

REVIEW

Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC

G B Frisoni, P h Scheltens, S Galluzzi, F M Nobili, N C Fox, P H Robert, H Soininen, L-O Wahlund, G Waldemar, E Salmon

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Neuroimaging is a mainstay in the differential diagnosis of patients with cognitive impairment. The often equivocal clinical pictures, the prognostic uncertainty of the earliest stages of mild cognitive impairment, and the subtle brain changes mean that neuroimaging techniques are of potentially great incremental diagnostic value. A number of methods, ranging from very simple subjective visual ratings to highly sophisticated computerised tools, have been developed, which allow rating of structural and functional brain changes. The choice of the method is not obvious, and current guidelines provide no indications on which tools should be preferred. In this paper, we give indications for tools with demonstrated accuracy for detecting regional atrophy, cerebrovascular disease, and regional brain function, and discuss these according to increasing technological complexity, ranging from those with high feasibility that can be used at the patient's bedside to highly technological ones that require trained personnel and specific hardware and software.

Furthermore, the rate of atrophy progression has been suggested as a feasible surrogate marker for trials of disease modifying drugs,⁹ and indeed, atrophy measures have now been adopted in several current trials in MCI and AD.¹⁰

Available criteria for vascular dementia^{11–12} require brain imaging criteria that define minimum extension, topography, and severity of vascular lesions. In the NINDS-AIREN criteria, leukoencephalopathy involving at least 25% of the total white matter must be present to diagnose small vessel cerebrovascular disease. Tools to rate quantitatively the vascular load in the brain might increase the diagnostic accuracy of vascular dementia.

The practising dementia specialist can find few literature indications on how to exploit the potential of neuroimaging. Diagnostic guidelines issued by the European Federation of Neurological Societies¹³ and the more recently issued practice parameters of the American Academy of Neurology¹⁴ suggest that at least one structural CT or MR examination should be made over the course of a dementing disorder to rule out space occupying or vascular lesions, and that SPET and PET should be used in cases of significant diagnostic uncertainty. Moreover, they suggest that, although not required by guidelines, more specific CT/MR parameters measuring atrophy and subcortical vascular lesions and SPECT/PET parameters of perfusion/metabolism may be diagnostic aids in the evaluation of patients with cognitive impairment. However, no indication is provided as to how images should be rated to extract clinically useful information.

Paradoxically, scores of methods to rate structural and functional changes in the brains of patients with cognitive impairment can be found in the literature.¹⁵ Methods range from very simple subjective visual ratings to highly sophisticated computerised tools. The choice of the method is not obvious. The diagnostic accuracy (sensitivity and specificity) generally

imaging in dementia or cognitive impairment is moving from a negative, exclusionary role to one that adds positive diagnostic and prognostic information. Only 10 years ago, the practice parameters of the American Academy of Neurology regarded computed tomography (CT) and magnetic resonance (MR) as "optional" examinations.¹ The belief is now widely held that quantitative ratings of structural and functional changes can have an impact on the clinical management of the patient.²

The increased social awareness of cognitive disturbances brings patients to first medical observation in earlier stages of the dementing disorder,^{3–4} when the diagnosis is often uncertain and imaging can represent a significant aid to the differential diagnosis. Hippocampal atrophy on MR,⁵ and medial temporal or temporoparietal cortical hypoperfusion/hypometabolism on single photon emission tomography (SPET)^{6–7} and positron emission tomography (PET)⁸ have been shown to be among the most accurate markers of conversion of patients with mild cognitive impairment (MCI) to Alzheimer's disease (AD).

See end of article for authors' affiliations

Correspondence to:
Dr G B Frisoni, Laboratory
of Epidemiology &
Neuroimaging, IRCCS San
Giovanni di Dio-FBF, via
Pilastroni 4, 25125
Brescia, Italy;
papers@centroalzheimer.it

Abbreviations: AD, Alzheimer's disease; ARWMC, Age Related White Matter Changes; CT, computed tomography; MCI, mild cognitive impairment; MR, magnetic resonance; MTL, medial temporal lobe; MMS, Mini Mental State; PET, positron emission tomography; SPET, single photon emission tomography

Table 1 Levels of increasing technological intensity of tools to rate structural imaging findings in patients with cognitive impairment

Level	Medium	Technical requirements	Regional atrophy		Subcortical cerebrovascular disease	
			Measurement	Experience	Measurement	Experience
CT 1	Film	Routine acquisition*	None	—	Visual rating scales: ARWMC scale ²¹	1–2 weeks
CT 2	Film	2–3 mm thick slices on temporal lobe plane	Linear measures: minimum thickness of the MTL ²² and radial width of the temporal horn ²⁷	1–3 days	None	—
MR 1	Film	Routine acquisition†	Visual rating scales: Scheltens' MTL atrophy score ³⁰ Linear measures: width of the temporal horn ²⁴	1–3 days 1–3 days	Visual rating scales: ARWMC scale ²¹	1–2 weeks
MR 2	Digital	3D T1 acquisition manual or semiautomatic post-processing	Volumetric measures: hippocampal and entorhinal cortex volumes ^{38, 39}	2–4 weeks	Volumetric measures: thresholding of WMH ⁴¹	1 day
MR 3	Digital	3D T1 acquisition software for computerised post-processing serial scans	Prospective whole brain assessment: brain boundary shift integral ⁴⁵	—	None	—

ARWMC, Age Related White Matter Changes; MTL, medial temporal lobe; WMH, white matter hyperintensities; ROI, region of interest.

*Orbitomeatal line, slice thickness of 8–10 mm; †including coronal T1 acquisition through the MTL.

Experience denotes the training time needed to obtain accurate measurements.

ranges between 70 and 90%^{15, 16} and, although it is likely that more sophisticated methods are more accurate, there is little evidence that this is the case. Moreover, the accuracy of any method is heavily affected by personal expertise and clinical composition of the population of interest, and the incremental diagnostic accuracy by number and type of other diagnostic tests. Thus, as is often the case in medicine,¹⁷ the dementia specialist will choose more on the basis of practical considerations (availability, accessibility, cost, technical feasibility) than strict scientific evidence.

The aim of this paper is to highlight those instruments that the practising dementia specialist might use in the clinical setting. The paper is a consensus produced by the Neuroimaging Working Group of the European Alzheimer's Disease Consortium (EADC). The EADC is a consortium of 43 Alzheimer's centres in 13 European countries (principal investigator Pr. B Vellas, Toulouse, France, www.alzheimer-europe.org/EADC), and is funded by the European Union with the purpose of defining operational standards of excellence for the diagnosis and treatment of patients with cognitive impairment. The first draft of the consensus was produced on 12 November 2001, in Toulouse, France, during one of the biannual meetings of the EADC. The first draft of the manuscript was produced in July 2002 and circulated for comments to all EADC centres, as was the final version.

The instruments have been selected by capitalising on the experience of previous reviews made by some of the authors.^{15–20} The instruments will be described according to increasing levels of technological complexity and feasibility so that physicians can choose those more consistent with the technological facilities of their clinical setting. Levels range

from unaided ratings (subjective visual) of films or hard copies obtained with routine acquisition protocols on a single occasion to sophisticated computer based measurements based on digital images obtained with non-routine specific acquisition protocols on two or more separate occasions (tables 1 and 2). The variables of interest will be the three main aspects in the assessment of cognitive disturbances, i.e. regional atrophy, subcortical cerebrovascular disease, and regional functional (perfusion/metabolism) defects. CT and MR will be addressed separately because generally different tools apply to the two techniques, while SPET and PET will be addressed together as the same tools can be used and the two techniques give grossly similar clinical information.

CT LEVEL 1: FILM WITH ROUTINE ACQUISITION (ORBITOMEATAL LINE, SLICE THICKNESS 8–10 MM) Subcortical cerebrovascular disease: visual rating scales

A number of rating scales to grade subcortical cerebrovascular disease (sCVD) on CT or MR films have been developed.¹⁸ The European Task Force on Age Related White Matter Changes reviewed instruments developed as of 1998, and concluded that the ideal rating scale did not yet exist.¹⁸ Based on this conclusion, they developed an instrument to rate sCVD, which was applicable to routine axial CT scans (the Age Related White Matter Changes (ARWMC) scale).²¹ This is a four-point scale that rates white matter changes separately in five areas: frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, and insula). The first three areas are scored as 0 = no lesions (including symmetrical, well defined caps or bands), 1 = focal lesions, 2 = beginning confluence of lesions, 3 = diffuse

Table 2 Levels of increasing technological intensity of tools to rate functional imaging findings in patients with cognitive impairment

Level	Medium	Technical requirements	Focal hypoperfusion/metabolism	
			Measurement	Experience
SPET/PET 1	Hardcopy	—	Visual assessment	1–2 weeks
SPET/PET 2	Digital	—	ROI sampling	1–3 days
SPET/PET 3	Digital	Software for computerised post-processing	Voxel by voxel analysis in the stereotactic space ⁶¹	—

ROI, region of interest.

Experience denotes the training time needed to obtain accurate measurements.

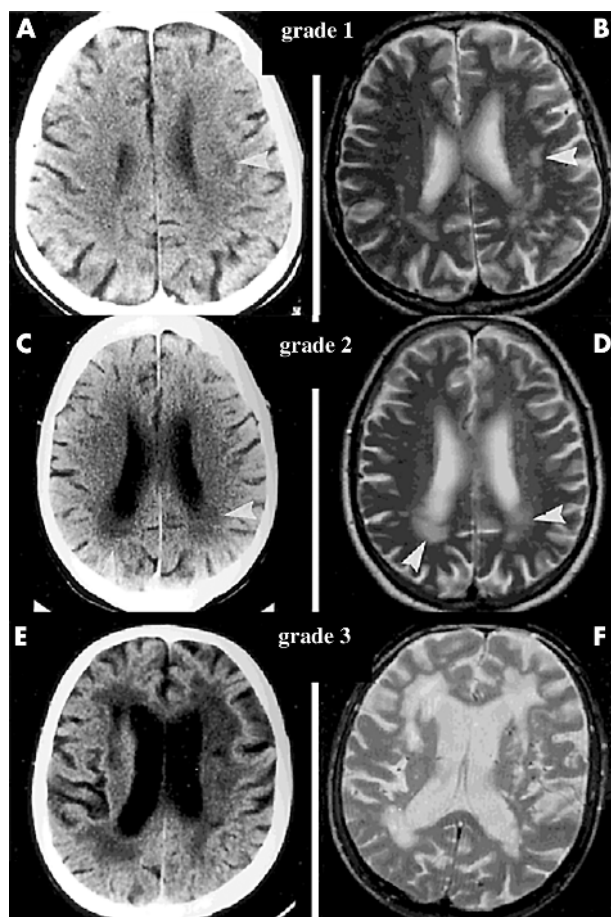


Figure 1 CT level 1 (left side images) and MR level 1 (right side images) for cerebrovascular disease: a visual rating scale based on CT and MR films (the Age Related White Matter Changes scale²¹). Grade 1, focal lesions; grade 2, early beginning confluent lesions; grade 3, confluent lesions with diffuse involvement of a lobe, with or without involvement of U fibres. Image pairs (CT/MR) are matching slices of the same patient. Reprinted with permission from American Heart Association.

involvement of the entire region, with or without involvement of U fibres. The infratentorial/cerebellum and basal ganglia are scored as 0 = no lesions, 1 = only one focal lesion (>5 mm), 2 = more than one focal lesion, 3 = confluent lesions. The final result of the rating is 10 separate scores (five for the right and five for the left hemisphere) ranging between 0 and 3, rating the different brain regions (fig 1).

The inter-rater reliability was found to be moderate ($k = 0.48$). The ARWMC scale was applied on both CT and MR films. A good correlation between the two imaging modalities was found; in more than 50% of patients CT and MR scored equal in all areas. However, in 31% of patients MR scored parieto-occipital lesions better than CT, and scored infratentorial lesions better in 23% of patients. The clinical features of the 77 patients with white matter changes used to validate the ARWMC scale were not described, and data on known group validity were not reported.

The novelty of the ARWMC scale is that images due to different pathology such as lacunes (featuring axonal loss) and white matter lesions (featuring demyelination with little or no axonal loss) are rated separately. The main limitation is represented by the unavailability of a global measurement of severity, as the sum score of the 10 ratings has not yet been validated. There are no data on the added diagnostic value of this scale.

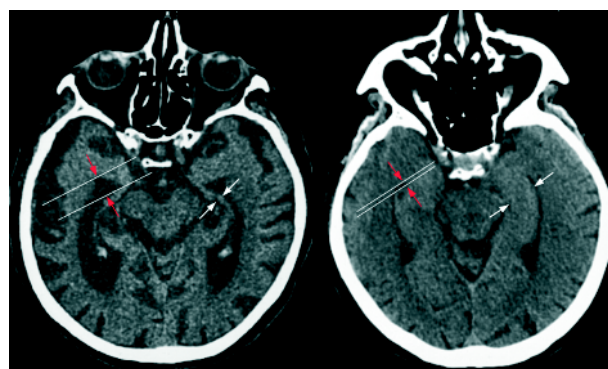


Figure 2 CT level 2 for regional atrophy: linear measurements of medial temporal lobe atrophy based on CT films. Minimum thickness of the medial temporal lobe²²: the measurement is taken in the parahippocampal gyrus region where the portion between the anterior and posterior aspects of the brainstem is thinnest (white arrows). Radial width of the temporal horn²⁷: the measurement is the distance between two parallel lines drawn tangential to the tip of the temporal horns where its width is maximum (red arrows). Right side, non-demented elderly person; left side: Alzheimer's disease.

CT LEVEL 2: FILM WITH 2–3 MM THICK SLICES ON THE TEMPORAL LOBE PLANE

Regional atrophy: linear measures

Atrophy in the medial temporal lobe (MTL) is usually not obvious on CT films because the scan angle routinely used does not give the best image of this region.²² However, with a different scan angle (slice orientation parallel to the plane of the temporal lobe, i.e. 15–20° caudal to the infraorbitomeatal line),²³ atrophy of the MTL can be detected with linear measures in AD patients.

The minimum thickness of the MTL is the most widely recognised linear CT measurement.²² The technical requirements for this measurement are the orientation of the CT scan parallel to the plan of the temporal lobe and thin slice thickness (2–3 mm). The measurement is taken with a calliper in the parahippocampal gyrus region, where the portion between the anterior and posterior aspects of the brainstem is thinnest (fig 2). In a group of 44 pathologically confirmed AD patients with mean (SD) Mini Mental State (MMS) scores of 9.3 (6.9), Jobst *et al* found that the minimum thickness of the MTL separated AD patients from non-demented controls with a sensitivity of 92% and specificity of 95%. Two recent studies of mild AD patients found lower sensitivity values: 48% in 33 patients with MMS of 22 (2.1) compared with 31 controls,²⁴ and 75% (specificity 90%) in 60 with MMS of 19.6 (4.5) v 17 patients with vascular dementia, 14 with depression and nine with paraphrenia.²⁵ Jobst *et al* showed that the progression of MTL atrophy thus measured was a sensitive marker of incident cognitive deterioration in subjects who were cognitively normal at baseline.²⁶

Recently, a CT based measurement of MTL atrophy has been developed based on enlargement of radial width of the temporal horn.²⁷ The measurement is sufficiently reliable, accurate, and feasible to be routinely employed.²⁷ CT scans are acquired according to the technique of Jobst *et al*, and the measurement can be taken also on MR scans. As the greatest proportion of hippocampal atrophy typical of AD takes place in the hippocampal head,²⁸ the radial width of the temporal horn measurement is devised so as to capture atrophy in this region. The measurement is taken at the tip of the temporal horn with a precision calliper (fig 2). Intraclass correlation coefficients for inter- and intra-rater reliability were between 0.94 and 0.98. Using a cutoff of 5.3 mm, the sensitivity and

specificity were 93 and 97% in separating 42 mild to moderate AD patients (MMS of 21 (2.3)) from 29 nondemented controls. In a small group of patients with mild cognitive impairment, the measurement has been shown to have sensitivity and specificity of 80 and 95%.²⁹ There are no data on the added diagnostic value of these measurements.

MR LEVEL 1: FILM WITH ROUTINE ACQUISITION (ROUTINE T2 AXIAL, ROUTINE T1 CORONAL THROUGH THE MEDIAL TEMPORAL LOBE)

Regional atrophy: visual rating scales and linear measurements

While CT imaging of the temporal lobe allows appreciation of the indirect signs of hippocampal atrophy (such as the enlargement of the temporal horns), MR can directly visualise the hippocampus and other critical MTL structure in substantial cytoarchitectonic detail. Scheltens *et al*³⁰ have developed a subjective visual rating scale to assess MTL atrophy on plain MR films (the subjective MTL atrophy score). T1 weighted sequences are used and six coronal slices (slice thickness of 5 mm) parallel to the brainstem axis are acquired from a midsagittal scout image, the first image being acquired directly adjacent to the brainstem. The score is assigned based on visual rating of the width of the choroid fissure, width of the temporal horn, and height of the hippocampal formation. The resulting scores are 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe MTL atrophy (fig 3A).

In 21 AD patients and 21 controls, the subjective MTL atrophy score yielded a sensitivity of 81% and specificity of 67%. The score correlated well with linear measurements of MTL atrophy.³¹ Moreover, in 41 patients with AD and 66 nondemented controls, the subjective MTL atrophy score showed

a correct classification of 96%, slightly higher than the correct classification given by volumetry (93%).³¹ In the same study, visual rating yielded a diagnostic gain over the mini-mental state examination (MMSE) score alone, while volumetry did not.³¹ Lastly, in a prospective study of 31 patients with minor cognitive impairment, the subjective MTL atrophy score and hippocampal volume improved the predictive accuracy of age and delayed recall score for AD at follow up.³² Although the overall predictive accuracy of hippocampal volume measurement was better than that of the score (100% *v* 83%), qualitative rating was suggested as a good alternative.³²

The sensitivity and specificity of linear measurements of the width of the temporal horn were investigated on coronal MR films where the measurements were taken according to a standard method (fig 3B).^{24, 30} In 46 AD patients and 31 controls, the width of the temporal horn had a sensitivity of 74% in mildly and 82% in moderately severe AD patients with specificity set at 95%.²⁴

Subcortical cerebrovascular disease: visual rating scales

When the ARWMC scale is applied on MR films, acquisition is made by routine axial T2 weighted or (preferably) fluid attenuated inversion recovery (FLAIR) sequences. Lesions are rated similarly to CT (fig 1). The inter-rater reliability on MR was good ($k = 0.67$). The scale was validated comparing the degree and distribution of white matter changes on CT and MR films in the different areas. MR was superior for detecting small white matter changes, whereas larger lesions were detected equally well with both CT and MR. MR detected significantly more white matter changes than did CT in the parieto-occipital and infratentorial areas.²¹

Although the ARWMC scale is a reliable tool to quantify sCVD on both CT and MR films, whether the CT or the MR version should be preferred for clinical applications still needs

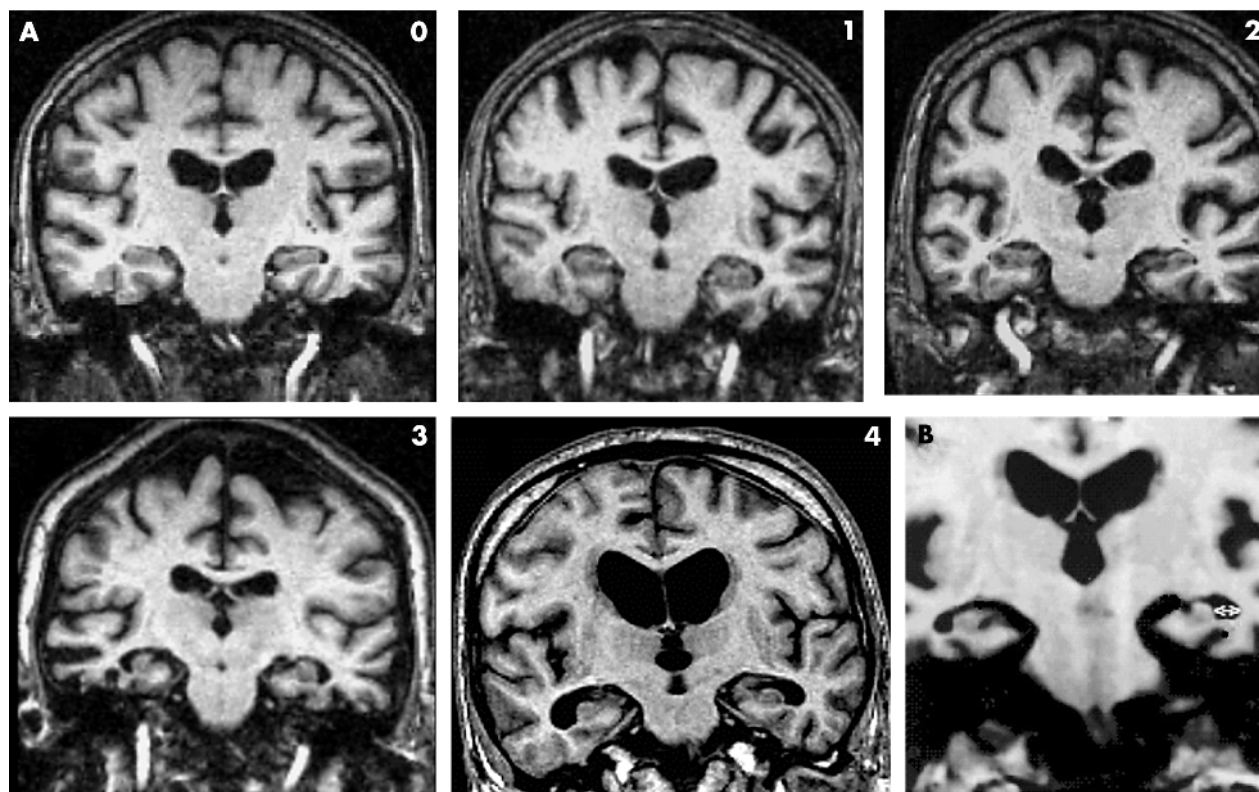


Figure 3 MR level 1 for regional atrophy: visual rating and linear measurements of the medial temporal lobe atrophy based on MR films. (A) subjective medial temporal lobe atrophy score: 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe.³⁰ (B) Width of the temporal horn.²⁴

to be determined. While MR is more sensitive than CT, the latter might be preferred in clinical practice for its greater specificity in order to reduce false positives.^{33–35} Studies are needed to compare the CT and MR based versions of the ARWMC scale. There are no data on the added diagnostic value of either the CT or MR based version of this scale.

MR LEVEL 2: DIGITAL WITH 3D ACQUISITION AND MANUAL OR SEMIAUTOMATIC POST-PROCESSING

Regional atrophy: volumetric measurements

The need for biological indicators of AD with high sensitivity and specificity is of great importance in pre-dementia forms of AD (MCI), where the clinical picture is less distinctive, the clinical diagnosis more difficult, and biological markers of the disease might yield significant incremental diagnostic value.³⁶ Although there are yet no studies assessing the accuracy of different techniques in the diagnosis of MCI due to AD, it is likely that MR levels 2 and 3 might be particularly useful.³⁷

Some protocols of hippocampal volume measurement have been validated.^{38,39} A T1 weighted 3D technique is employed for MR image (acquisition magnetisation prepared rapid acquisition gradient echo, MP-RAGE; or spoiled gradient recalled). After acquisition of the MR scans, the digital data must be available for post-processing. Images need to be reconstructed on coronal, 1–2 mm thick slices perpendicular to the orbitomeatal line or to the long axis of the hippocampus. The hippocampus is then manually traced on all the contiguous slices where it can be seen (fig 4A). Volumes are calculated in mm³ by computing the number of voxels within the traced images.

In expert hands, the reliability is high, intraclass correlation coefficients for hippocampal measurements being 0.95 for intra-rater and 0.90 for inter-rater variability.³⁹ Sensitivity and specificity values of hippocampal volumes in a relatively

large series of 55 mild AD patients and 42 controls were 94 and 90%, respectively.⁴⁰ Small hippocampal volume has been found to be predictive of subsequent conversion to AD in 80 patients with amnesic MCI independently of neuropsychological tests, apolipoprotein E genotype, and cerebrovascular comorbidity.⁵ Of the 13 MCI patients with hippocampal volume 2.5 SDs below the age specific mean, six (46%) converted to AD within the following 3 years; of the 54 with hippocampal volume between the mean and 2.5 SDs below, there were 19 converters (35%); and of the 13 with hippocampal volume above the mean, only two (15%) converted.⁵

The incremental value of hippocampal volumetry in the differential diagnosis between AD and other dementias has been addressed by Wahlund *et al* in a small patient group (n = 77) with a stereological technique, a simplified version of manual tracing,³¹ and compared with visual rating of the medial temporal lobe. The authors found that the correct classification rate of the MMSE alone (63%) was increased by both techniques (volumetry, 73%; visual rating, 71%).

Subcortical cerebrovascular disease: thresholding of white matter hyperintensities

Quantification of the volume of white matter hyperintensities (WMH) based on MR can provide an objective measurement of the severity of sCVD.

A number of semi-automated methods have been developed, most based on the notion that pixels of normal white matter can be accurately separated from those of hyperintense white matter. One of the first methods was developed at the National Institute of Health by DeCarli *et al*⁴¹ (QUANTA) but many others have followed.⁴² A conventional spin echo, double echo T2 or FLAIR sequence in the axial orientation is used for MR acquisition. Optimal results are obtained with scanners with field power of at least 1.0 Tesla.

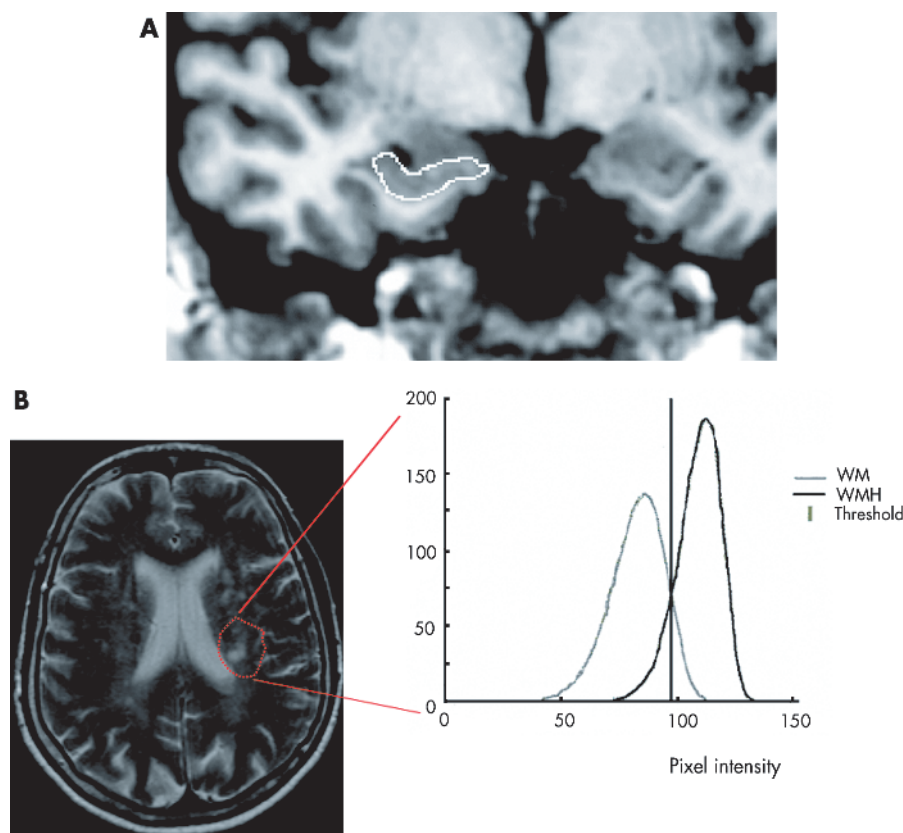


Figure 4 MR level 2 for (A) regional atrophy; volumetrics of the hippocampus based on digital MR.^{38,39} Example of manual tracing; (B) Cerebrovascular disease: thresholding of white matter hyperintensities (WMH) based on digital MR.⁴¹ example of distribution intensity of pixels on MR. Thresholding techniques automatically identify the value of pixel intensity that best separates normal white matter (WM) from WMH.

Digital information is generally transferred for processing and analysis to a separate workstation. Measuring involves manual tracing followed by automatic thresholding. Manual tracing is carried out on a crudely defined region of interest (ROI) within the white matter, which completely includes all the hyperintense white matter. Automatic segmentation comprises the following phases: histogram representation of the pixel intensity distribution, Gaussian modelling of the pixel distribution separately for normal and hyperintense white matter, and identification of the optimal intensity cutoff to separate normal from hyperintense white matter pixels on the basis of maximum likelihood functions (fig 4B). WMH volumes are computed in cm^3 by multiplying the number of pixels assigned to hyperintense white matter in all the pertinent slices by the pixel volume. More automated techniques have also been developed.⁴³

Intra- and inter-rater reliabilities of this method are good.⁴¹ WMH volume has been found to correlate with other features believed to be indicative of sCVD (parkinsonism and depression) and was predictive of cognitive impairment in a group of 369 cognitively intact community dwelling older men.⁴⁴ There are no data on the added diagnostic value of this tool.

MR LEVEL 3: DIGITAL WITH 3D ACQUISITION, COMPUTERISED POST-PROCESSING, AND SERIAL SCANS

Regional atrophy: whole brain assessment with the brain boundary shift integral

Serial scans within the same subject have the advantage that the wide inter-individual variability of brain morphology is not an issue, and comparing before and after images of the same subject(s) carries much less error than comparing a case with controls. Although the method is not available for clinical use, its potential clinical applications are such that the practising physician should be aware of its existence.

According to the brain boundary shift integral (BBSI) algorithm developed by Fox and Freeborough,⁴⁵ serial (at least two) T1 weighted volumetric MR scans need to be acquired with a 3D technique as described in MR level 2. Serial scans are positionally matched so that differences in the two scans can be visualised by subtracting one scan from the other (fig 5). An automated subtraction algorithm is then used to measure the difference in brain volume. Brain volume changes are measured by calculating the integral of the shift in the brain-cerebrospinal fluid boundary taken over

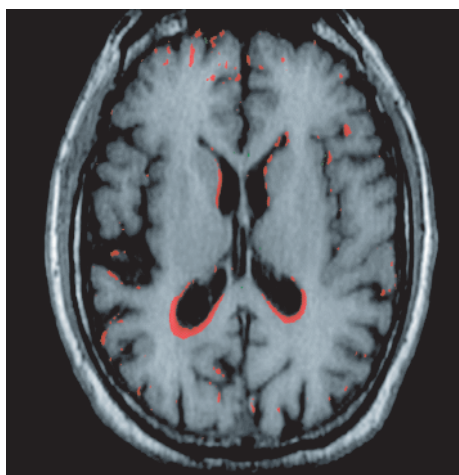


Figure 5 MR level 3 for regional atrophy: Fox and Freeborough's brain boundary shift integral (BBSI) based on digital MR⁴⁵ greater than normal loss of atrophy over 1 year in a patient with AD (voxels marked in red).

the brain surface. Volume loss is expressed as a percentage of initial brain volume and converted into a rate of atrophy in cm^3 per year.

The reproducibility of this technique is good: the mean coefficients of variation of brain volumes for inter- and intra-rater reproducibility were 0.55% (range 0.07–1.1%) and 0.54% (range 0.03–1.5%).⁴⁶ The rate of atrophy in a group of 18 AD patients was significantly greater than in 31 controls (2.78% v 0.24% per year with no overlap between the groups).⁴⁷ Moreover, the rate of global cerebral volume loss was strongly correlated with the rate of cognitive change measured with the MMSE in 29 AD patients.⁴⁸ Although there are no explicit data on the added diagnostic value of the technique, the method allowed detection of loss of brain tissue in asymptomatic individuals carrying an autosomal dominant mutation known to cause AD more than 2 years before the appearance of symptoms.^{49–50}

Although the use of the BBSI in MCI patients to predict conversion to AD is tempting, the need for prospective scans spaced at least 1 year apart and the high conversion rate in some clinical series (up to 25% per year) might lead to a significant proportion of converters by the time the test is positive. The technique might be more useful in truly asymptomatic persons at high risk for AD, who might have first year conversion rates close to zero, such as apoE 4/4 carriers or APP or presenilin mutation carriers. In four persons coming from families with early onset AD resulting from known autosomal dominant mutations (APP V717G, PS1 M139V, and PS1 intron 4), the technique was shown to be sensitive to the volumetric reduction of the brain parenchyma more than 1 year before the onset of the mildest symptoms and about 4 years before the patient fulfilled criteria for AD.⁵⁰

SPET/PET LEVEL 1: HARDCOPY

Visual assessment

Measurements of regional blood flow with SPET and of regional glucose metabolism with PET can detect cerebral functional impairment at the cellular level and complement information on structural changes obtained by structural imaging methods in the evaluation of dementia.^{51–54} In conditions where a normal coupling of metabolism and perfusion can be expected, SPET can provide data reasonably comparable to those of PET with significant cost savings.⁵²

For ¹⁸F-DG-PET, the subject should be studied in the fasted state, and a minimum of 30 min to allow brain accumulation of the radiotracer is recommended. Other requirements (injected dose, scanning time, reconstruction, position) depend on the machine and the acquisition mode. Conditions of examination should be kept constant to allow comparison between local normative and patient data.

The currently used analysis method in most nuclear medicine departments is that of subjective visual assessment of SPET/PET colour coded hardcopies, showing in AD a typical pattern of temporoparietal hypoperfusion/hypometabolism (fig 6), although frontal defects are also very common even in the early stage.⁵³

A clinical pathological study⁵⁴ evaluated the sensitivity and specificity of the visual assessment of SPET in 70 patients with dementia and 70 controls. Sagittal, coronal, and axial SPET orientations were evaluated by experienced personnel and rated as normal or abnormal (hypoperfused) in the lobar region, cerebellum, and subcortical structures in each hemisphere. Criteria for the presence of AD were previously agreed upon to include either bilateral or asymmetric temporal or parietal lobe hypoperfusion, or both. SPET significantly improved the diagnostic accuracy of AD; a positive SPET scan raised the likelihood of pathological AD from 84%, as defined by clinical diagnosis, to 92%. Few studies included

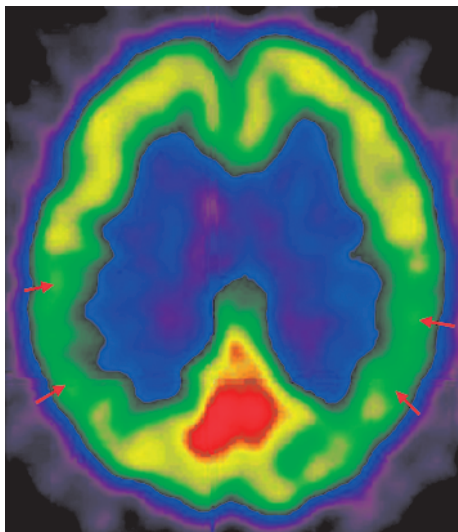


Figure 6 SPET/PET level 1: visual assessment based on SPET/PET hardcopy: ^{18}F FDG-PET hardcopy, showing in AD a typical pattern of bilateral parietal hypometabolism (arrows).

both MRI/CT and SPECT and compared diagnostic utility or added value.^{55–56} The study by Scheltens *et al*⁵⁷ in a population based sample concluded that SPECT did not have an added value over MRI.

The sensitivity and specificity of the visual assessment of PET has recently been evaluated in 284 patients with dementia, 146 of whom had a 2 year follow up and 138 had pathological confirmation.⁵⁸ PET films were classified by criteria established beforehand as positive or negative for presence of AD. The inter-rater reliability was good: assigned PET classifications were concordant in 94% of cases. PET identified patients with neuropathologically based AD with a sensitivity of 94% and a specificity of 73%. The initial pattern of cerebral metabolism was significantly associated with the subsequent progression of cognitive impairment. The results were similar for questionable and mild dementia. For this group, sensitivity and specificity values were 95% and 71% respectively, with overall accuracy of 89%, that is, as high as for the whole group.

As these figures of diagnostic accuracy are not significantly higher than those achieved with clinical assessment plus structural imaging, current guidelines recommend SPET/PET and visual assessment in selected cases where diagnostic uncertainty is relevant and the examination can provide significant incremental information.^{13–14}

SPET/PET LEVEL 2: DIGITAL WITH REGION OF INTEREST SAMPLING

The semiautomatic assessment of brain perfusion and metabolism deficits is a quantitative approach. With PET, models are available to obtain absolute values of cerebral blood flow (CBF) or metabolic rates of oxygen or glucose consumption, to be compared to normative data. Alternatively, the analysis of SPET and PET data may be based on ratios of activity between brain ROIs where uptake in the cerebellum or occipital cortex is held as reference (fig 7). This approach has the advantage of increasing the consistency of image interpretation more independently of reader experience than visual assessment. Most scanners have built in software that allows drawing of ROIs. Exporting digital images from the SPET/PET scanner to a peripheral workstation is an easy alternative.

O'Brien *et al*⁵⁹ found that regional cerebral blood flow assessed with SPET in anterior and posterior frontal, parietal,

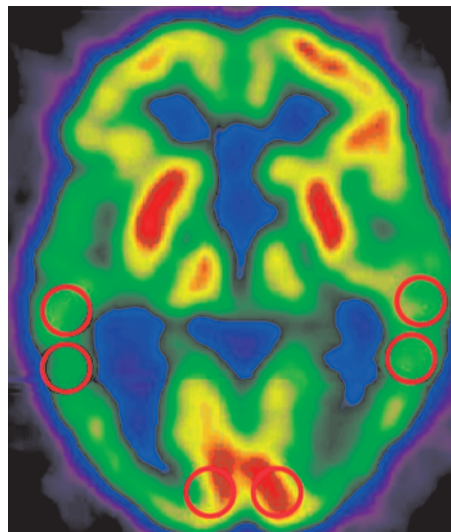


Figure 7 SPET/PET level 2: ROI sampling on digital ^{18}F FDG-PET. ROI are located in the temporoparietal (two ROIs for each side) and occipital (one ROI for each side) regions. Metabolism in the parietal regions is computed as the ratio of tracer uptake in the parietal and occipital ROIs.

occipital, and mesial temporal cortex using an ROI analysis with the cerebellum as a reference area was able to separate 30 AD patients from 22 controls with 77% sensitivity and 82% specificity. In 30 MCI patients, Okamura *et al*⁷ found that the ratio of a cerebrospinal fluid biomarker of AD (tau protein) to posterior cingulate perfusion could identify those patients who progressed to AD with sensitivity of 88.5% and specificity of 90%.

The issue of inter-individual variability is not fully resolved by this technique because the selection of ROIs depends on the observer's a priori choice and hypothesis, implying a preconception about the topography of the deficit. Moreover, the technique is time consuming if coverage of the entire brain volume by a large number of ROIs is required.^{60–61}

On the other hand, localisation of precise brain structures can be obtained on MRI and superimposed on co-registered PET image. Studies that combined functional and anatomical imaging have suggested that inter-group comparisons of regional metabolic values are diagnostically superior to volume measurements in AD.⁶² An MRI driven ROI analysis was used in a longitudinal study of initially normal elderly controls where glucose metabolism in the entorhinal cortex was shown to predict cognitive decline to MCI or even to AD.⁶³

SPET/PET LEVEL 3: VOXEL BY VOXEL ANALYSIS IN A STEREOTACTIC SPACE

The recent development of computer assisted analysis provides objective and reliable assessment of functional brain abnormalities. This approach is a voxel by voxel analysis in a stereotactic space to avoid subjectivity and to adopt the principle of data driven analysis⁶¹ (fig 8).

Although voxel by voxel analysis in stereotactic space was not originally devised to analyse individual cases, Signorini *et al*⁶⁰ have validated a protocol based on statistical parametric mapping (SPM) that allows estimation of functional defects in individual cases. The method gives a false positive rate of about 5% (specificity of 95%) but the false negative rate (sensitivity) has not yet been satisfactorily addressed. It should be noted that the method requires a group of normative images taken with the same scanner in cognitively normal elderly controls.

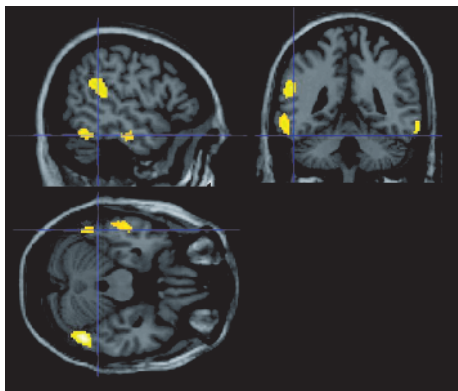


Figure 8 SPET/PET level 3: voxel based analysis of PET data showing metabolic decrease in a single AD patient compared with 21 elderly controls. Significant metabolic impairment ($p < 0.01$) in superior and inferior temporal cortex is superimposed on a canonical MR picture.

Herholz *et al*⁶⁴ showed in a study of 395 patients with AD and 110 controls that automated PET analysis with SPM reached 93% sensitivity and specificity in the distinction of mild to moderate AD from controls, and 84% sensitivity and 93% specificity in the detection of very mild AD ($MMSE > 24$). With another voxel based method of analysis, a metabolic pattern similar to that observed in AD was reported in cognitively normal carriers of the apolipoprotein E $\epsilon 4$ allele with a familial history of AD, and a significant decline in glucose metabolism was observed over an interval of approximately 2 years.⁶⁵ The authors have emphasised the availability of PET to test the efficacy of treatments for attenuating this metabolic decline.

The usefulness of these methods in the clinical routine is promising but there are yet no data on their added diagnostic value.⁶⁵⁻⁶⁷

DISCUSSION

The sophisticated clinical questions that modern physicians need to answer require equally sophisticated tools and methods. Patients with cognitive impairment have additional complexity in that the clinical picture may not be sufficiently characteristic, brain changes are subtle, and diagnosis and management would benefit from precise neuroimaging information. As outlined above, the dementia specialist has a wide range of options to extract quantitative information from neuroimaging examinations, which may assist in the positive diagnosis of dementia. Options range from tools with high feasibility that can be used at the patient's bedside to highly technological tools that require trained personnel and specific hardware and software. The quality of the obtained information is obviously different, although there are yet no indications as to which tool is more useful or has the highest cost/benefit ratio in clinical practice. The dementia specialist will thus need to match clinical requirements with technological demands and local opportunities.

A number of questions remain open that will deserve attention in the near future.

The differential diagnosis of the dementias: detecting patterns of atrophy or brain functional impairment with computational imaging

Imaging research of the last 10 years has led us to believe that the dementias have relatively specific imaging patterns.⁶⁸ Although a detailed review is beyond the scope of this work and can be found elsewhere,^{15, 69} a few key facts should be highlighted. Pick's disease often shows asymmetric anterior frontal and/or temporal atrophy of the cortex and white

matter, with enlargement of the ventricular horns so severe that quantitative measures are superfluous. The frontal variant of frontotemporal degeneration shows more prominent frontal and temporal atrophy than AD but milder hippocampal atrophy.⁶⁸ Dementia with Lewy bodies shows hippocampal atrophy milder than AD, no occipital lobe atrophy, and occipital SPET hypoperfusion or PET hypometabolism.^{68, 70, 71} The pattern of atrophy of Parkinson's disease with dementia is similar to AD.^{39, 68} Vascular dementia features hippocampal atrophy less severe than AD in addition to cortical and/or subcortical signs of vascular damage.^{39, 68} Although atrophy pattern detection might be useful diagnostic information, to date there is no single tool that allows detection of the patterns in a given patient, and the physician will need to compound two or more of the quantitative tools described in this paper. Newly developed computerised tools based on high resolution MR images such as voxel based morphometry⁷² and cortical pattern matching⁷³ allow unbiased assessment of atrophy and, with appropriate changes to make them suitable to single case analyses,⁷⁴ might be the future answer.

The clinical topographic correlates of subcortical cerebrovascular disease

The high prevalence of subcortical cerebrovascular disease in patients with AD⁷⁵ and its contribution to cognitive impairment⁷⁶ account for the development of many CT and MR based rating tools.¹⁸ However, these have failed to enter the clinical routine for at least two reasons. First, it is not clear to what extent some images (diffuse leukoaraiosis and patchy lesions on CT, and punctate and confluent hyperintensities on MR) denote vascular pathology. Although clinicopathological correlations are available,⁷⁷ more work is clearly needed. Secondly, the clinical correlates of subcortical cerebrovascular disease are unclear. WMH have been associated with cognitive impairment,⁷⁸ parkinsonism,⁷⁹ late life depression,⁸⁰ and psychosis,⁸¹ but it is unclear why some patients develop one rather than another syndrome. Recently, Benson *et al*⁸² have used an automated segmentation method to separate pathological from normal white matter in 16 elderly subjects with and 12 without mobility impairment. With voxel based morphometry applied to WMH, they showed that frontal periventricular WMH were sensitive (93%) and parieto-occipital WMH were specific (100%) in detecting mobility impairment in this group of subjects.⁸² This or other computerised neuroanatomy techniques may help in better understanding the clinical correlates of WMH.

The prediction of conversion of mild cognitive impairment to Alzheimer's disease

Three parameters are the acknowledged predictors of the conversion of MCI to AD, and two are based on imaging: low hippocampal volume,⁵ hypoperfusion of the temporoparietal cortex,⁸³ and elevated tau protein in the CSF,⁸⁴ with decreased a-beta.⁸⁴ However, none of the predictors taken alone seems to yield sufficiently satisfactory accuracy. For example, only 46% of MCI patients with severe hippocampal atrophy (2.5 SDs or more below the age specific mean) and 35% of those with minimal to moderate atrophy (from 0 to 2.5 SDs below) have converted to AD 3 years after baseline assessment.⁵ Compounding imaging and biological information to enhance the accuracy of the prediction seems a more promising strategy. Okamura *et al*⁷ have studied 30 MCI patients, 22 of whom had and eight did not have progression of the cognitive impairment in the following 3 years, and found that a high ratio between tau in the CSF and posterior cingulate perfusion on SPET could identify progressors with sensitivity of 89% and specificity of 90%. Alternatively, compounding structural information on atrophy in more

than one structure might enhance the predictive power (for a comprehensive review see Chetelat and Baron⁸⁵). Future studies will need to identify the most accurate and feasible combination of predictors of conversion.

Probes for β -amyloid with PET/SPET

The most promising area of research in functional imaging is the use of blood-brain barrier permeable radio probes specific for plaques, enabling SPECT or PET visualisation of these lesions in living AD patients. A variety of agents targeting α -beta deposits have been developed,^{86–87} and studies in living patients have already begun.^{88–89} The difficulty in developing these tools lies in the need for the agents to cross the blood-brain barrier while recognizing α -beta with high sensitivity and specificity.⁹⁰

Assessing the clinical usefulness of diagnostic imaging

In most medical fields, the evidence to support the use of diagnostic tests is scarce, and cognitive neuroscience is no exception. Of the tools presented here, evidence of added diagnostic value (that is the diagnostic accuracy compared to current clinical accuracy for the diagnosis) was available for only two (visual rating of the medial temporal lobe on MR and visual rating of color coded hardcopies on SPET images). Ideally, any diagnostic test should pass four phases before entering clinical practice, aimed at answering the following questions:

- Do test results in patients with the target disorder differ from those in normal people? (phase I)
- Are patients with certain test results more likely to have the target disorder than patients with other test results? (phase II)
- Does the test result distinguish patients with and without the target disorder among patients in whom it is clinically reasonable to suspect that the disease is present? (phase III)
- Do patients who undergo this diagnostic test fare better (in their ultimate health outcomes) than similar patients who are not tested? (phase IV).

Diagnostic tests are usually supported by phase I, seldom by phase II and almost never by phase III and IV studies.⁹¹ As a consequence, tests are used based more on likelihood, extension, and analogy rather than direct evidence.⁹² One of the boldest challenges of the future will be to fill the gap between the rapid increase of diagnostic tools driven by technological developments and the collection of evidence of their clinical usefulness.

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Authors' affiliations

G B Frisoni, S Galluzzi, Laboratory of Epidemiology & Neuroimaging, IRCCS San Giovanni di Dio-FBF, Brescia, Italy
P h Scheltens, Alzheimer Center, Department of Cognitive Neurology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands
F M Nobili, Division of Clinical Neurophysiology, Department of Internal Medicine, University of Genoa, Italy
N C Fox, Dementia Research Group, Department of Clinical Neurology, Institute of Neurology, University College London, London, UK

P H Robert, Centre Memoire, Unite d'Evaluation des Cognitions, Hopital Pasteur, Centre Hospitalier Universitaire de Nice, France
H Soinen, Department of Neurology, Kuopio University Hospital, Kuopio, Finland
L-O Wahlund, Department of Clinical Neuroscience, NEUROTEC, Karolinska Institutet at Huddinge University Hospital, Huddinge, Sweden
G Waldemar, Department of Neurology, Copenhagen University Hospital, Copenhagen, Denmark
E Salmon, Department of Neurology and Cyclotron Research Centre, University of Liege, Liege, Belgium

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NEURONLINE.....

Clinical neurophysiology on the internet: www.neurophys.com

Straightforwardly, this website, www.neurophys.com pitches itself as "clinical neurophysiology on the internet". It does indeed cover the spectrum of neurophysiology from basic science to neurophysiology on through to clinical practice; however, there is clearly more of an emphasis on the physiology of the nervous system than on what we now accept as the realm of

clinical neurophysiology and its quantitative analysis of the nervous system. There is some useful coverage of fundamental neurophysiological principles and neuroanatomy and its functional components with concise text and clear diagrammatic representations. This is helpful from an educational point of view and providing a refresher of those neural pathways that you know

you should know. There are many useful links to the relevant neurophysiological organisations, institutions, and journals. This site, however, appears to rely on the array of various links rather than on its own intrinsic content. There is an attempt at comprehensive coverage of EEG, EMG, and evoked potentials, but overall the depth of information available is limited. Use of the search engine for such topics as alpha coma and neuromyotonia was also disappointing.

The basic requirements of a good and useful site are its design and layout, allowing easy use and retaining the user's focus while also providing thorough coverage of the subject matter. On both counts I found this site somewhat lacking. The graphics are dated and some interactive content would be helpful. There are also an annoying number of broken links. The information available is limited, with whole areas, such as intraoperative monitoring and sleep, receiving scant attention.

Overall I found the site of limited interest. The positive aspects being in neurophysiological theory rather than its treatment of clinical matters of practical interest and concern to the clinical neurophysiologist or neurologist.



R MacDonagh
 Department of Clinical Neurophysiology, Leeds
 General Infirmary, Leeds LS17 8TP, UK;
 rmacdonagh@hotmail.com