>-0.19</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>-0.26*</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Logical Memory (24 h-delayed)</td>
<td>-0.39**</td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-0.01</td>
<td>0.21</td>
<td>-0.11</td>
</tr>
<tr>
<td>General Cognitive Factor</td>
<td>-0.11</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>Verbal Memory Factor</td>
<td>-0.26*</td>
<td>0.13</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Correlation is significant at the $P = 0.05$ level (two-tailed); **Correlation is significant at the $P = 0.01$ level (two-tailed). $n = 86$ for all tests except Raven’s Standard Progressive Matrices ($n = 84$), Logical Memory ($n = 85$), Visual Reproduction ($n = 85$) and Logical Memory (24 h-delayed; $n = 50$) and the General Cognitive and Verbal Memory Factors ($n = 82$).
derived Verbal Memory Factor. Cho/Cr also correlated positively with the Benton Visual Retention Test, Visual Reproduction and the Auditory–Verbal Memory Test. Higher adjusted Cr levels were associated with worse performance on Logical Memory, Logical Memory 24 h-delayed and the Verbal Memory Factor. All of the remaining cognitive variables correlated in a negative direction with adjusted Cr and the strength of many of these correlations approached statistical significance. There were no correlations between NAA/Cho ratios, adjusted NAA levels or adjusted Cho levels and cognitive tests or the derived factors.

This is the largest study to examine brain metabolite–cognition associations in a healthy human sample and is the first to demonstrate these relationships. The findings have implications for the understanding of the mechanisms underlying the considerable variations in cognitive ageing. However, the findings also raise important issues concerning the use of metabolite ratios instead of absolute values. Most 1H-MRS studies do not use water-referencing or phantom-referencing for the calculation of metabolite levels and thus express results as ratios. Traditionally, Cr levels are thought to show less inter-individual variation (Catani et al., 2001) and thus are commonly used as the denominator. They are also considered to change little in disease, or only as a result of marked disease. The practice of using ratios may also be because of the emphasis placed on NAA as a marker of neuronal integrity. Some studies of normal ageing have reported reductions in NAA/Cr (Angelie et al., 2001). In most published papers, reductions in NAA/Cr are interpreted as signifying reductions in absolute NAA, but, clearly, increases in Cr would have the same arithmetical effect, and perhaps the previous studies should be reanalysed in this light. Using the traditional method of analysis, the present findings would suggest that higher NAA and Cho levels are associated with better cognitive function. However, the regression analysis suggests that higher Cr levels might better explain the correlations between NAA/Cr and Cho/Cr ratios and cognitive variables rather than lower NAA or Cho levels, because the adjusted Cr levels showed the most consistent pattern of correlations. Alternatively, the correlations with adjusted Cr might reflect the association of reduced levels of both NAA and Cho levels with cognitive variables. Only measurement of the absolute levels of these metabolites would resolve these alternatives.

There is some evidence that Cr levels may themselves be important in the pathophysiology of cognitive ageing. Some 1H-MRS studies using absolute metabolite concentrations have reported higher Cr levels in healthy ageing brains compared with healthy younger brains (Pfefferbaum et al., 1999b; Saunders et al., 1999; Leary et al., 2000; Schuff et al., 2001). Creatine levels as detected by 1H-MRS reflect the sum of PCr and Cr. PCr is present in the brain at high levels, providing a store of phosphate for phosphorylation of ADP and thus maintaining ATP levels. The conversion of PCr to ATP is catalysed by creatine kinase. Creatine kinase levels, activity and forward flux decrease with ageing (Smith et al., 1991; Smith et al., 1997), while P31-MRS studies have shown increasing PCr levels in the ageing rat (Pettegrew et al., 1990). Pettegrew and colleagues identified a cognitively normal man of 55 years of age who had P31-MRS changes suggestive of dementia (Pettegrew et al., 1995). Follow-up over 46 months showed a progressive decline in cognitive function to frank dementia, paralleled closely by a linear rise in PCr; control subjects showed no changes in PCr (Pettegrew et al., 1995). Although the number of studies and their samples sizes are small, together these findings suggest the possibility that the conversion of PCr to ATP may be impaired in ageing, accounting for an accumulation of PCr. Thus, increased levels of Cr may be a marker of decreased brain energy metabolism (Wyss and Kaddurah-Daouk, 2000), which may be associated with ageing-related mild cognitive impairment as well as, in more extreme cases, frank dementia.

We did not find any relationship between adjusted NAA and cognitive function. This may reflect the healthy state of our participants since NAA is thought to be a marker of neuronal number and integrity. Other studies, with subject numbers of between 30 and 50, have reported that NAA is not reduced in the white matter of healthy elderly subjects (Chang et al., 1996; Lundbom et al., 1999; Pfefferbaum et al., 1999b; Saunders et al., 1999), although one study did find decreased NAA in 50 healthy elderly subjects (Brooks et al., 2001). Broadly speaking, however, these findings fit with stereological findings suggesting that brain atrophy in healthy ageing is not caused by neuronal death (West et al., 1994).

Adjusted Cho levels did not correlate significantly with any cognitive variables. Interpretation of Cho levels derived from 1H-MRS is difficult as free Cho is increased both in membrane breakdown (e.g. necrosis) and increased formation (e.g. gliomas). This confusion is reflected in the variety of findings for Cho changes with ageing: higher Cho in grey matter (Chang et al., 1996; Pfefferbaum et al., 1999a, b), lower Cho in grey matter (Charles et al., 1994) and no change in Cho levels in white matter (Lundbom et al., 1999; Pfefferbaum et al., 1999b; Saunders et al., 1999; Schuff et al., 1999, 2001) have all been reported.

There are several methodological limitations of the present study which should be noted. Without determining absolute concentrations of metabolites, interpretation of the results must remain speculative. We attempted to look for the unique variance for each metabolite using regression analysis but, as with ratios, the biological significance of metabolite values generated using this method is unclear. Techniques which generate absolute values are extremely time consuming and, especially with older people, the long scanning times make large scale studies impractical. Even with techniques that generate values to be used in ratios, 1H-MRS is not problem-free, in that subjects must lie still for considerable periods; in large groups it is likely that a proportion of subjects will not tolerate these long scanning times. Even in co-operative subjects, there may be problems with the technique, like poor shimming, which preclude obtaining measurable spectra. The
study is cross-sectional, so we do not yet know yet whether individual differences in metabolite levels are longstanding at this stage in life or whether they represent differences accruing with brain ageing that may preclude overt dementia.

In conclusion, this study provides evidence that individual differences in metabolite levels relate significantly to variations in cognitive function at age 65–70 years. The pattern of results seen in the ratios, as well as the regression analysis, suggest that Cr but not Cho and NAA are associated with these variations. This is in contrast to studies focusing on neurodegenerative diseases, which suggest that lower NAA levels are associated with cognitive decrements. Further H1-MRS studies using spectroscopy protocols that can generate absolute levels of these metabolites are essential to clarify the nature of these associations. The use of P31-MRS may also help to understand the relative concentrations of PCr and Cr in the ageing brain and to examine further the hypothesis that individual differences in cognitive ageing may stem in part from changes in brain energy metabolism.

Acknowledgements
We thank Evelyn Cowie, Annette Blane and Jim Cannon for technical support. We thank Martin Connell for writing the in-house software. The work was funded by a Medical Research Fellowship and a Project Grant from the Scottish Hospital Endowments Research Trust, and a Research Development Grant from the Scottish Higher Education Funding Council. The brain imaging work was performed in the SHEFC Brain Imaging Research Centre for Scotland.

References


Orndridge RJ, Cresshull ID. The correction of transient b0 field shifts following the application of pulsed gradients by phase correction in the time domain. J Magn Reson 1986; 69: 151–5.


Pettegrew JW, Klunk WE, Panchalingam K, McClure RJ, Stanley...


Received February 19, 2002. Revised July 8, 2002. Accepted July 9, 2002