



The Academy of  
Medical Sciences

# Restoring Neurological Function:

*Putting the neurosciences to work  
in neurorehabilitation*



A report from the  
Academy of Medical Sciences

March 2004

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*Registered Charity No.: 1070618*  
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*Registered in England*  
ISBN No: 1-903401-07-0

*Designed and produced by Quattro 020 7766 5225*



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## Acknowledgements

The Academy of Medical Sciences is most grateful to Professor Richard Frackowiak, Professor Raymond Tallis and the members of the Working Group for conducting this inquiry. It would also like to thank the Review Group, the Academy Fellowship and all the respondents to the consultation for their instructive comments and support. This important exercise could not have been carried out without the generous support of the Medical Research Council and UHA.

### Cover Photograph:

*Illustration of a network of nerve cells in the brain.*

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This report is published by the Academy of Medical Sciences and has been endorsed by its Officers and Council. Contributions by the Working Group and respondents to the call for evidence are made purely in an advisory capacity. The Review Group added a further 'peer-review' stage of quality control to the process of report production.

The members of the Working Group and Review Group and the respondents participated in this report in an individual capacity and not as representatives of, or on behalf of, their individual affiliated hospitals, universities, organisations or associations (where indicated in the addenda). Their participation should not be taken as an endorsement by these bodies.

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# Summary

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The disabling consequences of neurological disease present a great challenge. Many neurological diseases are age-related and populations in the developed world are ageing. While some progress has been made in preventing conditions such as stroke and in attenuating symptoms in progressive conditions such as Parkinson's disease (PD), it has been slow and so the major focus has been on neurorehabilitation.

Neurorehabilitation seeks to lessen the disabling impact of neurological disease when there is limited potential for reversing the underlying pathological process. There is evidence of its effectiveness in many conditions but the degree of disability carried by many patients remains high. Though a simplification, it is useful to divide neurorehabilitation into measures primarily aimed at assisting adaptation to impairment and those primarily aimed at reducing impairments. The latter address underlying neurological deficits more directly but are relatively poorly developed.

In the last two decades there has been remarkable progress in neuroscience, transforming our understanding of the extent to which functional recovery is possible following neural damage and how it may be promoted. There have been advances on several fronts, which are set out in the 'Evidence' to this Report. They include:

- new methodologies in clinical trial design, measurement of outcome, and research synthesis;
- appreciation of the role of activity and environmental input in driving neuroplasticity in healthy and injured brains;
- new investigations such as neuroimaging, electro- and magneto-encephalography (EEG/MEG), and transcranial magnetic stimulation (TMS), singly or in combination, to investigate brain pathophysiology and to monitor treatment;
- better understanding of brain-behaviour relationships through cognitive neuroscience and the role of factors such as attention, motivation, mood and goal setting in neurorehabilitation;
- new treatment modalities such as transcranial magnetic stimulation TMS, deep brain stimulation (DBS), neural transplantation, neuroprotective agents and gene therapy that are in different stages of development.

A new clinical science of **restorative neurology** therefore lies within our grasp. It depends on closer integration of the basic and clinical agendas. Currently, neuroscientists and clinician scientists are often unaware of each other's work. The Academy has identified this as a serious obstacle to translating advances in neuroscience into more effective neurorehabilitation treatments.

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## Recommendations

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The Academy's recommendations seek to translate advances in basic and clinical neuroscience into neurorehabilitation treatments that benefit patients.

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*Recommendation one: The NHS and academic community should collaborate to create a number of Regional Neurorehabilitation Research Centres (RNRCs) each closely associated with one or more universities.*

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- By co-locating service delivery and research the proposed RNRCs will become the intellectual foci for clinicians and scientists interested in neurorehabilitation, foster sustained collaboration, encourage dissemination of a research culture through the clinical community and facilitate patient recruitment for clinical trials. They may also act as nodes for wider web-based 'Virtual RNRCs'.
- Universities reviewing their research portfolios and departmental research plans should take note of opportunities arising from an integrated modern scientific approach to neurorehabilitation research.
- Close collaboration between RNRCs, district general hospitals (DGHs) and community services should be fostered and planned in the design of clinical trials in neurorehabilitation. The RNRCs should be at the centre of a 'Hub-and-Spokes' Model supporting the integration of clinical research activity. The Academy envisions that RNRCs will initiate major programmes of research, DGHs will initiate smaller projects and participate in the major programmes, and community-based and other services will contribute

by helping determine research priorities and enrolling patients.

- The proposed research structure closely reflects the recommendations of the Academy's '*Strengthening Clinical Research*' report<sup>(1)</sup>, which calls for disease specific translational research networks covering the seven major causes of mortality and morbidity in the UK. Given the potential benefit to patients offered by research into neurorehabilitation there is clearly potential for neurorehabilitation to be the focus of one of the proposed networks.
- Neurorehabilitation research planning should be strategic, with long as well as medium-term goals, as it will take time to realise some of the clinical possibilities opened up by advances in neuroscience.

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*Recommendation two: Recruitment, training and career structures should be improved as incentives for those undertaking or wishing to undertake research into neurorehabilitation.*

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- The training relationship between RNRCs, DGHs and community services should be formalised in a 'concordat' with explicit support from Strategic Health Authorities, Workforce Confederations, Medical Royal Colleges and universities.
- Current initiatives for cross-disciplinary undergraduate and postgraduate training for neurorehabilitation research should be strengthened. Attention should be paid to planning the manpower needs of neurorehabilitation research and service delivery at a national level.
- For non-clinical neuroscientists the issues of job security and academic promotion in a clinical environment must be addressed.
- For clinician scientists the Department of Health (DH) must consider the workforce requirements of the RNRCs. New clinical academic posts in neurorehabilitation will be needed and recruitment problems resulting from rigid training schemes noted in the Academy report: '*The Tenure Track Clinician Scientist: a new career pathway to promote recruitment into clinical academic medicine*'<sup>(2)</sup> must be addressed.

- For nurses and professions allied to medicine the Academy recommends a clear commitment to the support of high-quality research by appropriate contractual arrangements for trainees and established staff.
- For clinical neuropsychologists the Academy recommends that the DH should establish clinical academic research posts in neurorehabilitation. Fellowships should be established for non-clinical psychologists, educationalists and social scientists to work alongside laboratory and clinical researchers in neurorehabilitation.

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*Recommendation three: The Higher Education Funding Councils (HEFCs) and DH should provide funding, in the first instance, for one to three RNRCs whilst the research councils and medical research charities should provide a portfolio of enabling funds.*

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- The HEFCs and DH should provide funding to create a national network of internationally competitive, interdisciplinary, research-orientated RNRCs with infrastructure that includes laboratories in clinical environments.
- Potential centres should be invited to make bids for RNRC status. The initial aim should be to create one to three such centres
- The research councils and medical research charities should provide a research portfolio of 'enabling' funds. These should consist of competitive programme and project grants and targeted career development awards to create cadres of clinical, translational and biomedical researchers expert in the skills needed for neurorehabilitation research.
- Research funding bodies should examine their peer-review processes, so that they can accommodate applications of a high standard that include laboratory, translational and clinical components.

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*Recommendation four: A research culture should be fostered within the RNRCs to ensure knowledge is disseminated.*

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- A research culture should be fostered through



the RNRCs. Neurorehabilitation interventions of uncertain benefit or safety should be assessed formally. Untested interventions should be identified and prioritised, and funding for clinical research identified.

- Cross-disciplinarity needs to be fostered by joint meetings and other fora that cross boundaries between basic and clinical neuroscience.
- There should be greater investment in research synthesis.

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## References

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<sup>(1)</sup> Academy of Medical Sciences (2003)  
*Strengthening Clinical Research*  
Available from:  
<http://www.acmedsci.ac.uk>  
( Jan 2004).

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*The Tenure-track Clinician Scientist: a new career pathway to promote recruitment into clinical academic medicine*  
Available from:  
<http://www.acmedsci.ac.uk>  
(Jan 2004).



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# Preface

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The rehabilitation of patients with chronic neurological diseases is quite properly the central preoccupation of health and social services in developed countries. Enablement of people with chronic diseases goes beyond medical care narrowly construed. This is a position acknowledged in the World Health Organisation (WHO) Framework that looks beyond pathology and the bodily impairments that they bring and focuses on daily activity and the ability of individuals to participate in the worlds of work and leisure<sup>(1)</sup>. A fundamental insight of rehabilitation is that limitations imposed on an individual by a disabling disease are not simply proportional to the quantity of biological impairment but also reflect material and social circumstances that individuals contend with.

Even so, the degree of impairment resulting from neurological disease is a significant determinant of disability. This Report is prompted by the belief that recent advances in neuroscience should benefit individuals with neurological disability by reducing impairment; and also by the perception that such advances are not being exploited clinically as fast as they might. One reason for this may be a lack of efficient transfer of knowledge between basic and clinical science. This Report recommends how the barriers between basic neuroscience and clinical neurorehabilitation might be broken down.

The scope of neurorehabilitation is huge. This Report deals only with research opportunities, whilst acknowledging that they constitute but one of many equally relevant issues within the field. It does not address behavioural, psychosocial, environmental or health economic issues relevant to neurorehabilitation. Nor does it consider the implementation of new techniques in everyday practice or service design, delivery or organisation. It is acknowledged that if current best practice were universally available the outcome for patients would be greatly improved.

A neuroscience-based approach to the reversal of impairment will not replace a multi-disciplinary, multi-agency approach that combines science-based medicine with care and support more widely interpreted. Anyone involved in neurorehabilitation appreciates the complex mixture of cognitive,

behavioural, psychosocial and environmental elements that are often major limiting factors to recovery of function. They form the backdrop against which the impact of neurobiological intervention must be evaluated. There are also reasons, from basic science and clinical experience, for believing that new biologically-based techniques will benefit patients only as part of an holistic rehabilitation package.

In short, the specific focus of this Report is an appraisal of recent neuroscientific advances and the opportunities they present for improving outcome in patients disabled by chronic neurological disease. The Report should be read in conjunction with the recent Academy of Medical Sciences Report '*Strengthening Clinical Research*'<sup>(2)</sup>. It exemplifies, in one field, the more general concerns and recommendations of '*Strengthening Clinical Research*' relevant to translating advances in basic and clinical science into improvements in patient care.

Finally, the focus in this document is mainly on adults. There are specific issues in paediatrics that will need to be addressed separately, elsewhere.

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- <sup>1</sup> Barnes, M. P. (2003) Principles of neurological rehabilitation. *Journal of Neurology, Neurosurgery and Psychiatry*, 74 (supp IV), iv3 - iv7.
- <sup>2</sup> Academy of Medical Sciences. 2003. *Strengthening Clinical Research*. London: The Academy of Medical Sciences.



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## Part one - *Background*

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### The burden of neurological disability

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- 1.1 Patients with neurological disability present one of the greatest challenges to health and social services in developed countries and will continue to do so in the foreseeable future. Most major chronic disabling neurological diseases, for example, Alzheimer's disease, stroke and PD have a pronounced association with age and our population is ageing.
- 1.2 In some cases there are opportunities for prevention of disability and much has already been achieved. For example, evidence suggests that the risk of disabling disease associated with hypertension can be restored to normal after five years of anti-hypertensive treatment. There is strong evidence from controlled trials that it is possible to have an impact on the incidence of stroke by treating hypertension, using anti-platelet agents, by appropriate use of carotid endarterectomy and most recently, from the Heart Protection Study, by lowering cholesterol<sup>(1)</sup>. There is also a large body of evidence on the effectiveness of interventions that prevent road traffic injuries and avoid secondary insults<sup>(2)</sup>.
- 1.3 However, the full effect of preventative measures, even if universally implemented, will take time to be reflected in a reduced incidence of disability. Whilst effective treatment not only reduces deaths it also moves severe disability to moderate disability. In some cases, where there is unchanged incidence and lower case fatality, as is seen in stroke<sup>(3)</sup>, there may be an increase in disabled survivors, though disabilities will be less severe. Moreover, as in the case of head injury, there are few sufficiently large trials of acute treatments. Dickinson *et al.* recently showed that of 203 trials in head injury none was large enough to detect reliably a 5% absolute reduction in death or disability<sup>(4)</sup>.
- 1.4 Whilst there are some treatments that work, such as nimodipine for spontaneous subarachnoid haemorrhage, this is not the case for many diseases. In many cases prevention of disability is not yet possible and even where there is effective treatment, as in PD, benefits are often lost as a disease progresses. In other neurological conditions, such as multiple sclerosis, the underlying cause is unknown, current treatments are unsatisfactory and preventive measures have limited efficacy. There is a significant population of children with severe neurological damage in whom there are no satisfactory remedies. Even in stroke, where the causal chain of events before and immediately after an insult is reasonably well understood, the benefits of acute treatment have been minor. Therefore, the focus of the management of chronic disabling neurological diseases has been on rehabilitation rather than on cure.
- 1.5 The scale of the challenge presented to neurorehabilitation services, as measured by the prevalence of disabled sufferers from chronic neurological disease, is daunting. At present, there are 700,000 sufferers from Alzheimer's disease, 135,000 people with long-term effects of brain injury, 110,000 people with cerebral palsy, 85,000 with multiple sclerosis and 300,000 disabled sufferers from stroke in the UK<sup>(5)</sup>.
- 1.6 **This report addresses opportunities for improving neurological rehabilitation arising out of advances in basic neuroscience. It does not address important issues related to the organisation of services, although it is self-evident that prospects for patients could be greatly improved by their better delivery and the universal application of the knowledge we have at present.**
- 1.7 Neurorehabilitation encompasses a series of complex and varied measures designed to mitigate the disabling effects of neurological disease when there are limited opportunities for modifying an underlying pathological process. Those components of rehabilitation that assist a patient to adapt to impairments (crossing 'the ecological gap' between the patients' abilities and the demands of the world) can be distinguished from those aimed at

reducing impairment. Strategies that focus predominantly on adaptation to impairment include the provision of aids, appliances and adaptations; retraining; education and counselling; the prevention of secondary complications; and advice about benefits and support for carers. A huge variety of 'hands-on' techniques used by physiotherapists, occupational therapists, speech therapists, clinical psychologists and others aim at reducing impairment. These include intensive gait retraining, anti-spastic positioning, progressive resistive exercises, sensory stimulation, perceptual cueing and a variety of forms of speech therapy.

- 1.8 There is evidence for the effectiveness of the overall neurorehabilitation package for most patients with most conditions. An important example is integrated stroke care, one element of which is early and appropriate rehabilitation. Mortality is reduced by about 20% and combined severe disability and mortality by up to 30%. At least a proportion of this is attributed to rehabilitation rather than acute medical care<sup>(6)</sup>. Even so, the burden of disability carried by many stroke patients remains high<sup>(6)</sup>.
- 1.9 Of even greater concern, is that it is not clear precisely which elements of a rehabilitation package are effective because many 'hands-on' techniques have not been properly evaluated<sup>(7)</sup>. Many such treatments are based on custom, practice and experience rather than neuroscience. From the information available, it appears that in many cases gains come mainly from helping patients to adapt to impairments rather than by their reduction<sup>(8)</sup>.
- 1.10 In general, rehabilitation programmes aim to reduce levels of disability, handicap and burden, and improve quality of life. To achieve these goals, treatments often aim to reduce, or substitute for, loss of physiological, psychological, or anatomical structure or function, collectively known as impairment. Understanding how rehabilitation treatments reduce impairment is thus crucial to advances in neurorehabilitation and is the area to which the clinical neurosciences can make a unique contribution. This approach contrasts with a focus, driven by a need to demonstrate effectiveness by outcome improvements at the level of disability, handicap, quality of life and burden, on whether, rather than how, rehabilitation works.
- 1.11 Recovery after neurological insults is complex, particularly when the effects of ongoing disease in deteriorating and progressive neurological conditions complicate it. In these circumstances rehabilitation aims to be helpful rather than intrusive, and to focus on adaptation to change and psychosocial issues. Study of the simpler model that follows single-incident neurological damage, when there is improving and/or chronic motor and/or cognitive disability and neural recovery is potentially mutable, provides a better opportunity to explore how rehabilitation treatments work. By contrast, in deteriorating neurological conditions, arrest of ongoing cellular damage is the treatment and research priority and a study of how rehabilitation techniques work, if at all, is difficult because ongoing disease processes confound interpretation.
- 1.12 The Academy is aware that there is considerable scope for tailoring services to the needs of individuals and improving the organisation of care delivery. However, it is also appropriate to examine the possibilities for improving the outlook for patients with neurological disease arising from attempts at reversal of impairment by modification of underlying pathological processes and biologically adaptive responses to them.
- 1.13 Although this is the focus of the Academy's Report, attempts to reverse impairments should not be seen in isolation. There is extensive scientific evidence and clinical experience suggesting that biologically based techniques will not deliver improved outcomes for patients except as part of an overall package of care that includes training, education, counselling and support. Experience, in the widest sense, drives reorganisation<sup>(9)</sup>.

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## Part two - *Advances in neuroscience*

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2.1 The last two decades have seen unprecedented advances in neuroscience that have transformed our understanding of the extent to which functional recovery is possible following neural damage, how this recovery takes place and how it may be promoted.

A summary of some of these advances is given below. Further details can be found in the 'Evidence' section of this report.

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### New research methodologies

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**A:** Evaluation of clinical effectiveness: from individual patient studies to mega-trials

2.2 Many varieties of clinical research designs are now available to assess promising new interventions for neurorehabilitation. They range in scale and complexity from small single centre observational studies to multicentre randomised controlled trials. Larger studies will provide reliable evidence to bring about rapid change in clinical practice.

**B:** Evaluation of clinical effectiveness: outcome measures

2.3 The development of outcome measures that are scientifically illuminating, capture changes that are relevant to the treatment evaluated and reflect what is of importance to patients in the real world presents a particular challenge to rehabilitation research. Neurorehabilitationists have made significant progress in this respect but there is much more work to be done.

**C:** Research synthesis

2.4 A pre-condition for efficient progress is to ascertain, by systematic reviews, what is already known from research that has been completed. Scientifically defensible reviews of existing clinical research have had a substantial impact on decision making in clinical practice and in helping to prioritise new studies. The application of a similar, systematic and scientific approach is needed to identify and analyse existing evidence, thus maximising the benefit of relevant prior research.

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### Understanding brain damage and recovery

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**D:** Developmental neuroscience

2.5 The understanding of neuroplasticity has increased rapidly over the past ten years and has revealed a remarkable capacity of the developing brain to be shaped by activity and environmental input. Relatively recent technical developments, e.g. functional neuroimaging, have provided important opportunities to examine similar plasticity in the adult brain. Such plasticity is likely to depend on a number of neurodevelopmental mechanisms that are amenable to more precise definition by appropriate animal studies. This research suggests a potential use of behavioural and pharmacological means to modify the mechanisms of plasticity to promote functional recovery.

**E:** Advances in cognitive neuroscience

2.6 There have been recent major advances in cognitive neuroscience - the study of brain-behaviour relationships. They are helping our understanding of normal human cognition and emotion, how they interact, and how they break down in brain damage, impaired brain development or disease. These advances are resulting in new treatments, though translation from laboratory to therapy is in its infancy.

**F:** Neuroimaging

2.7 Non-invasive monitoring of local brain function with Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), EEG and MEG singly or combined, opens up a range of possibilities for objectively monitoring the mechanisms of disability and those underlying its reversal, whether natural or therapeutic.

**G:** Transcranial magnetic stimulation (TMS)

2.8 TMS is a safe, non-invasive and painless way to excite or inhibit the human cortex in order to measure the effects of changes in its excitability, as in learning or recovery, or to study brief 'virtual

lesions'. In the last decade it has been used to increase our understanding of the role of plasticity and more recently as a potential new method for specific treatment. Recent evidence suggests it has great potential in combination with neuroimaging.

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## New treatment modalities

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### **H:** Deep Brain Stimulation (DBS)

2.9 DBS is now used to alleviate tremor, rigidity and dyskinesia associated with a variety of movement disorders. Different brain targets for DBS have been identified for different types of movement disorder. For example, in PD DBS can relieve patients of the need to take anti-parkinsonian drugs and return them to a normal quality of life for long periods of time. The technique, which can also be used to control chronic pain, and muscle spasm in dystonia, was developed as a result of experimental work in primate models of disease.

### **I:** Neuroprotection and plasticity

2.10 Many diseases depend on common mechanisms of pathogenesis such as aggregation of abnormal proteins, impaired cellular handling of toxic metabolites or active processes leading to cell death. Such processes can potentially be retarded by treatment with 'neuroprotective' molecules that block toxic mechanisms such as oxidative stress, excitotoxicity, inflammation and apoptosis. Alternatively, endogenous or novel 'trophic factors' that promote cell survival and growth are being evaluated. Major advances are being made in developing technologies for targeted, controlled delivery of these powerful agents into specific sites in the brain. Early clinical trials, for example using the trophic factor Glial Cell Line-Derived Neurotrophic Factor (GDNF) in PD, look promising. In diseases such as Huntington's, which are of primarily genetic origin, safe and specific gene therapies may be developed that halt disease progression by replacing missing genes and proteins or by blocking expression of mutant genes in critical tissues.

### **J:** Neural transplantation

2.11 Embryonic neurones can survive transplantation into the brain in experimental animals. This has

led to clinical trials of grafts in PD that alleviate symptoms in patients for up to 10 years. The sources of cells and conditions of transplantation are critical to a good response. Trials are underway that seek to extend cell repair technologies to Huntington's disease, multiple sclerosis, stroke and spinal cord injury, although it is still too early to determine whether any of these will eventually prove effective. Considerable advances are being made in finding alternative sources of cells, such as stem cells and xenografts. These advances may overcome dependence on fresh human foetal cells, which profoundly limits more widespread application of this technology in both research and the clinic.

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## Advances in current therapeutic approaches

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### **K:** Maximising participation through rehabilitation

2.12 The translation of gains at a molecular, cellular, or physiological level into meaningful benefits in performance or participation depend upon 'higher level' factors, for example, training, goal setting, developing morale or environmental adaptation. These are the subject of much current research. It appears that real world performance and hence meaningful benefit from rehabilitation are very sensitive to external contexts. Treatment of impairments must recognise these contexts if it is to lead to useful benefits.

### **L:** Physical therapies to restore movement

2.13 Improvement in motor function following physical therapy is associated with brain reorganisation after stroke, revealing a continuing potential for plasticity even in adulthood. Promising restorative therapies based on this finding and other evidence about the drivers to recovery are being developed and tested.

### **M:** Rehabilitation engineering

2.14 A wide range of assistive technologies have been developed for sensory motor neurorehabilitation of patients with major disability. Applications of these devices include assessment of disability and augmentation of therapy as well as substitution for lost function.

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## Conclusion

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2.15 The implication of all these developments is that there are exciting opportunities to build on current rehabilitation techniques that focus primarily on adaptation to impairments, by using techniques that extend our ability to reverse impairments. The problem is that research does not inform clinical practice.

2.16 The potential benefits to patients of the new neuroscience will not be realised unless there is closer integration between basic and clinical studies in integrated research programmes that are based on comprehensive knowledge-sharing

between scientists and clinical practitioners. There are already some good models of such integration in institutions and programmes supported by research councils and medical research charities, such as the Wellcome Trust and Stroke Association (see the 'Evidence' section). But, given the scale of the problem of neurological disability and the challenge of developing and assessing new treatments, these attempts at integration are on too small a scale. There is a need to increase the scale of relevant integrated research and to ensure that it is co-ordinated and more clearly related to an overall rehabilitation strategy.



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## Part three - *Recommendations*

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3.1 The Academy believes patients with neurological disabilities require better outcomes and better services. There is much scope for improving the way services are organised and delivered to ensure that best practice is universally available. In order to make major inroads into the burden of neurological disability we need to re-think radically the nature and scope of neurorehabilitation, raising the ambitions of practitioners and the expectations of patients. This Report and its recommendations address one aspect of neurorehabilitation, that of promoting the acquisition of new knowledge through scientific research and its application in clinical practice.

3.2 In the light of recent scientific advances we have to challenge the assumption that damage to the biology of the central nervous system underlying disability is irreversible. Compensatory and restorative strategies should be seen as equal components of an integrated approach to neurorehabilitation. Furthermore, conventional rehabilitation techniques such as exercise, training, education and counselling will themselves be necessary to maximise benefits from new techniques emerging in neuroscience.

3.3 The forthcoming National Service Framework (NSF) for Long Term Conditions, which focuses on neurological conditions, will highlight some of the deficits in research evidence that need to be addressed, see 'Other sources' of information below. Therefore, it is timely to look at gaps in the evidence and to explore new neuroscientific opportunities.

3.4 Helping patients to realise their full potential for recovery of function will require a collective research effort on a much greater scale than at present. Research will require greater co-ordination to bring together a wide variety of approaches, from molecular medicine to whole patient care. Collaboration across a wide range of disciplines is necessary to secure the greatest gains for patients from the examples given in the 'Evidence' section of this report.

3.5 The recent Academy of Medical Sciences report: '*Strengthening Clinical Research*'<sup>(1)</sup>, identified a substantial gulf between basic discoveries and their translation into innovations that directly benefit patients or prevent disease. These impediments include:

- a lack of appropriate facilities and infrastructure;
- a lack of appropriately trained clinical scientists and a career structure to support them;
- inadequate funding support for both experimental medicine and all types of clinical trials;
- a failure to utilise the opportunity provided by the NHS to generate high-quality clinical data for such studies;
- the increasingly complex, bureaucratic, legal and ethical frameworks in the UK and European Union.

Many of these issues were also raised in the Biosciences Innovation Growth Team report '*Bioscience 2015: Improving National Health. Increasing National Wealth*' report<sup>(2)</sup> and specifically apply to the field of neurorehabilitation.

3.6 The Academy's recommendations aim to minimise barriers to research of the kind required to capitalise on recent and anticipated advances in basic and clinical neuroscience. They are, in part, modelled on examples of good research practice both in the United Kingdom and abroad. They address a number of constituencies: on the one hand the researchers and clinicians, and on the other funders and science policy makers. These constituencies include the DH, the research councils, universities, industry, the medical research charities and patient advocacy groups.

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*Recommendation one: The NHS and academic community should collaborate to create a number of Regional Neurorehabilitation Research Centres (RNRCs) each closely associated with one or more universities.*

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3.7 Major new opportunities are arising from

modern integrated scientific approaches to neurorehabilitation. The 'Evidence' section in this report provides examples of such work, illustrating how a wide academic constituency works in partnership with a variety of clinical disciplines.

3.8 New treatments that might be derived from this research will need to undergo high-quality clinical trials before they are introduced into clinical practice in order to ensure patients derive maximum benefit. Often these clinical trials will have innovative methodologies and novel measures of outcome. To achieve this goal an exchange of knowledge across traditional disciplines, in both clinical and basic science, is required. The participation of patients, research charities, industry and patient/carer groups will be essential to this process.

3.9 Already the UK has some well recognised centres of excellence that conduct research into neurorehabilitation. These include: The Oxford Centre for Enablement and the MRC Cognition and Brain Sciences Unit in Cambridge, which includes the Oliver Zangwill Centre. Other similar models in Leeds, Newcastle and North West Thames all include a co-ordinated network of clinical services with a regional rehabilitation unit acting as a central focus for research and training for all professions involved in rehabilitation.

3.10 Such co-location of service delivery and research provides intellectual and academic foci for both clinicians and basic biomedical scientists. This in turn facilitates collaboration between the two groups. However, in the UK co-location of service delivery and research is not on the same scale as that of the US.

3.11 Therefore strategic collaborations should be established between the NHS and the neuroscience /neurorehabilitation academic community to create a network of Regional Neurorehabilitation Research Centres (RNRCs), each closely associated with one or more universities. In addition, the opportunities arising from the research discussed in the 'Evidence' section of this report should be considered by universities when reviewing their research portfolios and departmental research plans.

3.12 Close collaboration should be fostered between the proposed RNRCs, DGHs and community services when designing clinical trials. Such collaboration should help ensure that research results emanating from the RNRCs are conveyed to competent research orientated clinicians working with patient populations in the care of service orientated colleagues. The Academy believes this strategy will more efficiently exploit the resources controlled by busy clinicians, who treat large numbers of patients and who desire involvement in research but are presently unable to participate due to lack of time or supportive infrastructure.

3.13 One means to achieve collaboration and integration of research activity would be a 'Hub-and-Spokes' model. This would encompass: the RNRCs that would initiate major programmes of research; smaller centres, such as DGHs, that would both initiate smaller projects and participate in larger programmes established in the RNRCs; and other care providers who are unable, for a variety of reasons, to initiate research projects but who nevertheless want to contribute to research by enrolling patients and helping to shape research protocols. Such a model has been very effective in the National Translational Cancer Research Network (NTRAC) (see 'Other sources of information' below).

3.14 There would be many advantages to a network of RNRCs. The incorporation of research into the mission of neurorehabilitation units, just as oncology research is now a standard part of the mission of oncology research units, would ensure that a research culture was widely disseminated. In addition, the RNRCs would provide an opportunity for patients to enter registers as potential recruits for research. Whilst the ethical and administrative issues associated with such registers will need to be resolved in a manner that promotes rather than inhibits research<sup>(3)</sup> there is an opportunity to establish national initiatives to address the challenges of recruiting patients into clinical rehabilitation studies. Furthermore, there are also opportunities for new models of collaboration. Web-based 'Virtual RNRCs' may be a way to overcome difficulties arising from dispersion of patients when rare disorders or specific cohorts are needed for trials. Rapid

electronic communication between researchers with different expertise, and between units with specialised or unique equipment, should become easier with the implementation of the UK GRID programme and electronic records within the NHS. 'Virtual RNRC's' could also provide a basis for significant international collaboration.

3.15 The proposed research structure closely reflects the recommendations of the Academy's '*Strengthening Clinical Research*' report, which calls for disease specific translational research networks covering the seven major causes of mortality and morbidity in the UK. It is proposed that these networks would be under the overall umbrella of a National Network for Clinical Research that would oversee Phase III trials, experimental medicine and enabling technologies.

3.16 '*Strengthening Clinical Research*' establishes that, based on experience with NTRAC, a relatively modest investment in clinical research and experimental medicine yields disproportionately large returns. Given the potential benefit to patients offered by research into neurorehabilitation there is a clearly potential for neurorehabilitation to be the focus of one of the proposed networks.

3.17 The measures we recommend will take time to deliver effective new treatments for patients. Since neurological disability will become more prevalent in a growing and ageing population we consider it important that any research strategy be coherent and well planned rather than *ad hoc*, reactive or piecemeal. Planning should be for the medium to long-term, but leave opportunities for 'blue skies' research, while providing the infrastructure that will ensure efficient exploitation of new discoveries.

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*Recommendation two: Recruitment, training and career structures should be improved as incentives for those undertaking or wishing to undertake research into neurorehabilitation.*

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3.18 Increased numbers of active neurorehabilitation researchers are required to ensure the generation of research - and thus treatments - that benefit patients. However, those possessing the skills specific to neurorehabilitation research, for example, evaluating complex interventions in disability, are in short supply. As the research

enterprise in this area expands, these shortages will become more acute.

3.19 Whilst untapped resources can be utilised, for example through collaborations between clinicians and basic biomedical scientists in the proposed RNRCs, it is clear that improved training, incentives and career structures for those undertaking research into neurorehabilitation are required.

3.20 Current initiatives for cross-disciplinary undergraduate and post-graduate training for neurorehabilitation research should be strengthened and new full-time academic research posts will be needed. In addition, attention should be paid to the manpower needs of neurorehabilitation research and service delivery at a national level<sup>(9)</sup>.

3.21 For clinician scientists, the DH should consider workforce requirements resulting from an assessment of how many RNRCs will be necessary to satisfy the population's needs in both the medium and long-term. Initially the Academy recommends a gradual, culture-shaping approach with one to three centres established nationally following a directed call for applications - judged on their excellence by international peer-review. Establishment of new clinical academic research posts in neurorehabilitation at consultant-equivalent and specialist registrar-equivalent levels must be planned and monitored. However, the problems resulting from rigid clinical training schemes must also be addressed in parallel, if an expansion in the number of clinician scientists is to occur successfully<sup>(4)</sup>.

3.22 Specifically, the training relationship between the proposed RNRCs, DGHs and community services should be formalised in a 'concordat' with explicit support from the Strategic Health Authorities, Workforce Confederations, Royal Colleges and Universities.

3.23 For non-clinical neuroscientists the issues of job security and academic promotion in a clinical environment must be addressed. Outside clinical-scientific institutes, such as the Institute of Neurology and National Hospital for Neurology and Neurosurgery in London, career pathways for non-clinical neuroscientists engaged in sustained

collaboration with clinicians are often inadequate. There are always opportunities for informal collaboration, but specialised RNRCs with specific goal-orientated objectives may not be attractive to basic scientists unless special provision is made to provide job security and opportunities for academic promotion. There already are models for such arrangements within the Engineering and Physical Sciences Research Council (EPSRC) Advanced and Senior Research Fellowship schemes and further discussion is provided in the Academy's 'Non-Clinical Scientists on Short Term Contracts in Medical Research' report<sup>(6)</sup>.

3.24 Currently the Research Assessment Exercise (RAE) does not give adequate recognition to areas of clinical research such as neurorehabilitation, particularly where they address complex issues requiring innovative research designs<sup>(1)</sup>. Without such a mechanism it will be difficult to attract rehabilitation professionals into the academic posts that will carry out translational and clinical research. This should be tackled in the next RAE.

3.25 There is great potential for professions other than clinician scientists and non-clinical neuroscientists to contribute to research into neurorehabilitation. Nurses, physiotherapists, occupational therapists and speech and language therapists collectively constitute a very large part of the NHS workforce and have skills that are especially useful in this area. There should be a clear-cut commitment to the support of high-quality research by appropriate contractual arrangements for nurses and professionals allied to medicine. It should be possible to build a significant research component into the job descriptions of new clinical leaders in the NHS (consultant and specialist therapists and nurses) who have the appropriate research skills and experience. There are precedents already in a few such posts.

3.26 Institutions training allied health professionals should review the place of research education and 'hands-on' research experience during training. Opportunities for such experience will arise in the context of the integrated research-service structures (RNRCs) that we recommend. There should also be a research component to postgraduate specialist training for therapists as is customary in the training for medical consultants.

3.27 Full-time research should also be a realistic option in the career pathway of appropriately qualified practitioners. Such practitioners should not be penalised and their specific skills should be recognised and accredited by the relevant professional bodies.

3.28 Clinical neuropsychologists have strong research skills as well as clinical training and are well placed to strengthen links between basic cognitive neurosciences and clinical practice. The DH should establish clinical academic research posts in neurorehabilitation.

3.29 Rehabilitation is essentially about learning to live in a new world. The role of non-clinical psychologists, educationalists and social scientists should not be divorced from that of clinical and non-clinical scientists. Alongside laboratory and clinical scientists there are research opportunities in these professions that could be realised by means of fellowships, postdoctoral fellowships and senior fellowships.

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*Recommendation three: The Higher Education Funding Councils (HEFCs) and DH should provide funding, in the first instance, for one to three RNRCs whilst the research councils and medical research charities should provide a portfolio of enabling funds.*

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3.30 If the identified research potential is to be realised, specific funding will be required. There have been notable initiatives in funding neurorehabilitation research in the UK; for example, the Medical Research Council (MRC) Co-operative Group Grant (COGG) initiative, DH Research and Development (R&D) initiative, medical charities (e.g. the Stroke Association Therapy Research Unit), the European Union and industry. These have not, however, resulted in research programmes on a scale envisaged in this document.

3.31 Therefore, the HEFCs and DH should prioritise base or institutional funding to create the proposed internationally competitive, interdisciplinary, research-oriented RNRCs with an infrastructure that includes laboratories in clinical environments. Potential centres should then be invited to make bids for RNRC status.



- 3.32 Each RNRC will need a core support structure consisting of a Scientific Director, an Epidemiology and a Clinical Trials Unit, a Patient Care and Recruitment Unit, a number of basic science laboratories, including molecular, cellular and systems science with imaging, all associated with an academic hospital in a university environment. Initial support should depend upon existing facilities.
- 3.33 In the first instance there should be from one to three Regional Neurorehabilitation Research Centres possibly under the umbrella of the National Network for Clinical Research funded by the DH and managed through a Special Health Authority as envisaged in *'Strengthening Clinical Research'*.
- 3.34 Ongoing funding should be contingent upon outputs, evidence of ability to interact with the wider clinical community in the way envisaged in this Report and the impact on clinical rehabilitation.
- 3.35 In addition the research councils and medical research charities should provide a portfolio of enabling funds consisting of competitive programme and project grants and targeted career development awards intended to create cadres of clinical, translational and laboratory researchers, expert in the skills needed for research into neurorehabilitation.
- 3.36 Research funding bodies should examine their peer-review processes so they can accommodate applications of a high standard that encompass laboratory, translational and clinical components. Grant-giving bodies should pay attention to the appropriateness of the expertise recruited to peer-review grant applications in the neurorehabilitation field. Scientific judgements must be sought from authorities appropriate to the research area, clinical expertise or interdisciplinary component. There should also be significant input from patient focus groups to the review process.

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*Recommendation four: A research culture should be fostered within the RNRCs to ensure knowledge is disseminated.*

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- 3.37 The knowledge base relevant to neurorehabilitation is broad and drawn from disparate sources.

Researchers within a particular field may not be familiar with knowledge and insights already available in allied areas. Thus, information transfer between disciplines, especially between basic neuroscientists, clinical neuroscientists and practitioners, needs to be efficient and comprehensive.

- 3.38 A research culture should be fostered through the proposed RNRCs. It should be increasingly the case that neurorehabilitation interventions of uncertain benefit and safety should be evaluated by clinical research. Thus, untested interventions should be identified and prioritised for funding.
- 3.39 There should be sustained efforts to counteract the belief, still prevalent among some practitioners, that research is unnecessary, a luxury or even detrimental to patients. Awareness of current limitations of treatment, of the deficiencies in the evidence base for what is currently practised and of the ethical imperative to evaluate treatments whose efficacy and safety is uncertain needs to be reinforced.
- 3.40 As part of this research culture academics should be mindful of the debt they owe to the patients who consent to offer themselves to clinical research and remember to respect and recognise them as equal partners in the research endeavour.
- 3.41 Cross-disciplinarity should be fostered by joint meetings with the explicit aim of sharing knowledge across disciplinary boundaries as exemplified in the (British) Society for Research in Rehabilitation and the European Federation for Research in Rehabilitation. Other fora, such as collaborative websites and special issues of journals, should also be encouraged.
- 3.42 There should be more investment in research synthesis. Funding bodies should place greater emphasis on scientifically defensible reviews of the literature in grant applications for both biomedical and clinical research thereby helping to avoid bias and wasteful duplication of effort. Further downstream, the role of bodies such as the National Institute for Clinical Excellence in ensuring that evidence-based best practice is implemented nationally will be a crucial contribution to knowledge dissemination.

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# Evidence



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# Evidence

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## New research methodologies

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### A - Evaluation of clinical effectiveness: from individual patient studies to mega-trials

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- A.1 The treatment of neurological disability is a major challenge for translational research, and a crucial step will be the development of clinical trials of potential new rehabilitation techniques suggested by basic science. The long process of evaluation must begin with in-depth single case and small group studies, but it may eventually culminate in large-scale (or 'mega') parallel group randomised controlled trials of the kind that have already proved their worth in the evaluation of pharmacological approaches to the treatment of stroke and heart attack<sup>(1)</sup>.
- A.2 The MRC has recognised the complexity inherent in neurorehabilitation and issued a guide to researchers on how to set up a trial<sup>(2)</sup>. Broadly speaking, there are three stages: a testing phase involving the development of questionnaires and other trial materials, a small-scale randomised pilot study or feasibility phase, and the trial itself.
- A.3 The MRC identifies a number of steps that should be completed before any feasibility work takes place. First, and essentially, there should be a systematic review of the evidence, followed by the development and more precise definition of the therapy, in collaboration with professionals from different disciplines.
- A.4 The Stroke Unit Trialists' Collaboration offers a good model<sup>(3)</sup>. In its first cycle the researchers reviewed randomised trials in which patients had been allocated to an organised stroke unit or to receive standard care, generally on a medical ward. Although patients' outcome was measured crudely, by death from all causes, analysis clearly showed that care on a stroke unit was associated with a lower risk of death and disability than treatment on a medical ward.
- A.5 The collaboration then went on to explore the processes involved in this differential effect, and also took into account patients' survival free of disability. After that came a qualitative phase in which, working with individual stroke units, they attempted to understand and define the intervention more narrowly. They will now try to validate their findings by mining the clinical databases to find out which components of stroke unit care are most closely associated with improved patient outcome.
- A.6 When it comes to the pilot study, there is a choice of design: the 'discrete pilot' or the 'feasibility phase'. A discrete pilot study involves recruiting a small number of subjects, allocating them randomly to treatment or control groups, completing their follow-up, stopping recruitment, and finally analysing and reporting the data. Such a study is useful for proof of concept for refining or determining hypotheses or if the intervention needs to be modified - for instance by adjusting intensity or method of delivery - and it may make use of an intermediate or surrogate marker of clinical outcome. But it has a major disadvantage in that patients and professionals lose momentum after recruitment stops.
- A.7 A randomised feasibility study avoids this problem, and is preferable where the intervention has already been clearly defined in previous studies and the measures of outcome well established. It assesses acceptability to patients and professionals and estimates recruitment rates in various centres, to arrive at a total number of centres needed. If the feasibility targets match the resources available, and an independent monitoring committee judges that the full-scale study is still required, recruitment can continue into the main phase of the trial without interruption.
- A.8 The intermediate or surrogate marker used in a pilot study could be a physiological variable measured electrically - peripheral nerve conduction, or corticospinal pathway transmission, for instance. Or it could be a brain imaging technique, such as fMRI. These have to be reliable, repeatable, and clearly related to a

clinically important outcome such as disability. The appearance of new lesions of demyelination as detected by MRI is a promising candidate in multiple sclerosis, but as yet there are no reliable markers for the outcome of stroke. In collaboration with experimental neuroscientists, however, more intermediate markers are likely to be identified for a range of neurological conditions.

A.9 Techniques that have become available in the last decade have revolutionised the measurement of outcome in neurological patients. Whereas traditionally this has been assessed in terms of muscle weakness or other indicators of impairment, there are major initiatives to create tools which can gauge patients' function, activity and participation in most aspects of their daily lives<sup>(4)</sup> (see 'Evidence' section B: 'Evaluation of clinical effectiveness: outcome measures').

A.10 Statistical techniques have also improved. For instance, there are now analytical tools that assess the heterogeneity of treatment effect, as well as methods for measuring trial quality and avoiding sources of bias<sup>(5)</sup>.

A.11 The final stage of the evaluation of some approaches may need to be a mega-trial. Mega-trials influence clinical practice because of the strength of the evidence they generate and also because they educate clinicians and disseminate research findings<sup>(6)</sup>. Until recently, however, neurorehabilitation has not proved particularly amenable to the large-scale approach, and single case studies, observational studies and single centre trials have been the norm. Mega-trials will be particularly appropriate for neuroscience-based interventions targeted at the restorative side of neurorehabilitation.

A.12 Typically, a mega-trial recruits between 10,000 and 40,000 patients across multiple centres in a parallel group design with a placebo control. Inevitably there has to be standardisation of the therapy, and the measures of outcome tend to be simple, such as 'death from all causes' or 'survival free of disability'. But both standardisation of therapy and simple definition of outcome are problematic where neurorehabilitation techniques are concerned because of their complexity. A

physiotherapist may provide both physical and psychological support, for instance, and the way in which he or she delivers that support may depend on the personalities of both therapist and patient. For that reason, there has in the past been reluctance on the part of both professionals and patients to participate in such studies.

A.13 Research exploring people's reluctance to participate in clinical trials has also helped to improve trial design. A study of potential participants in a trial of thrombolytic therapy for acute ischaemic stroke by Koops and Lindley is a good illustration<sup>(7)</sup>. Their insights regarding people's attitudes to future disability and to participating in a trial when their condition might potentially compromise their ability to give informed consent led to the refinement of the design of the Third International Stroke Trial of thrombolytic therapy (IST-3).

A.14 Interdisciplinary collaboration at every stage of the development of the clinical trial is crucial. Besides involving laboratory scientists and social scientists, there must be true collaboration between clinicians, practitioners, statisticians, trial experts, data managers, programmers and patient representatives. Thoughtful consultation and strong trial leadership are the other vital ingredients of a successful, large-scale clinical trial.

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Website for the STEP group, an interdisciplinary group developing evidence-based rehabilitation.
- c. [www.dcn.ed.ac.uk/csrg](http://www.dcn.ed.ac.uk/csrg)  
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## B - Evaluation of clinical effectiveness: outcome measures

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- B.1 Accurate and reliable measurement of outcome is critical to the success of any evaluation of an intervention. Complex interactions between the individual and their environment make outcome measurement a particular challenge in the field of neurological disability. The primary solutions are to use rigorous research designs as appropriate to the question and to choose appropriate outcome measures.
- B.2 The International Classification of Functioning Disability and Health<sup>(1)</sup> provides a useful framework for assessing outcomes, emphasising that outcome can be considered at the level of impairment, or activity (disability) or societal participation (previously referred to as 'handicap'). Whilst doctors and scientists have traditionally focused on reducing impairment, affected individuals and their families are more concerned with impact at the levels of functional activity and participation<sup>(2)</sup>. Patients who participate in any clinical evaluation are increasingly recognised as equal partners in the research process - it therefore makes sense to assess outcomes that they themselves consider to be important.
- B.3 Rehabilitation research in the last two decades has made considerable strides in developing robust measures at these different levels. Many measures are available<sup>(3)</sup>, some of which have been subjected to rigorous psychometric evaluation. Detailed analysis has also increased our understanding of the multi-dimensional characteristics of commonly applied measurement tools<sup>(4)</sup> and their behaviour in different contexts and cultural conditions<sup>(5)</sup>.
- B.4 Researchers with experience of outcome evaluation in neurological rehabilitation therefore have a major contribution to make towards the evaluation of interventions, both in terms of the choice of measurement tools, and in interpretation of the resultant impact both at physical and wider psychosocial levels\*.
- B.5 Nevertheless, there is work still to be done, and the demonstration of success from innovative neuroscience techniques will depend on the parallel development of appropriate and responsive outcome measures.
- As yet there is no established system for agreeing the appropriate instrument to use under which circumstances. As a result the use of different measures frequently prevents comparative or meta-analytic use of data<sup>(6)</sup>.
  - Even well validated widely used measures, such as the Functional Independence Measure or the Barthel Index, currently demonstrate heterogeneity across different settings and cultures.
  - These standardised global measures of disability provide a valid assessment of overall independence. However, they are not necessarily sensitive to focal changes, which may nevertheless have a profound effect on the individual's well-being or quality of life
  - Societal 'participation' has taken the place of 'handicap' in the latest WHO classification, and represents a significant departure. Instruments that were developed to assess handicap cannot simply be applied in reverse to measure participation. A new set of measures must be developed and validated to provide assessment in this domain.
- B.6 More work is needed to develop robust and responsive measures for focal disability, and for social and quality of life issues, and to understand the relationship between these and existing standardised measures when applied in different settings. Cross-cultural validity is particularly important where large multi-centre or international scale studies are needed to recruit sufficient numbers.
- B.7 In the current climate of scarce resource within the health service, it is not enough simply to show that interventions are effective - they need also to be demonstrably cost-effective. Where an individual is able to return to full socio-economic independence, the benefits may be self-evident. However, in the context of complex disabling neurological conditions, this may be too much to expect. Some patients who would otherwise have

<sup>15</sup> This includes medical imaging



died will survive with significant disability. Others may gain considerably in quality of life, but not necessarily in terms of care burden or longevity.

B.8 New interventions in neuroscience and neurorehabilitation are likely to have significant cost-implications, at least in their introductory

phase, and yet have the potential to transform quality of life for affected individuals and their families. It will be important to establish methodologies to address the evaluation of cost-effectiveness in this context if the interventions are to be widely taken up in routine clinical practice.

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*\*One prime example is in multiple sclerosis research where the Kurtzke Extended Disability Status Scale, used in all trials of interferon beta, is probably the least sensitive and most inappropriate measure to use, and this was known to rehabilitationists when the trials were designed.*

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## C - Research synthesis

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- C.1 Scientific knowledge is cumulative, and the results of a particular study cannot be interpreted with any confidence unless it is seen in the context of other studies addressing the same or similar questions.
- C.2 Research synthesis is the practical application of this principle<sup>(1)</sup>. Not only does it reflect the cumulative nature of science, it must itself be scientific. As in all their research, scientists must strive to reduce bias and the effects of chance to avoid arriving at false conclusions. Because reviews of research have often not been rigorously scientific, advice on some life-saving therapies has been held back for more than a decade, while other treatments have been recommended long after controlled research has shown them to be harmful<sup>(2)</sup>.
- C.3 Although most of the evidence relates to failures among clinical scientists<sup>(3)</sup>, it seems just as likely to be a problem among basic biomedical scientists<sup>(4)</sup>. Sandercock and Roberts note that the failure to accumulate systematically the results of animal experiments can have dire human consequences<sup>(5)</sup>.
- C.4 For instance, a recent systematic review of the effects of the calcium antagonist nimodopine in an animal model of focal cerebral ischaemia<sup>(6)</sup> has raised questions about whether that drug should ever have proceeded to clinical trials involving nearly 7000 patients<sup>(7)</sup>.
- C.5 Applying scientific rigour to research synthesis has exposed several problems. Much of the published research is variable in quality and most studies are too small to achieve acceptable reductions in the effects of chance. Additionally, there is the pervasive problem of biased under-reporting - which is found wherever it is sought, in every sphere of science.
- C.6 Researchers are less likely to present ambiguous or negative findings at scientific meetings, or to publish them in journals. They are less likely to publish them promptly, in full, in English, and in journals with a wide readership. Even if such studies are published, other researchers are less likely to cite their findings in subsequent research.
- C.7 This publication bias can have potentially lethal effects. In 1993, investigators published a study of a class one anti-arrhythmic drug that had been carried out 13 years earlier. They reported nine deaths among patients given the drug compared with only one amongst a similar number of placebo controls. Because they put the higher death rate associated with the drug down to chance, and the drug development process was abandoned for commercial reasons, they did not publish the study at the time it was carried out.
- C.8 The authors presented their findings after the prolonged delay as an example of publication bias, because it could have provided an early warning that this class of drugs was potentially lethal<sup>(8)</sup>. At the peak of their use in the late 1980s, it is estimated that anti-arrhythmic drugs were causing between 20,000 and 70,000 premature deaths every year in the United States alone<sup>(9)</sup> - an annual toll on a par with the total number of American deaths in the Vietnam War.
- C.9 Recent evidence suggests that grossly biased under-reporting may be a particular problem in studies of genotype-phenotype associations<sup>(10)</sup>. Under-reporting of the results of basic science studies may not have the adverse impact on patients that it does with clinical trials, but inevitably it leads to unnecessary duplication and inefficient use of resources; and when that involves research involving animals, that duplication becomes an ethical problem. The failure of academia to apply itself seriously to research synthesis<sup>(11)</sup> also means that policy makers, practitioners and patients lack the information they need to make informed choices about healthcare.
- C.10 Electronic publishing and access to databases has made it easier to find some relevant information, but it has also created a bias in reviews towards recent studies. Scientists today make fewer visits to the library and it can be difficult to get electronic access to old back copies of journals<sup>(4,12)</sup>. Moreover, although tools for research synthesis are improving rapidly, problems persist.
- C.11 A systematic review of neural transplantation for

PD, an area relevant to this report, provides an apt illustration. The authors of this review rejected almost half of the studies they identified in their initial search because they did not meet their inclusion criteria<sup>(13)</sup>. For the 11 studies that did meet those criteria, they provided a good descriptive analysis of the outcome. But when it came to a more formal analysis, they concluded that, 'the variable standards for reporting data precluded the use of more powerful and accurate meta-analysis'.

C.12 A culture should be promoted in which a systematic, scientifically defensible review of the existing evidence is an essential precursor to all research endeavours. The promotion of full and accessible reporting of clinical findings, preferably accompanied by the data itself, whether or not those findings are regarded as 'positive' or 'negative', is also essential. This poses a major challenge to clinical scientists, funding agencies, editors and publishers, but it is a goal that is both scientifically and ethically desirable.

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## Understanding brain damage and neurological recovery

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### D - Developmental neuroscience

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- D.1 Every year, approximately 3000 children in the UK suffer acute brain injury and require rehabilitation. Because the causes are diverse, including traumatic and non-traumatic encephalopathy and stroke, and because brain damage is rare in children compared to adults, no single British centre or even region sees enough affected children to develop expertise in their rehabilitation.
- D.2 The lack of centres of excellence means that there is an urgent need for a collaborative network of epidemiologists, clinical scientists and clinicians to build a national register of children suffering from brain injury. Such a register would provide a basis for the development of clinical trials for new, child-oriented rehabilitation techniques. Models for it already exist, in the form of several local registers for cerebral palsy which have proved highly successful, see 'Other sources' below.
- D.3 The need for collaborative research is illustrated by the contrast between the rehabilitation services currently available for adults and children who have suffered stroke. Practices with regard to children vary and adverse outcomes are common<sup>(1)</sup> with death occurring in 10% of patients and neurological deficits or seizures in 70%. Paediatric stroke research is at a very early stage of development and fundamental differences in cerebrovascular and coagulation systems, stroke pathophysiology and the potential plasticity of the nervous system mean that findings in adults are rarely applicable to children<sup>(2)</sup>.
- D.4 Key to improving paediatric rehabilitation is an understanding of the mechanisms of brain plasticity. It used to be thought that those mechanisms were always self-reparative, but it is now clear that their capacity for repair is secondary to their role in normal, experience-driven development, and that following a brain insult they can sometimes lead to a reorganisation of the brain that produces undesirable outcomes.
- D.5 Work over the last decade has revealed the enormous capacity of the developing brain to respond to activity and environmental stimuli. Reorganisation can occur not only within modalities but also between modalities, and can even lead to transfer of functions between cerebral hemispheres<sup>(3)</sup>. The advent of brain imaging and other techniques have enabled researchers to show, for instance, that the brain's visual areas respond to somatosensory or touch cues in the blind<sup>(4)</sup>.
- D.6 Research in animals shows that some neural systems are shaped by experience during critical periods. There are variations in the critical period for different functions that influence the susceptibility to impairment, ability to recover from injury or that influence maturation and responsiveness to experience. The critical period in which experience shapes the brain need not be determined by time, but by the nature of the experiences, which is of critical relevance to recovery of function<sup>(5)</sup>.
- D.7 A good example is visual acuity. This normally matures in children between the ages of six and eight. Only up to the age of four, however, does a child who suffers early cataracts maintain the capacity to recover and achieve full adult acuity later on. Between the ages of four and ten, cataracts will permanently impair a child's visual acuity. In other words, although the critical periods for maturation, permanent damage and capacity for recovery overlap, they are not the same. Other systems do not appear to be sensitive to critical periods. For instance, motor reorganisation following limb amputation can occur to a significant extent throughout life<sup>(6)</sup>.
- D.8 Despite the diversity and specificity inherent in this plasticity, animal studies suggest the reliance on a limited number of neurodevelopmental mechanisms, such as differences in the timing of expression of receptors that control synaptic plasticity. New research is demonstrating that behavioural and pharmacological interventions could potentially steer these mechanisms to promote recovery, and that this potential exists not only in childhood, but also to a certain extent at

all ages. Now is the time for those researchers investigating neural plasticity in animals to collaborate with those studying neural plasticity in humans. Knowledge about critical periods in humans, when the brain is most susceptible to such interventions, could guide the development of neurorehabilitation techniques.

D.9 One particular intervention already suggests itself for the repair of brain damage in premature infants: stem cells. In England and Wales approximately 10,000 premature babies are born every year weighing less than 1500g. 90% of these infants now survive thanks to advances in intensive care, but they are highly susceptible to brain injury. 10% will develop cerebral palsy, and between 25% and 50% will experience cognitive or behavioural deficits in later life.

D.10 The most common form of brain injury in these infants is periventricular leucomalacia (PVL), which is the result of localised ischaemia in the white matter surrounding the brain's fluid-filled cavities or ventricles. This disrupts the axons or fibre-like extensions of neurons in the cortex, leaving their cell bodies intact. They send out new axons, but these fail to cross the area of injury and instead make aberrant connections within the cortex.

D.11 Animal studies have shown that stem cells migrate preferentially to the site of the ischaemia, graft themselves there and respond appropriately. It has also been shown that cells in human umbilical cord blood are multipotent, and can be multiplied in culture and persuaded by the addition of growth factors to behave like neurons. Since advances in radiological scanning mean that brain lesions can be identified very early on in premature babies, it is therefore at least theoretically possible to inject cord blood-derived stem cells into the baby's brain to repair any ischaemic injury. If repaired early enough, while the brain is still 'wiring' itself, the axons sent out by cortical neurons would then be able to find the appropriate targets and form synapses.

D.12 However, to make this theory a reality and evaluate its so far speculative potential as a neurorehabilitation technique will require the collaboration of basic scientists with expertise in stem cell research and animal experimentation, with clinical scientists who specialise in neonatal neurology. If such a collaboration were successful, and it became possible to repair periventricular lesions in premature babies, the rewards would be enormous—both socially and economically<sup>(7,8,9)</sup>.

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## E - Advances in cognitive neuroscience

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- E.1 Insights from cognitive neuroscience are driving the development of effective and sometimes counter-intuitive techniques for the rehabilitation of neurological patients.
- E.2 Cognitive neuropsychologists explore the relationship between brain and behaviour to understand both normal cognitive and emotional functions, as well as how those functions break down following damage, disease or arrested development. They make use of a range of techniques, including lesion studies, brain imaging, electrophysiological recording and computer modelling, to test hypotheses generated by theoretical models of cognition, emotion and their interaction. Central to the endeavour is the idea that by understanding the impaired brain we will learn more about how the healthy brain functions - for instance, how it generates consciousness.
- E.3 A core assumption of cognitive neuropsychology is that cognitive and emotional systems are, at least in part, modular. In other words, specific functional modules, based in specific brain regions, have dedicated information processing and output characteristics that have evolved for highly specialised cognitive and emotional functions. The identification of such modular systems has rested largely on detailed single case studies of patients with localised cortical lesions - studies that follow in the great tradition of Wernicke, Broca and others. Over the last decade, much of the brain's functional architecture has been described, and many such systems identified - including those dedicated to face and object recognition, autobiographical memory, visual imagery and spatial attention.
- E.4 However, most complex behaviours involve the interplay of different modular systems, with one module influencing another in either an inhibitory or facilitatory manner. Activation of verbal language functions have been shown to inhibit the ability to perceive visual illusions, for instance<sup>(1)</sup>. Attention modules in the brain's fronto-parietal circuits can 'gate' activity in perceptual and motor modules<sup>(2,3)</sup>. And in an example of facilitation that has produced perhaps surprising clinical benefits that are nevertheless firmly embedded in cognitive neuropsychology<sup>(4)</sup> vibration of the neck muscles can bring about adjustments in a person's egocentric frame of reference, according to whose coordinates he or she perceives the world and moves through space<sup>(5)</sup>.
- E.5 This is relevant to patients who suffer from a condition called spatial neglect, as a result of, say, a stroke in their right cerebral hemisphere. This causes them to behave as if the left half of the world does not exist. Their body's frame of reference is shifted to the right, and in practical terms, the deficit prevents them from re-learning to walk, renders them dependent on carers and dramatically reduces their quality of life. But a recent study has shown that the application of a standard electro-mechanical vibrator to the left neck muscles of left-sided neglect patients, while they are engaged in visual search exercises, can lead to a significant improvement in their condition - and hence in their quality of life<sup>(6)</sup>. The improvements seen after 15 sessions of neck vibration delivered over three weeks, in combination with visual exploration training, were long-lasting and hence, clinically important.
- E.6 Similarly impressive results have been achieved with another new neglect treatment grounded in cognitive neuropsychology: prism adaptation training, which is also designed to manipulate a person's spatial coordinates. In this case, the patient is asked to wear a pair of prism spectacles that shift the visual world 10 degrees to right or left<sup>(7)</sup>. Other techniques are emerging including limb activation training during which patients are asked to make small movements of the affected side of their body, to improve their ability to attend to that half of their visual field<sup>(8)</sup>. Research has shown that acute neglect patients receiving this simple adjunct treatment are discharged from hospital on average 28 days earlier than patients who do not receive it<sup>(9)</sup>. There are other examples; patients with early memory impairment caused by Alzheimer's disease benefit from cognitive memory training<sup>(10)</sup>. Although in the early stages of clinical application, they illustrate a general point that findings in cognitive neuroscience can inform more effective therapies.

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## F - Neuroimaging

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- F.1 A range of non-invasive brain monitoring techniques now exists for studying mechanisms and processes of functional restitution after brain injury. These fall into three categories: those that analyse anatomy, those that analyse function, or a combination of the two.
- F.2 Examples of anatomical techniques are specialised MRI, including diffusion tensor-based (DTI) white matter tractography for tracking fibre paths in white matter; voxel-based morphometry (VBM), a method of whole brain analysis that is useful for, among other things, determining the extent of structural neuropathology; and computerised tomographic or magnetic resonance-based angiography, which provide detailed pictures of blood vessels and other tissues.
- F.3 Some techniques use radioactive tracers injected into the blood to map brain function. These include PET and single photon emission tomography (SPECT). fMRI, MEG and EEG do not use radioactive tracers nor does electro-physiological recording of spontaneous or evoked activity and single shot or repetitive TMS.
- F.4 Combined approaches are in the process of being developed and validated. These include simultaneous EEG and fMRI for localising sources of brain activity, VBM analysis of structural MRI for elucidating the relationship between structure and function, and repetitive TMS with fMRI for monitoring the specific modification of brain excitability. (See 'Evidence' section G: "Transcranial magnetic stimulation (TMS)")
- F.5 All these techniques can be used in both healthy volunteers and patients for investigating the impact on the brain of specific tasks, neuropharmacological interventions or therapy of any sort. Each one has its strengths and weaknesses, and may be more or less suitable in a given experimental context.
- F.6 The MRI-based methods provide excellent spatial localisation and whole brain coverage with millimetre cubic resolution but poor temporal resolution – no better than a second or so. The electrophysiological techniques provide millisecond temporal resolution but uncertain spatial resolution. By combining MRI and electrophysiological recording researchers are beginning to be able to identify the structures from which electrophysiological activity originates. This combination can also provide complementary information about where and when changes in brain activity take place.
- F.7 Statistical methods have now been validated that allow for multiple comparisons of imaging data. They can be applied to complex experimental protocols and provide statistically valid inferences that can be generalised to groups or whole populations. An example of the implementation of these methods in the analysis of imaging data is Statistical Parametric Mapping (SPM).
- F.8 New methods of analysis are constantly being developed. It is now possible, for instance, to assess the functional connections between different brain areas. Soon there will be tools for tracing the structural connections that underlie those functional associations, using DTI tractography<sup>(1)</sup>. Then researchers will be able to ask how evoked responses in one brain area depend upon the state of the others with which they are in communication.
- F.9 All these techniques are relevant to neurorehabilitation. PET and structural MRI have helped to explain, for instance, why cochlear implants provide an effective treatment for hearing loss, despite their sparse sampling of the auditory environment. Usually, 15-25 electrodes are implanted in the inner ear, compared to the 50,000 or so neurons normally innervating the ear's hair cells. Yet, in combination with speech therapy, cochlear implants usually produce excellent auditory comprehension within a year of implantation. Mapping of the brain's functional connections has shown that, over time, auditory and visual systems develop a cooperative interaction, increasing the efficiency with which auditory signals are processed and hence comprehended<sup>(2)</sup>.

- F.10 PET and fMRI have also thrown light on how DBS alleviates the symptoms of PD. This surgical intervention is the culmination of basic scientific findings and theories about how cortical and sub-cortical brain regions interact to control motor responses. But imaging has elucidated these motor 'loops' still further, by showing that high frequency stimulation of their subcortical components releases the premotor cortex, as well as other parts of the frontal cortex that are critical for initiating movement, from excessive inhibition. The techniques have even shown that one subcortical structure, the STN, is a more effective target than another, the internal globus pallidum<sup>(3)</sup> - leading to a refinement by neurosurgeons of their approach.
- F.11 Another novel PD therapy involves the implantation of stem cells in the striatum of PD patients - a region of the brain associated with willed movement. By radioactively tagging the chemical precursor of the neurotransmitter dopamine, which is depleted in the brains of PD patients, researchers have been able to monitor the distribution and viability of the implanted cells after surgery using PET. Since an increase in the precursor correlates with an improvement in the patient's condition and time since surgery, it has become clear that the viability and functional integrity of those implanted cells is the cause of the clinical benefits<sup>(4)</sup>.
- F.12 Repeated fMRI studies have been carried out to track the brain's reorganisation following stroke or other brain injury<sup>(5,6)</sup>, and appear to confirm findings from animal studies that damaged cortex is capable of greater plasticity than healthy cortex. They have shown increased activation and enlargement of regions in the damaged motor cortex that control motor output. Now, using the same techniques, it will be possible to observe the effects of pharmaceutical, physical or cognitive therapies on that reorganisation, and to correlate those effects with recovery.
- F.13 It is also now easier to detect and monitor diffuse degenerative diseases such as Alzheimer's disease. Researchers can monitor the progression of atrophy and describe, topographically, the damage caused by stroke. They can then relate these to the patient's clinical status and the functional relationships between brain regions. Soon, it will also be possible to measure the thickness of the cortex at localised sites and thus detect thinning caused by disease or injury, or to investigate the integrity of white matter fibre tracts linking different parts of the brain<sup>(7,8)</sup>.
- F.14 Functional and modern anatomical methods have direct relevance to research in neurorehabilitation. There are established techniques, such as angiography and Doppler ultrasound, and newer emerging techniques, such as optical imaging, electrical impedance or optical coherence tomography that may also have a role to play.
- F.15 Finally, because these novel techniques are automated and objective, they are helping to eliminate much of the observer bias that has inevitably been a problem in the interpretation of imaging data.
- F.16 All of these techniques can be used to assess what happens in the human brain during spontaneous or therapeutically induced recovery at the level of brain systems and gross anatomy. The integration of basic knowledge at the molecular and cellular level towards an understanding of what is happening in the brain in supporting recovery is helped by the evidence provided by these methods. Ultimately it should guide the development of therapy.

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## G - Transcranial magnetic stimulation (TMS)

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- G.1 TMS is a safe, non-invasive and painless way to excite or inhibit the human cortex. It creates a flow of current in the brain that can produce a muscle twitch, visual phosphene (bright spot), scotoma (blind spot), or cognitive effect, depending on which area of the brain is being stimulated. In the last decade it has provided insights into the role of plasticity in recovery following brain injury, and more recently, it has begun to show possible therapeutic worth in the context of neurorehabilitation<sup>(1,2)</sup>.
- G.2 TMS can be applied in three or more different modes within the field of rehabilitation research. First, it can be used to detect changes in excitability or activity of the stimulated cortex, which may have occurred, for example, through learning, or in recovery from a stroke. Second, TMS can induce short lasting 'virtual lesions' that can directly test the relevance of brain plasticity and address the question of whether or not such reorganisation has actually improved brain function. For this purpose, TMS combines good spatial, temporal and functional resolution for the study of vision, attention, speech and language<sup>(3)</sup>. Third, repetitive TMS (rTMS) can itself produce changes in excitability and connectivity of the stimulated cortex, inducing short-term reorganisation in the way the brain works. Extrinsic factors (such as the intensity of stimulation) and intrinsic factors (including the functional state of the cortex) both influence the magnitude and direction of changes. These conditioning effects are not only limited to the stimulated cortex however, and so rTMS can be used to investigate plasticity within a distributed network within the brain and may have therapeutic potential. Chen describes the practical aspects of many such experiments<sup>(4)</sup>.
- G.3 With prolonged periods of stimulation that are required for a clinical therapeutic benefit, TMS has been applied in clinical depression<sup>(5,6)</sup>. Meta - analysis has shown a beneficial effect of rTMS, although requiring the treatment of up to 2 - 3 patients to show a benefit in at least one. Determining the extent and duration of the anti-depressant effect of rTMS with a comparison to more standard electroconvulsive therapy is awaited, together with further experimental applications that currently include schizophrenia. There is a lively debate in this area however, and several controlled trials are ongoing (see 'other sources' below) with previous data hindered somewhat by small sample sizes. Although depression is not strictly a neurological disability, this example demonstrates how enduring changes can be brought about in cerebral function that are of clinical benefit. Repetitive TMS is also being experimentally applied for the relief of chronic pain and the assessment of PD, and for the rehabilitation of stroke patients in combination with constraint-induced therapy (see Evidence 11).
- G.4 Direct questions can now be addressed therefore, with respect to the study of brain plasticity in recovery, cognition and therapy. Following injuries to (or beneath) the cerebral cortex for example, TMS has been used to demonstrate changes in the size, location and excitability of responses to experimental nerve block (see below) and during the relearning of new movements, following events such as stroke. Human TMS experiments can also be combined with drug studies to examine changes at the receptor (molecular) level. Accordingly, similar experimental forearm nerve block (with a blood pressure cuff) combined with low frequency cortical TMS upregulates the plastic changes caused by the nerve block. Single doses of specific drugs have shown that this increase involves rapid removal of inhibition by particular chemicals in the brain (GABA) and short-term changes in the communication between brain cells (synaptic efficacy). Longer lasting reductions in intracortical inhibition within the cortex<sup>(7)</sup> are also thought to be related to how the brain cells discharge (long - term potentiation) and the involvement of other receptors (NMDA).
- G.5 With regard to longer-term changes in the brain, work combining TMS with drugs that boost the activity of receptors for GABA have demonstrated its role in the plasticity of motor cortex that accompanies practice of a movement. That in turn will have implications for our understanding of recovery of function after brain damage<sup>(8)</sup>.

G.6 TMS is therefore poised to generate exciting new ideas and answer questions that are directly relevant to the rehabilitation of neurological patients.

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## New treatment modalities

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### H - Deep brain stimulation (DBS)

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- H.1 DBS is used all over the world to alleviate tremor, rigidity and dyskinesia associated with PD and a variety of other movement disorders. It is a success story that arose out of the dynamic interplay of basic and clinical science.
- H.2 DBS involves the chronic, high frequency electrical stimulation of specific brain targets through implanted electrodes. It is reversible, because the electrodes can be removed, and therefore preferable to surgical treatments that involve making lesions in the brain - pallidotomy or thalamotomy, for instance.
- H.3 The process that led to the development and therapeutic application of DBS began with a chance clinical observation.
- H.4 In 1983, the chemical MPTP was identified as the cause of PD-like symptoms in young American drug addicts who had taken the street version of a synthetic drug that contained it<sup>(1)</sup>. In the same year, based on that observation, researchers injected MPTP into monkeys to create a similar PD-like state<sup>(2)</sup>. Subsequent recordings of activity in the basal ganglia of both healthy and MPTP - treated monkeys showed that a part of the basal ganglia, the STN, was over-active in the monkeys that had been given the drug.
- H.5 The basal ganglia form part of a loop in which information cycles from the cortex, through the basal ganglia and thalamus, and back to the cortex. One of the functions of this loop is thought to be the selection and initiation of deliberate movements.
- H.6 The findings regarding the STN were based on single neuron recordings in awake, active monkeys, and also on the mapping of brain areas of under- and over-activity as measured by metabolic markers<sup>(3,4)</sup>. And that body of research provided the conceptual framework for much of the work on the basal ganglia and movement disorders that has been conducted since.
- H.7 In 1990, it was shown that lesions of the STN in monkeys could completely and permanently reverse the effects of MPTP<sup>(5,6)</sup>. Three years later, Benabid's group in Grenoble treated three PD patients with DBS of the STN. That was the first report in humans, although the same group had already used DBS in the human thalamus as early as 1987. They implanted their electrodes on both sides of the brain, which remains the standard approach to the treatment of PD<sup>(7)</sup>. In 1997 the US Food and Drug Administration approved the use of DBS in the thalamus, and four years after that, in the STN.
- H.8 Although it is now known that DBS suppresses activity in the over-active STN of PD patients, much more research is needed to understand how it actually works. It may block electrical conduction in local circuits, generate inhibitory activity or desynchronise pathological brain rhythms. It may be that other brain sites would provide as good or better therapeutic targets, but this remains largely unexplored.
- H.9 Other movement disorders are treated with stimulation of other brain structures. DBS has been shown to produce long-term benefits in the treatment of dystonia, for instance-a much rarer disease than PD and one that affects children<sup>(8)</sup>. It has also been used for a long time to provide relief from chronic pain<sup>(9)</sup>. But the majority of DBS operations are carried out in PD patients.
- H.10 In the UK, there are 10,000 new cases of PD every year. One percent of those over the age of 65 are affected, and there are an estimated 120,000 sufferers in all. Around a fifth of those are considered suitable for DBS, and those who benefit are once again able to participate fully in family and society, and to regain their former quality of life. The longest surviving patients have had stimulators in for around eight years, without suffering any adverse effects.
- H.11 Yet, despite the fact that around 20,000 patients with movement disorders have so far been treated with DBS, with a high degree of success, there is surprisingly little evidence as to its effects from randomised clinical trials<sup>(10)</sup>. One such trial is now being carried out by the MRC<sup>(11)</sup>.

H.12 DBS is still only offered by a few centres in the UK. This is partly due to the high cost of the treatment, including the stimulators and electrodes, which are supplied almost exclusively by one company, Medtronic Inc., see 'other sources' below. According to current estimates,

however, the cost of DBS will be recouped in around five years, because patients who have received the treatment will become less reliant on medication and may even be able to return to work.

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## I - Neuroprotection and plasticity

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- 1.1 The discovery of natural trophic compounds, molecules that protect neurons from death, and promote regeneration in the damaged nervous system has led to the present interest in developing novel strategies for neuroprotection and for boosting brain plasticity to improve recovery after injury or disease.
- 1.2 The first of those trophic compounds to be identified was nerve growth factor (NGF)<sup>(1)</sup>. In 1952, Rita Levi-Montalcini and colleagues discovered that this molecule was responsible for the survival of nerves in the developing chick nervous system. Thirty years later, Yves-Alain Barde and Hans Thoenen isolated another such molecule, brain-derived neurotrophic factor (BDNF), by large-scale purification and screening in an *in vitro* system<sup>(2)</sup>.
- 1.3 Both NGF and BDNF were found to protect cells against apoptosis, or programmed cell death. In contrast to necrosis, the classic form of cell death, apoptosis is a form of self-destruction that involves the production of a cascade of proteins that are lethal to the cell. These toxic processes are under precise genetic control. They include excitotoxicity, the lethal activation of excitatory glutamate receptors; interference with mitochondrial function leading to disturbances in the cell's energy production; oxidative stress, caused by disruption of the cell's ability to scavenge free radicals and other damaging reactive oxidative species; and dysregulation of the cell's ion channels that are important for signalling.
- 1.4 In many forms of brain injury and disease, these processes interact to generate a lethal cycle of neurodegeneration<sup>(3)</sup>. The many dozens of neurotrophic factors that have been identified since Levi-Montalcini's pioneering work have a wide range of effects on both developing and mature neurons. They have been shown to promote survival and differentiation of different neuronal populations in cell culture, they can protect cells from apoptosis induced *in vitro* by excitotoxins, and they can retard cell death caused by similar toxic insults in the living brain.
- 1.5 The task now is to identify ways of delivering potent neuroprotective compounds to the brain, both to slow cell death and to promote plasticity in the nervous system. Work in this area has shown that the organisation of the brain in normal development, and its rearrangement following insult in later life, are both regulated by a variety of precise control mechanisms that are amenable to therapeutic manipulation. However, present technologies for manipulating these mechanisms are crude, and the results of most pilot studies designed to recruit them for clinical benefit have proved disappointing.
- 1.6 For instance, stroke causes a site of necrotic damage that is surrounded by a 'penumbra' in which degeneration occurs via apoptotic mechanisms, particularly excitotoxicity<sup>(4)</sup>. Animal experiments have shown that these penumbral neurons can be rescued if treated with anti-excitotoxic agents such as the NMDA antagonist MK-801, but the results of clinical trials have been less than promising<sup>(5)</sup>.
- 1.7 Similarly, there is now clear evidence that a variety of neuroprotective, anti-oxidative and anti-apoptotic agents can yield modest protection in the nervous system. However, the effects of individual agents are typically small, and large - scale trials such as the recent evaluation of the drug remacemide with or without co-enzyme Q10, for neuroprotection in Huntington's disease, have also proved disappointing<sup>(6)</sup>.
- 1.8 Some studies have focused on specific mechanisms of neurotoxicity associated with a particular disease. The apparent neuroprotective effect provided by selective Monoamine Oxidase - B (MAO-B) inhibitors suggested by a preliminary study in 1993<sup>(7)</sup> rapidly led to the widespread use of deprenyl (selegiline) for the management of PD. But a full study later failed to find a significant effect of the drug<sup>(8)</sup>, while others have brought into question both the mechanism of action of this class of drug, and even suggested that they may be harmful<sup>(9)</sup>.
- 1.9 Of the many trophic molecules that have been tested for the protection they afford to dopaminergic neurons, the cells that are lost in PD, Glial



Cell-line Derived Neurotrophic Factor (GDNF) has proved the most potent. It is therefore considered a primary candidate among potential neuroprotective agents for the treatment of PD. A recent pilot study provides grounds for optimism. Five patients given brain infusions of GDNF not only developed symptoms more slowly, but the treatment led to a significant alleviation of their existing symptoms <sup>(10)</sup>. Using a similar delivery strategy, other researchers have tested NGF as a neuroprotective agent in Alzheimer's disease <sup>(11)</sup>, but the difficulties in providing sustained brain infusion outweighed the small benefits gained.

1.10 Ciliary neurotrophic factor (CNTF) is another molecule that has been shown, *in vitro* and in animal models, to protect motor neurons in the brain's striatum and in the spinal cord. It is now in clinical trials for the treatment of Huntington's

disease and amyotrophic lateral sclerosis, or Lou Gehrig's disease. Because delivery of CNTF into the peripheral nervous system can be toxic, these trials are also stimulating developments in the technology for targeted delivery of large trophic molecules into the central nervous system <sup>(12)</sup>.

1.11 These technological developments, in combination with progress in the basic science of neuroprotection and plasticity, justify the present optimism that rapid therapeutic advances will be achieved in this area over the next decade <sup>(13)</sup>.

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## J - Neural transplantation

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- J.1 Clinical trials of neural transplantation for the treatment of PD have provided proof-of-principle for this novel technique. Although its application to other neurodegenerative diseases and injury is at an early stage of development, there is considerable optimism that the next decade will see new therapies for conditions that have hitherto proved refractory to treatment.
- J.2 The first demonstration that neural transplantation could alleviate behavioural deficits in an animal model of PD took place in 1979<sup>(1)</sup>, and many others followed<sup>(2)</sup>. The first clinical transplants were performed in 1985, but because of ethical concerns about the use of human foetal tissue, they were carried out with cells taken from the adrenal glands of the patients themselves<sup>(3)</sup>. These had very little effect and it is now widely accepted that adrenal grafts neither survive well nor specifically replace depleted dopamine in the parkinsonian brain.
- J.3 Through the 1980s it became clear from animal work that the most promising approach was to use grafts of embryonic brain tissue of the correct cell type, taken from the same species. It therefore became necessary to reconsider the ethics of using human foetal tissue, and that led to the adoption of the first European consensus guidelines<sup>(4)</sup>, similar versions of which have now been adopted in many European countries including the UK.
- J.4 In 1990, Lindvall and colleagues in Lund, Sweden were the first to show convincingly that human foetal tissue taken from the substantia nigra - the group of dopaminergic cells in the midbrain that is affected in PD - could survive transplantation in the parkinsonian brain and alleviate motor symptoms<sup>(5)</sup>. Their findings have now been replicated in several other centres throughout the world<sup>(6)</sup>. Two recent controlled trials sponsored by the US National Institutes of Health have produced disappointing results. However, there are significant concerns about the experimental design and transplantation methods used in these two studies<sup>(6,7)</sup>.
- J.5 The last decade has seen the refinement of methods for cell preparation and implantation. It is now known that the survival and function of embryonic cells can be enhanced by preparing them with neuroprotective agents<sup>(8)</sup>. Post-mortem studies of transplant patients have revealed good graft survival, differentiation and integration<sup>(9)</sup>. And in living patients brain imaging techniques have shown that grafts are fully incorporated into the patient's neural circuitry, where they function appropriately and release dopamine in a regulated way<sup>(10,11)</sup>.
- J.6 However, for ethical and practical reasons, a therapy that relies on donations following elective abortions for its source of graft cells will never be widely available, so there is now active research being carried out into other potential sources. What is needed is a reliable supply of tissue of high-quality and purity.
- J.7 One such source being considered is xenografts<sup>(12)</sup>. Pigs or other animals can be farmed under quality-controlled conditions, and used to provide embryonic tissue for transplantation. However, this approach also has its limitations. Strategies for suppressing the host's immune system in order to protect the graft from immune attack are currently unreliable. There are also safety concerns about the possibility of new diseases emerging through cross-species transplantation, particularly following the outbreak in the UK of bovine spongiform encephalopathy (BSE) and its human form, variant Creutzfeldt-Jakob disease.
- J.8 Another potential source of graft tissue is stem cells<sup>(13)</sup>, which are defined by their capacity to replicate indefinitely and to differentiate into any of the cell types in the human body. Researchers are now able to expand or multiply them indefinitely in the laboratory, but the conditions that control their differentiation into a specific cell type needed for the treatment of a given disease are not well understood.
- J.9 There is also an ongoing debate about the best source of stem cells. Embryonic stem cells, neural progenitor cells from the foetal brain, adult somatic cells from brain, blood or bone marrow and cells genetically engineered to be immortal are all under investigation. Cultured oligodendrocytes,

Schwann cells and olfactory glia are also being assessed for their potential as natural repairers of tissue damage<sup>(14)</sup>. Whichever source turns out to be the most appropriate, issues about ethical regulation, immune protection, safety and stability will have to be tackled. However, rapid advances are being made and researchers are optimistic that most of these problems will be solved in the near future.

J.10 The success of neural transplantation for the treatment of PD has raised the question of which other diseases may respond to similar strategies. Cell transplantation techniques are being developed for Huntington's and Alzheimer's diseases, multiple sclerosis, stroke, traumatic brain and spinal cord injury, as well as a variety of other developmental, genetic and neuroendocrine disorders<sup>(2)</sup>. Meanwhile, research into the mechanisms of graft function has highlighted several principles that may determine whether a particular disease or injury is amenable to the approach<sup>(15)</sup>.

J.11 First, cell replacement strategies favour diseases in which a specific cell type is affected, for instance dopaminergic cells in PD or oligodendrocytes in Multiple Sclerosis, rather than ones in which the loss occurs in many different cell types or is distributed widely through the brain – as in Alzheimer's disease or stroke.

J.12 Second, it is likely to prove far easier to promote recovery with grafted cells that exert a neuroprotective effect on the brain or that secrete a depleted neurochemical, than with cells that must replace connected neurons or reconstruct synaptic circuits.

J.13 And third, the repair strategy must be tailored to the fixed or progressive nature of the patient's condition. Different approaches will be required for acute injury where the goal is to repair past damage, than for degenerative diseases where it is to slow, arrest or reverse deterioration.

J.14 One area where cell replacement strategies are already looking promising is in the treatment of spinal cord injury. It is now possible to promote the regeneration of severed axons – the fibre-like extensions of neurons – in the spinal cord, which can in certain animal models re-establish damaged connections and to restore lost motor, sensory and autonomic functions.

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## Advances in current therapeutic approaches

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### K - Maximising participation through rehabilitation

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- K.1 Rehabilitation encompasses therapies that are aimed at reducing impairments, and therapies that are designed to help patients adapt to the impairments they have, so that they may participate as fully as possible in the activities of daily life<sup>(1,2)</sup>.
- K.2 The International Classification of Functioning, Disability and Health, the WHO's widely accepted framework for defining the determinants of health, describes rehabilitation as a complex process<sup>(3)</sup>. Inevitably, each individual has different needs and goals. In order to help them achieve those goals, advocates of restorative and adaptive therapies must collaborate.
- K.3 Restorative therapies aim to restore body structure and function. Adaptive therapies include the teaching of skills, the provision of information, the use of problem solving aids or appliances and environmental modification<sup>(1,2)</sup>. These interventions are often simple, but several different interventions may be needed for each patient or each task. When delivered in a skilled and coordinated way, they can have a valuable impact on task performance<sup>(4)</sup>.
- K.4 To perform well on a task requires certain conditions to be satisfied. Most of us can do some gardening, provided we have access to a garden, the weather conditions are not too hostile, we are adequately clothed and shod, and we are equipped with the necessary tools. People with neurological disease may have to overcome additional obstacles, such as muscle weakness or problems with balance, vision or perception. They may have to deal with a fear of falling, or the embarrassment associated with clumsiness. Their ability to walk outside may depend on them having a walking aid that they know how to use safely, as well as having specially adapted access to their garden, raised flower beds and modified tools. Their freedom of movement also depends on the support and understanding of relatives and carers.
- K.5 A systematic review of occupational therapy for stroke patients provides evidence for the value of a multi-faceted approach to improving task performance<sup>(5)</sup>. In assessing the factors that contributed to a reduction in patients' performance, the researchers took into account not only their impairments, but a range of other contributing conditions. For instance, they looked at the provision of appropriate tools and measures taken to reduce patients' apprehension, as well as efforts made to encourage them to alter their behaviour or avoid maladaptive habits. While they found no evidence that occupational therapy interventions reduced patients' impairments *per se*, when they followed them up they found that their performance on the same tasks had improved significantly.
- K.6 Research into neurorehabilitation strategies that focuses solely on impairments, and ignores other influences on task performance is potentially flawed. If emotional and educational factors are not taken into account, a therapy may well fail at the experimental stage. For one thing, a research laboratory may not be the most conducive environment to learning new skills. Not all researchers have the clinical expertise to put a patient at his or her ease. And if a therapy does prove successful in the lab, it is essential that the conditions in which it was delivered are noted, so that its benefits may be replicated and generalised to other settings.
- K.7 Research that focuses solely on adapting to impairments is similarly blinkered. If it is possible to restore even a fraction of a patient's bodily function, then he or she may be able to participate in a given activity with the help of fewer or simpler aids.
- K.8 It is important, therefore, to combine adaptive and restorative approaches. For instance, rehabilitation scientists are beginning to identify restorative physical therapies and to evaluate their effects on brain plasticity, movement, and ability to function. To develop new and improved approaches to

rehabilitation, others must now investigate the conditions under which those changes taking place at the cellular, organ or physiological level can be translated into meaningful benefits at the level of task performance or participation.

K.9 The boundary between adaptive and restorative approaches is now meaningless. Far from being incompatible, they are synergistic.

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## L - Physical therapies to restore movement

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- L.1 Targeted physical therapies have been shown to promote recovery following brain injury by stimulating reorganisation and beneficial plastic changes<sup>(1)</sup>. Researchers are now optimistic that they can develop new and better interventions that will improve the outcome for patients further.
- L.2 There is plenty of evidence that conventional physical therapies work for the rehabilitation of stroke patients. For instance, repetitive shoulder movements performed soon after the stroke improve the function of the arms<sup>(2)</sup>, while practice of reaching forward from a sitting position improves both reaching and standing up from a chair some time after the stroke<sup>(3)</sup>.
- L.3 These effects are reflected in what is known about brain recovery after injury. A study published in 2000 was one of the first to demonstrate that physical therapy after stroke could cause cerebral reorganisation, when it showed enlargement of the representations of body parts in the motor cortex of the affected hemisphere<sup>(4)</sup>. Another study showed altered activity in brain areas other than the primary motor cortex<sup>(5)</sup>.
- L.4 As scientific knowledge about the mechanisms of recovery grows, it reveals broad principles on which new therapies should be based. For instance, somatosensory or touch feedback from normal activity or repetitive exercises is now known to be an important driver to recovery<sup>(1)</sup>.
- L.5 However, systematic reviews of the evidence have so far failed to demonstrate that any one physical therapy approach is more effective than any other<sup>(6)</sup>. Nor have they yielded any insights as to which of the many interventions available are suitable for which patients, at what stage in the recovery process and in what dose<sup>(7)</sup>.
- L.6 Part of the problem is that many of those therapies are based on relatively uncontrolled clinical observations of their effects. That does not mean they should be discarded. In fact, the advent of new methodologies for generating standardised treatment schedules means that it will now be possible to measure their efficacy rigorously in controlled trials<sup>(8)</sup>. This research is underway, and in the meantime new therapies are constantly being developed.
- L.7 One comparatively new approach to the rehabilitation of stroke patients is Constraint Induced Movement Therapy (CIT), in which the patient is forced to use an affected limb because the 'good' one is constrained. This therapy came out of experimental evidence showing that the 'forced' use of limbs in monkeys could bring about functional improvements<sup>(9)</sup>. A small number of human studies have shown benefits in chronic stroke patients<sup>(10)</sup>. However, one clinical trial found no significant improvement in stroke patients receiving CIT versus a conventional, control treatment - there was some suggestion that those patients with sensory deficits or unilateral spatial neglect might benefit<sup>(11)</sup>.
- L.8 Another therapy that is in development is 'robot-aided' therapy, which makes use of devices to aid repetitive arm movements<sup>(12)</sup>. Simultaneous bilateral movements also have a potentially therapeutic effect, and work on the principle that if the lesioned and unlesioned hemispheres share motor commands such movements promote reorganisation and hence recovery<sup>(13)</sup>. And finally, animal studies suggest that treadmill exercise can help restore normal gait, although decisive clinical evidence is still lacking<sup>(14)</sup>.
- L.9 It is important when evaluating new physical therapies to take into account their effects on normal movement as well as their ability to restore a lost function. Different therapies with different goals also need different measures of outcome. To that end, researchers are beginning to incorporate biomechanical indicators of movement quality into their studies. They are also starting to study the changes in brain plasticity and altered transmission in corticospinal pathways that accompany the patient's response to a therapy.
- L.10 Musculoskeletal consequences of neurological injury are reversible and amenable to rehabilitation. Muscle wasting, weakness and cardiovascular de-conditioning should be targets of rehabilitation alongside other approaches. Nutrition and metabolism should also be considered in any package of holistic rehabilitation.



L.11 One other thing needs to be considered: the psychosocial interactions between patients, carers and therapists. Research is in progress on ways to enhance these therapeutic relationships<sup>(15)</sup>. As Gladman and Walker point out in 'Evidence' section K, we also need to understand the

environmental conditions that allow recovery to take place. By combining knowledge on all these different aspects of neuro-rehabilitation, we will be able to target physical therapies more precisely to the underlying mechanisms of disability.

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## M - Rehabilitation engineering

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- M.1 The goal of rehabilitative bioengineering is to develop systems that restore sensorimotor function. It works on the premise that tissues and biological systems in general are adaptive, with properties and behaviours that change as a function of therapeutic intervention strategies and time. It draws on clinical expertise in orthopaedics, neurology, physiotherapy and occupational therapy, and non-clinical disciplines such as engineering, psychology, neurophysiology and biomechanics.
- M.2 The success of this approach to rehabilitation is built on the ability to measure impairment. In the 1970s and '80s Nashner and colleagues carried out a series of studies investigating the neuromuscular mechanisms involved in maintaining balance in both neurological patients and healthy adults<sup>(1)</sup>.
- M.3 They made their measurements using specially designed and instrumented platforms which could move with multiple degrees of freedom to perturb a person's balance, and then gauge the body's compensatory postural reflexes. Using this approach, they showed that postural instability arises from impaired, slow and weak or uncoordinated recruitment of these postural responses.
- M.4 In a parallel development focusing on the arm, in the 1980s and '90s researchers including Mussa Ivaldi at the Massachusetts Institute of Technology (MIT) in Boston developed hand-held, robot-like machines that could generate complex force fields for disrupting and hence analysing goal-oriented reaching movements<sup>(2)</sup>. They showed how the central nervous system programmes and modifies the torque or turning moment operating between interacting joints - for instance, between the shoulder and elbow when a person reaches for an object.
- M.5 These and other efforts to develop means of assessing disability have led to the design of assistive technologies for improving posture and reaching, as well as locomotion. For instance, robotic devices are being refined that help therapists deliver sensorimotor training in a controlled environment where the repetition of movements can be closely monitored. The training usually involves varying the speed and amplitude of movements, and encourages the development of both predictive and reactive controlled responses.
- M.6 An example of this enhanced sensorimotor training is partial body weight supported gait training, developed by Barbeau and colleagues in Montreal<sup>(3)</sup>. Because they are only carrying part of their own body weight, hemiparetic patients who are unable to walk unaided can practise and improve their locomotor skills with less support from therapists. Hesse and colleagues in Germany have gone on to develop a 'Gait Trainer'<sup>(4)</sup> which allows hemiparetic patients to practise complex gait cycles, also under partial body weight support. This is an example of a repetitive quasi-normal activity which has been known to induce plastic changes in the direction of those that support normal function.
- M.7 A group at MIT has now devised a technique for the restoration of arm function that exploits the same principle<sup>(5)</sup>, and there have been many other attempts to do the same<sup>(6)</sup>. In Europe, work continues on the GENTLE/S robotic aid for arm rehabilitation, led by a group at the University of Reading. GENTLE/S promotes repetitive task-oriented movements such as grasping, while providing virtual and motivational feedback<sup>(7)</sup>. It will be commercialised through industrial partners in the UK and Greece – although more research is needed before it becomes available in clinical practice.
- M.8 Commercial or corporate funding could help boost bioengineering research for neurorehabilitation by creating a market for healthcare technologies that satisfy a social need. One example of a company founded on the back of R&D in health care technologies is NeuroCom, set up by Nashner. However, the company does not provide funding for research.
- M.9 In the UK, a small but growing number of bioengineering projects are being supported by programmes with links to the DH. A few examples of recent funding initiatives include the Health Technologies Devices (HTD) programme, which replaced the MedLink scheme, European Co-Operation In The field Of Scientific And Technical

Research (Programme) (COST) and New And Emerging Applications Of Technology (Programme) (NEAT). HTD provided £13 million to support the development or improvement of new technologies put forward in its first call for

applications last year. NEAT supports the development of healthcare products and therapies that enhance the quality, efficiency and efficacy of health and social care.

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## Other sources of information

- a. <http://www.onbalance.com>  
Neurocom company website - provides a lot of useful information relating to clinical assessment of patients with balance and mobility problems.
- b. <http://interactive-motion.com>  
Illustrative stories about robot-assisted upper limb movement therapy for stroke victims, see news page.
- c. <http://rehabrobotics.org>  
International scientific meetings on rehabilitation robotics.
- d. <http://www.gentle.rdg.ac.uk/>  
EU fifth Framework project on robotic assistance in neuro- and motor rehabilitation, coordinated by the University of Reading.
- e. <http://isb.ri.ccf.org/biomch-l/>  
Home site for Biomch-L, an email discussion group for biomechanics and human/animal movement science.
- f. [http://userpage.fu-berlin.de/~bhesse/e\\_index.html](http://userpage.fu-berlin.de/~bhesse/e_index.html)  
Research projects including gait training at Laboratory for Movement Analysis and Therapy, Free University Berlin.
- g. <http://www.asnr.com>  
The American Society of Neurorehabilitation, see links page.
- h. <http://www.fastuk.org>  
The Foundation for Assistive Technologies website - includes a database of the available funding initiatives in rehabilitative bioengineering.

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## Addendum 1 - Acronyms and abbreviations

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BDNF:	Brain-Derived Neurotrophic Factor	MRC:	Medical Research Council
BSE:	Bovine Spongiform Encephalopathy	MRI:	Magnetic Resonance Imaging
CIT:	Constraint Induced Movement Therapy	NEAT:	New And Emerging Applications Of Technology (Programme)
CNTF:	Ciliary Neurotrophic Factor	NGF:	Nerve Growth Factor
COGG:	Co-operative Group Grant	NHS:	National Health Service
COST:	European Co-Operation in The field Of Scientific and Technical Research (Programme)	NSF:	National Service Framework
DBS:	Deep Brain Stimulation	NTRAC:	National Translational Cancer Research Network
DH:	Department of Health	PD:	Parkinson's Disease
DGH:	District General Hospital	PET:	Positron Emission Tomography
DTI:	Diffusion Tensor-Based Imaging	PVL:	Periventricular Leucomalacia
EEG:	Electroencephalography	RAE:	Research Assessment Exercise
EPSRC:	Engineering and Physical Sciences Research Council	R&D:	Research and Development
fMRI:	functional Magnetic Resonance Imaging	RNRC:	Regional Neurorehabilitation Research Centre
GDNF:	Glial Cell Line-Derived Neurotrophic Factor	rTMS:	Repetitive Transcranial Magnetic Stimulation
GENTLE/S:	Robotic assistance in neuro and motor rehabilitation	SPM:	Statistical Parametric Mapping
HEFC:	Higher Education Funding Councils	STN:	Subthalamic Nucleus
HTD:	Health Technologies Devices	TMS:	Transcranial Magnetic Stimulation
MAO:	Monoamine Oxidase	UK GRID:DTI	Core Programme for e-Science
MEG:	Magnetoencephalography	VBM:	Voxel-Based Morphometry
MIT:	Massachusetts Institute of Technology	WHO:	World Health Organisation



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## Addendum 2 - Working Group and Review Group Members

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## Addendum 3 - Terms of reference and work plan

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### Terms of reference:

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To identify, characterise and document opportunities arising out of advances in neuroscience to improve the care of patients with neurological disability.

In order to achieve this goal the Working Group sought to:

- identify the barriers to collaboration between researchers that hinder the translation of advances in basic neuroscience into treatments that will benefit patients;
- recommend methods by which these barriers might be overcome;

- suggest research structures that would promote exploitation of advances in neuroscience and indicate ways in which the short-fall of researchers in this field might be addressed;
- identify the resources, including funds, that are requisite to achieve these objectives.

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### Timetable:

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In 2002 the Council of the Academy of Medical Sciences approved the establishment of a Working Group to discuss the prospects for developing new treatments and to identify the obstacles to their implementation in neurorehabilitation. This followed an Academy scientific meeting of neuroscientists, clinical academics and NHS healthcare workers in April 2002 on the same issue.

The Working Group first met in September 2002 to agree work plans, scope and responsibilities. Working Group members, supported by the research capacity of the Academy secretariat, provided evidence, analysed issues and established strategic prioritisation at meetings in December 2002, February 2003 and May 2003.

A draft Report was modified in response to comments from a Review Group appointed by the Academy's Council. A second draft of the report was circulated for consultation at the end of August 2003. At the end of the consultation period a final draft of the Report was generated to take account of comments received.

*This draft was resubmitted to the Review Group and a final version submitted for publication in March 2004.*



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There was a two-month consultation period between August and October 2003. Drafts of the report were sent to the following individuals:

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*Date of publication: March 2004*