Neuroimaging assessments used to visualise seizure focus in refractory epilepsy

A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery

P Whiting,[1] R Gupta,[2] J Burch,[3] RE Mujica Mota,[4] K Wright,[3] A Marson,[2] U Weishmann,[2] A Haycox,[4] J Kleijnen[3] and C Forbes[3*]

[1] MRC HSRC, Department of Social Medicine, Bristol, UK
[2] Walton Centre, Liverpool, UK
[3] Centre of Reviews and Dissemination, University of York, UK
[4] Department of Pharmacology, University of Liverpool, UK

* Corresponding author

Executive summary

Health Technology Assessment 2006; Vol. 10: No. 4

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Executive summary

Background

Epilepsy is the commonest serious neurological condition with a lifetime cumulative incidence of 2–3%. Although for the majority of people with epilepsy the outlook for seizure control is good, between 20 and 30% will continue to have seizures despite ongoing treatment with antiepileptic drugs (AEDs). Of these, the majority have a symptomatic or cryptogenic localisation-related epilepsy, which for some may be successfully treated with surgical resection of the focus (epilepsy surgery). The prime aim of epilepsy surgery is to remove the seizure focus and hence bring about seizure freedom without causing other disability.

Neuroimaging technologies can provide information about (1) structural abnormalities, hence information about the underlying aetiology of seizures, which in turn will suggest a potential focus, and (2) functional abnormalities (metabolism and/or blood flow) and hence the likely focus of seizures. If effective, these technologies could have a number of potential advantages. First, these tests are non-invasive and for certain patients the need for, and risk of, invasive seizure monitoring could be avoided. Second, they may influence the outcome of epilepsy surgery by influencing patient selection and the procedure undertaken. Third, where imaging results predict the outcome of surgery, patients could be better informed of the likely outcome of surgery.

Objectives

To review the following:

1. The effectiveness and/or accuracy of different methods of imaging the cerebral cortex to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
2. The ability of different neuroimaging techniques to predict patient outcomes following surgery.
3. The effectiveness of imaging in the following subgroups:
   (a) People for whom a structural abnormality has been previously identified by other neuroimaging techniques.
   (b) People for whom no structural abnormality has been previously identified by other neuroimaging techniques.
   (c) People for whom surface or invasive EEG recording has isolated a seizure focus.
   (d) People for whom surface or invasive EEG recording has failed to isolate a seizure focus.
4. The cost-effectiveness of imaging the cerebral cortex to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

Methods

A systematic review was undertaken according to published guidelines.

Data sources

Studies were identified through searches of electronic databases, Internet searches, handsearching, scanning reference lists of included papers and consultation with experts in the field.

Study selection

Two reviewers screened titles and abstracts for relevance. Full papers of potentially relevant studies were obtained and assessed for inclusion by one reviewer and checked by a second. Published and unpublished studies in any language were eligible for inclusion.

Data extraction

Data extraction and quality assessment were performed by one reviewer and checked by a second.

Data synthesis

For the diagnostic accuracy studies, results were analysed according to the imaging test evaluated. For each study the proportion of patients who were correctly localised, not localised, partially localised or incorrectly localised by the index test was calculated. Heterogeneity of these proportions was investigated using the χ^2 or Q statistic and through visual examination of forest plots of study results. Owing to the significant heterogeneity present between studies, statistical pooling was not performed. Instead, a narrative synthesis of results is presented. ▶

For studies that used multivariate analysis to look at the association of neuroimaging findings and outcome following surgery, all factors considered in the analyses, whether related to the findings of neuroimaging assessments or not, were presented, whether statistically significant or not. The studies were grouped according to the neuroimaging technique investigated and the findings of the studies were discussed with reference to possible sources of heterogeneity between studies.

Sensitivity analyses were performed to investigate the usefulness of carrying out extensive literature searches and including studies published in languages other than English.

Results

No randomised controlled trials (RCTs) were identified, with the majority of studies being diagnostic accuracy studies, evaluating the diagnostic accuracy of various imaging techniques in the localisation of epileptic seizure foci.

Studies were heterogeneous with regard to study design, population characteristics, index test and characteristics, outcome measurements and reference standards. In addition, in the majority of studies, the data had been collected retrospectively or it was not reported whether data collection was prospective. The studies were generally of poor quality, largely owing to the inappropriate populations included in the studies. Only 4% of studies included an appropriate patient spectrum, defined as an unselected group of patients with refractory epilepsy being considered for surgery, prospectively enrolled in the study. The reference standards used varied, and included ictal EEG, a combination of tests, site of eventual surgery, magnetic resonance imaging (MRI), interictal EEG and a combination of ictal and interictal EEG.

The included studies investigated the following imaging techniques: single photon emission computed tomography (SPECT) (39 studies, 68 evaluations); MRI (30 studies, 40 evaluations); position emission tomography (PET) (18 studies, 25 evaluations); subtraction ictal single photon emission computed tomography co-registered to magnetic resonance imaging (SISCOM) (seven studies, 11 evaluations); magnetic resonance spectrosopy (MRS) (six studies); computed tomography (CT) (five studies); near-infrared spectroscopy (NIRS) (one study); combinations of more than one test (three studies). We found no studies evaluating functional magnetic resonance imaging (fMRI) or diffusion tensor imaging.

There was significant heterogeneity ($p < 0.05$) between studies for all imaging techniques for at least one of the localisation categories (proportions of patients who had a seizure focus correctly localised, not localised, partially localised and incorrectly localised). Statistical pooling was therefore not undertaken. It was difficult to draw any overall conclusions regarding the accuracy of any imaging technique owing to the differences between studies. Possible explanations for the heterogeneity of localisation categories between studies of the various imaging techniques include differing study designs, population characteristics, index test characteristics and reference standards.

One of the review objectives was to look at the accuracy of neuroimaging techniques to identify the seizure focus in the following four subgroups: people for whom a structural abnormality has/has not been previously identified by other neuroimaging techniques, and people for whom surface or invasive EEG recording has/has not isolated a seizure focus. These subgroups were considered as possible sources of heterogeneity but did not appear to account for any of the differences between studies for any of the imaging techniques evaluated.

Test performance was more promising in studies restricted to patients with temporal lobe epilepsy.

Ictal SPECT generally had more correctly localising and fewer non-localising scans than other techniques evaluated, with 70–100% correctly localising scans and 0–7% incorrectly localising scans in patients with temporal lobe epilepsy. Results for CT and interictal SPECT suggest that these tests are relatively poor at localising the seizure focus. Results for volumetric MRI and PET appear promising, but have been assessed in fewer studies than ictal SPECT. SISCOM and MRS have been assessed in fewer studies, but the results are less promising than those for ictal SPECT. T2 relaxometry was reported in only one small study, with inconclusive results.

A total of 32 studies (83 evaluations) provided data on the association of a localised scan with outcome following surgery. For 15 studies, it was not possible to calculate a relative risk (RR) and these were not included in the analysis. None of the studies included had an appropriate patient spectrum. The majority (24/33) of evaluations suggested that patients with a correctly or partially localised scan had a better outcome following surgery than those with an incorrectly localised or non-localised scan. However, only ▶

three studies showed a significant association between having a localised scan and outcome following surgery, two evaluating routine MRI [RR 2.74, 95% confidence interval (CI) 1.32 to 5.67; RR 1.28, 95% CI: 1.00 to 1.63) and the other SISCOM (RR 2.12, 95% CI: 1.01 to 4.44). Both found that patients with a localised scan had a significantly better outcome following surgery than those with a non-localised or incorrectly localised scan.

Nine studies used multivariate analysis to investigate the association of various imaging techniques with the outcome following surgery. The imaging techniques evaluated included MRI (seven studies), MRS and volumetric MRI (one study), PET (three studies), SPECT (one study) and SISCOM (three studies). There was heterogeneity between studies of the ability of various imaging techniques to predict outcome. However, there was a trend for positive localisation of abnormalities to be associated with a beneficial outcome.

Conclusions

Owing to the limitations of the included studies, the results of this review do little to inform clinical practice. We are unable to provide evidence for effectiveness or cost-effectiveness of imaging techniques in the work-up for epilepsy surgery. Results of diagnostic accuracy studies are confounded by limitations in the reference standard used, and studies are subject to both clinical and statistical heterogeneity as outlined above.

Studies investigating the prognostic importance of imaging results for the outcome following epilepsy surgery suggest that abnormalities on imaging are associated with a better clinical outcome. However, the data do not allow an accurate prediction of patient outcome, possibly owing to small sample sizes, and therefore many studies may lack sufficient power to detect a significant association.

Given the inadequacy of existing data, there is a pressing need for studies investigating the utility of imaging techniques in the work-up for epilepsy surgery. The most reliable research methodology for evaluating the influence of imaging technologies on the outcome for patients being considered for surgery is the RCT. RCTs could examine the influence of single tests or combinations of tests on patient outcome. A study of a single test could evaluate the additional benefit that a particular test offers over other routinely offered tests. For example, in a study evaluating PET, all patients would receive routine tests such as MRI, EEG and Wada tests, with those in the experimental arm also receiving a PET scan. Similarly, studies could include a set of routine tests in both arms with an additional combination of tests being offered in the experimental arm. An alternative approach would be to compare different test combinations in different intervention arms. Health economic data could be collected in parallel, allowing a thorough examination of cost-effectiveness. We suggest that it is important that clinicians, patient groups, policy makers and healthcare/research funders meet and debate the most appropriate way to investigate these technologies.

Publication

Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. *Health Technol Assess* 2006;**10**(4).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 02/05/01. The contractual start date was in June 2003. The draft report began editorial review in July 2004 and was accepted for publication in May 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Peter Davidson, Dr Chris Hyde, Dr Ruairidh Milne, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2006

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.