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fMRI for vegetative and minimally conscious states

A balanced perspective

Lynne Turner-Stokes professor of rehabilitation
lynne.turner-stokes@dial.pipex.com

Jenny Kitzinger professor of communications research

Helen Gill-Thwaites consultant occupational therapist

E Diane Playford reader in neurological rehabilitation

Derick Wade professor of neurological rehabilitation

Judith Allanson consultant in neurorehabilitation

John Pickard professor of neurosurgery

Affiliations are in the version on bmj.com

The BBC's Panorama programme *The Mind Reader: Unlocking My Voice* broadcast on 13 November 2012 provided important insights into the devastating experience of patients who live in vegetative or minimally conscious states and the families who support them. It also provided useful information on the use of functional magnetic resonance imaging (fMRI) to explore evidence of localised brain activity that might indicate underlying awareness. However, the programme did not distinguish clearly between the two states and gave the impression that 20% of patients in a vegetative state show cognitive responses on fMRI. This claim needs to be clarified and put into perspective.

There are important differences between the two states. Patients in a vegetative state have no discernible awareness of self and no cognitive interaction with their environment. Patients in a minimally conscious state show evidence of interaction through localising or discriminating behaviours, although such interactions occur inconsistently. It is clinically important to make this distinction, for prognostic reasons and because some evidence suggests that patients in a minimally conscious state experience symptoms (such as pain) in a manner indistinguishable from non-brain injured patients.^{1 2}

The programme presented two patients said to be in a "vegetative state" who showed evidence of cognitive interaction on assessment using fMRI in Ontario, Canada. The clinical methods used for the original diagnosis were not stated. In both cases, family members clearly reported that the patient made positive but inconsistent behavioural responses to questions. Within the programme, one of these patients was filmed responding to a question from his mother by raising his thumb and the other seemed to turn his head purposefully in response to having his earphones put on. These localising and discriminating

features suggest that these patients were probably in a minimally conscious and not a vegetative state.

Studies of diagnostic accuracy show that more than 40% of patients in a minimally conscious state are misdiagnosed initially as being in a vegetative state. Systematic clinical evaluation of behaviours and responsiveness, assisted by structured assessments administered serially over time, may lead to a more accurate diagnosis.^{3 4} It is essential to exclude factors that may impede recovery, such as chronic hydrocephalus. Techniques for assessing disorders of consciousness vary between countries.⁵ In the United States, the Coma Recovery Scale-Revised (CRS-R) is widely used as a standardised assessment tool.⁶ In the United Kingdom, the Wessex Head Injury Matrix (WHIM)⁷ and the Sensory Modality Rehabilitation and Assessment Technique (SMART),⁸ which provides a more comprehensive evaluation of responses to five different sensory modalities, are more commonly used. Each tool can give slightly different results, and congruence between them requires further investigation.

Unsurprisingly, patients in a minimally conscious state often interact more readily with family and friends than they do with professionals. SMART-INFORMS is an important component of SMART that records the level of responses observed by family and friends. Video recordings of these interactions made by relatives may help the evaluation process by giving clinicians the opportunity to determine whether responses are truly localising and discriminating, or if they simply represent reflexive or spontaneous activity.

The *Panorama* programme also featured a patient who was diagnosed clinically as being in a vegetative state after prolonged multidisciplinary clinical evaluation at the Royal Hospital for Neuro-disability in the UK. In his case, fMRI showed no evidence of cognitive interaction.

There are well documented cases where patients in a vegetative state, diagnosed according to current standards, have shown evidence of cortical responses on fMRI,⁹ but the 20% figure quoted in the programme is not supported by evidence. In the largest published series (a convenience sample of 54 patients),¹⁰ one patient in a minimally conscious state and four in a vegetative state (9% in total) generated fMRI activity in response to motor

or spatial imagery. The ability to respond to specific questions using this technique, however, has been reported in just one other case.¹⁰

The possibility that fMRI might open up potential avenues of interaction for patients with profound communication deficits is an important finding, but the paradigms for testing and interpreting the findings are still to be determined. About one in five normal volunteers cannot generate fMRI activity on motor imagery tasks, so negative results in patients do not necessarily indicate lack of awareness.

fMRI is not suitable for all patients with reduced consciousness. Patients with metalwork, with frequent spontaneous movements, and those unable to lie flat are excluded. Alternative techniques for use at the bedside, or that require no active participation by the patient, are therefore being explored.^{11 12}

Although the evidence so far is encouraging, it is still based on small numbers of highly selected patients. It is currently unclear whether fMRI can provide additional diagnostic information to that gained by careful and systematic behavioural assessment, or whether technological approaches have any prognostic use or could contribute to decision making in these patients.¹³ Currently, fMRI techniques are not sufficiently developed to form part of the standard assessment and should be applied only in the context of a registered national research programme. Imaging and other techniques must be accompanied by optimised clinical evaluation. This includes expert multidisciplinary assessment by appropriately experienced staff in specialist centres, conducted systematically using validated structured tools, and repeated over adequate periods of time.^{3 4}

Guidelines for the management of patients in vegetative or minimally conscious states are being prepared by the Royal College of Physicians (due for publication in 2013). They will deal with the evidence base for different approaches to assessment in more detail and make recommendations for management through all stages of care, including sympathetic and responsible communication with patients' families and friends.

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- News: Obama and Romney disagree on contraception in second presidential debate (*BMJ* 2012;345:e7112)
- News: Free birth control cuts rates of unwanted pregnancies and abortions in US (*BMJ* 2012;345:e6763)
- News: Democrats vow to strengthen Medicare and Medicaid and preserve women's health rights (*BMJ* 2012;345:e6103)

Contraception policies in the US are reactionary

Time to forget political posturing and focus on the evidence of gains from preventing unwanted pregnancies

Michelle J Hindin associate professor mhindin@jhsph.edu

Michele R Decker assistant professor

Caroline Moreau assistant professor, Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA

Over the past decade in the United States, contraception has become a political issue rather than a public health prevention strategy, despite evidence that easier access to contraception reduces unintended pregnancy,¹ thereby improving women's and children's health. Only 5% of unintended pregnancies occur among the two thirds of US women at risk of unintended pregnancy who practice contraception consistently and correctly.² In 2006 alone, publicly funded contraception averted an estimated 1.94 million unintended pregnancies, which translated into about 860 000 unintended births, 810 000 abortions, and 270 000 miscarriages.³ Contraceptive services are cost effective. Every \$1 (£0.62; €0.77) spent on public funding for family planning saves \$3.74 in pregnancy related costs, with annual savings of \$19.3bn.⁴ Protection against unintended pregnancy, particularly in adolescents, leads to gains in education, employment, and wealth in the longer term.⁵ Contraception also prevents unintended pregnancy in the 18% of women who experience sexual violence and lack control over when and with whom they have sex.⁶

Nevertheless, in the US, at federal and state levels, essential contraceptive services—including publicly funded clinics, insurance coverage for clinical contraceptive services and effective contraceptive methods, and over-the-counter contraceptives—have been seriously threatened. Restrictive policies, both proposed and enacted, are eroding women's and men's financial and physical access to contraception. The Affordable Care Act met serious resistance because of its proposed mandate for coverage of contraception by employer funded insurance. In response, the latest Health and Human Services Funding Bill for the fiscal year 2013 contains a provision ensuring “conscience protections” for organizations, which allows them to deny contraceptive coverage for their employees on moral grounds. In 2011, the Obama administration over-ruled the recommendation from the Food and Drug Administration to



Easy access to contraception is fiercely debated in the US

allow over-the counter (non-prescription) status for emergency contraception for women under the age of 17 years. The House of Representatives has repeatedly considered bills to cut all funding to Title X, a program enacted in 1970 to provide comprehensive contraceptive services and reproductive healthcare to all in need.

Such political opposition is fueled by “moral” opposition to contraception. Some equate contraception with abortion, the idea being that preventing a fertilized egg from implanting in the uterine wall is synonymous with induced abortion. Yet prevention of implantation is not the main mechanism by which most contraceptive methods work—rather, they largely prevent fertilization by changing the cervical environment, and in some cases suppress ovulation altogether. Others have argued that ready access to contraception leads to “promiscuity.” Studies dating back to the 1970s found no link between oral contraception and early premarital sex.⁷ More recent studies show that the availability of emergency contraception does not increase risky sexual behaviors.⁸ The promiscuity argument is even more dubious and suggests a dangerous double standard when considered in light of the rapid approval by the FDA and widespread availability of drugs to enhance men's sexual performance.

Continued disregard for the advantages of contraception may have important negative consequences for health and wellbeing in the US in the long run. The US performs poorly on reproductive health outcomes compared with other economi-

cally advanced nations. Despite recent reductions, more adolescent girls become pregnant in the US annually than anywhere else in the developed world,⁹ with a teenage birthrate 56% higher than that of the highest western European nation (the United Kingdom).⁹

Globally, policies to advance family planning are being rolled out and funded. Free contraception is part of national health insurance plans in countries from the UK to South Africa. Over-the-counter access to oral contraceptives, including emergency contraception, is widespread. In sub-Saharan Africa, task shifting interventions are under way to allow trained lower cadre health workers to provide injectable contraception to women who cannot access facilities staffed by nurses and doctors.¹⁰ Task shifting enables contraceptives to be delivered outside of health facilities, greatly increasing access, particularly for women and couples who live far away from the nearest health facility. In July 2012, at the London Family Planning Summit, foundations, country governments, and organizations pledged more than \$2.6bn to ensure that 120 million women have access to contraception by 2020.¹¹ Although the US did not pledge, through the United States Agency for International Development, the US is one of the largest donors for contraception for low income and middle income countries. At the same time, the US government continues to take backward steps away from ensuring that its own people have access to affordable contraception.

The time has come for the US to respond to evidence and join the international community in realizing the social, economic, and public health gains of ensuring access to contraception. Although voters spoke and removed from office many who most vocally campaigned against contraception in the 2012 US elections, opposition remains among many elected federal and state officials. Americans must not be complacent. The United Nations Population Fund's 2012 annual report declared that access to contraception is a fundamental human right.¹² Americans must demand policies that ensure financial and physical access to contraception for all.

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► Editorial: Translational research

(*BMJ* 2008;337:a863)

► Feature: Lost without translation?

(*BMJ* 2010;341:c4363)

**Success in an animal model
does not guarantee equal
success when treatments are
used in human subjects**

Improving the process of translational research

The application of reporting standards may lead to more useful animal studies

H Bart van der Worp neurologist, Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Heidelberglaan 100, 3584CX Utrecht, Netherlands h.b.vanderworp@umcutrecht.nl

Peter A G Sandercock professor of medical neurology and director, Edinburgh Neuroscience, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh, UK

Empirical evidence that deficiencies in the reporting of clinical studies are associated with overstatement of the efficacy of the treatment under study led to the development of the CONSORT statement for the reporting of randomized controlled clinical trials.¹ Accumulating evidence suggests that deficiencies in the reporting of animal studies may have a similar effect.²

In response to concerns that lack of transparency in the reporting of animal studies may have made the process of translation from bench to bedside inefficient and wasteful, the US National Institute of Neurological Disorders and Stroke (NINDS) convened a meeting of major stakeholders in translational research in June this year.³ Their aim was to develop recommendations for improving the reporting of the results of animal research, and recently they published in *Nature* a core set of reporting standards for animal studies.³ The group comprised academic researchers and educators, reviewers, journal editors, and representatives from funding agencies, disease advocacy communities, and the drug industry. The core standards deserve close attention.

Animal studies have been important in the development of many available medical treatment strategies. However, success in an animal model does not guarantee equal success when treatments are used in human subjects. On the contrary, most treatments that have been reported as highly promising in animal models have been disappointing when tested in clinical trials.² Successful translation of preclinical success into clinically effective treatments depends in part on reports of animal studies providing sufficient detail of the design, methods, conduct, and results to allow other researchers

to evaluate (and replicate) the findings. Deficient reporting may obscure important limitations of a study, and clinical trials based on positive but unreliable findings from flawed animal studies are likely to be unsuccessful or even lead to harm.

According to the recently published core set of reporting standards, investigators should at least report on sample size estimation, whether and how animals were randomized, whether investigators were blind to the treatment, and the handling of data. The last item includes the reporting of inclusion and exclusion criteria, of animals excluded from the analyses, and of predefined primary outcome measures. For clinical investigators and readers of clinical articles, who have been familiar with the CONSORT guidelines since 1996, these recommendations may seem superfluous. However, systematic reviews of interventions tested in animal models have consistently shown that reporting is often inadequate. For example, randomization and blinding were reported in a minority of articles, and sample size calculations, specified inclusion and exclusion criteria, and information on animals excluded from the analyses were reported in an often small minority.²⁻⁴

The development of the NINDS standards builds on important previous work.⁵⁻⁷ Comparable reporting guidelines have been published before, of which the recent ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines have probably been endorsed most broadly—more than 160 journals have now incorporated ARRIVE in their instructions for authors (www.nc3rs.org.uk/page.asp?id=1796).⁸ The ARRIVE guidelines were developed using the CONSORT statement as their foundation and are therefore intuitive to clinical readers. Their 20 item checklist is somewhat more inclusive than the NINDS standards.

Of course, deficient reporting alone cannot be held responsible for the failure of results from animal studies to translate to the clinic. Several other contributing factors have been proposed. Firstly, poor design or conduct of animal studies may have resulted in spuriously positive results. Secondly, lack of power, or the use of lower doses

in human subjects than the doses that were most effective in animals, may have led to negative results in clinical trials. Thirdly, some animal models may not faithfully reflect disease pathology in humans.²⁻⁹ Finally, bias towards publication of positive findings rather than neutral or negative results may lead to an overestimation of the efficacy of new treatments.¹⁰

Although the endorsement of reporting standards is a start, improving the quality of reporting will not be sufficient to reduce translational failure. We believe that a broader introduction of multicenter animal studies has a role to play too.¹¹ Multicenter randomized clinical trials have many features that maximize transparency: prospective registration of the study, publication of the protocol before data collection (including the primary measure of outcome and the data analysis strategy), many independent sites (with a possibility of comparing results between sites), and independent data monitoring. Few animal studies can currently boast these attributes. It is instructive that an early multicenter animal study identified major research misconduct in one of the centers (a very distinguished academic center).¹² There is therefore a case for more multicenter animal studies to adopt the key features of clinical trials. Not only might this increase the efficiency of translational research (larger sample size, replication, and cross validation of results between centers), but it may also allay concerns about transparency.

There is only circumstantial evidence that deficient reporting of animal studies leads to overstatement of efficacy and thereby contributes to translational failure. The proof of the pudding is in the eating. Only time will tell whether improvements in the reporting of animal studies will improve translational efficiency.

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The most powerful predictor of adverse outcome remains birth at a lower gestational age

Long term follow-up of extremely preterm neonates

Good outcomes data are needed now more than ever

Floris Groenendaal associate professor of neonatology, Wilhelmina Children's Hospital

Cuno Uiterwaal associate professor of clinical epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Netherlands C.S.P.M.Uiterwaal@umcutrecht.nl

Cohort studies have been used to investigate morbidity and mortality in preterm neonates since the early days of neonatal intensive care and have shown adverse sequelae in many of those who survive.¹ Such studies have identified many perinatal risk factors that affect outcome. This has improved quality of care and led to a decrease in the incidence and severity of cerebral palsy in preterm neonates.² Studies of children followed up into puberty identified risks of abnormalities in psychological development and behaviour associated with preterm birth that were not detectable at younger ages.³ Advances in neonatal intensive care in the 1990s mean that neonates who are born as early as 22-23 weeks' gestational age are now offered active treatment. Two linked research papers from the EPICure 2 study look at trends in mortality and long term morbidity in this highly vulnerable group.^{4, 5}

Costeloe and colleagues report on survival and neonatal morbidity for babies born at 22-26 weeks' gestation in England during 2006 and assess changes in survival and major morbidity since 1995 for babies born at 22-25 weeks of gestation.⁴ They explored whether more emphasis on evidence based interventions in preterm neonates and increased centralisation of delivery and intensive care treatment for the most premature babies had reduced mortality in neonates born before 26 weeks of gestation. They found that survival of babies born at 22-25 weeks of gestation had improved, specifically during the first week of life.

However, patterns of major morbidity and proportions of survivors with morbidity had not changed, and a greater absolute number of neonates had major morbidity. Fifty one per cent of survivors born at 26 weeks had major morbidity, and this increased to 77% for babies born at 23 weeks. Moreover, predictors of short term outcome had not changed substantially. Striking findings were the low reported proportion of neonates transferred antenatally to a



More babies survive but the burden of serious morbidity is high

tertiary centre, changing trends in ethnicity for extremely preterm neonates, the high proportion of patients with chronic lung disease and surgery for retinopathy of prematurity, and the high proportion of surviving patients with abnormalities on cerebral ultrasonography.

Moore and colleagues, using the same cohorts, compared rates of neurological and developmental impairment at the age of 3 years for extremely preterm babies.⁵ Because of the high rates of neurological sequelae reported in the earlier cohort (EPICure), the authors hypothesised that increasing survival of extremely low gestational age babies would lead to an absolute increase in neurological and developmental problems if the burden of major morbidity remained the same. They found that the prevalence of important adverse neurological and developmental outcomes had indeed not improved over the period between the two studies.

These authors have undertaken a huge research project. Causal explanations are obviously challenging. The authors considered the recent changes that have occurred in the organisation of neonatal care of premature babies, and the care itself, but other changes may have influenced the studies' findings. Comparison of longer term neurological and developmental outcomes was hampered by changes that had occurred in measurements, but an even

more important factor was the limited access to follow-up data because of legislation. A substantial number of the 2006 cohort were lost to follow-up, which might have made the two cohorts less comparable. However, the investigators used all available means to deal with these difficulties, and their findings seem to be the best available estimates of outcome.

The findings of these studies have substantial clinical implications. The most powerful predictor of adverse outcome remains birth at a lower gestational age. Although mortality for extremely preterm neonates declined between 1995 and 2006, the rate of serious sequelae did not. Therefore, a higher absolute number of affected babies need lifelong special care. Out of every 100 neonates born at 24 weeks, 60 will die despite intensive care, and of the 40 survivors 12 will have serious impairments.⁵ Only 11 out of 100 neonates born at 23 weeks will survive without impairments. Impairments were still present in 20% of neonates born at a gestational age of 26 weeks,⁵ who were used as the comparator group in Costeloe and colleagues' study.⁴ Cognitive development seems to be most affected. Similar outcome data are seen in the Netherlands, and neonatal intensive care is therefore not offered routinely to neonates born before 24 completed weeks' gestation. Cranial magnetic resonance imaging does not help predict which patients will have long term intellectual or behavioural impairment, so children born extremely prematurely must be carefully followed up long term in dedicated clinics.

It is a matter of concern that the authors of the current studies had limited access to follow-up data, because studies that can accurately estimate outcome are of utmost importance for counselling families and improving the planning of care offered by healthcare providers and society. Excellent follow-up is an essential part of neonatal intensive care, as the EPICure studies have elegantly shown. Access to outcomes data is needed now more than ever.

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