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Prolonged disorders of consciousness: a critical evaluation of the new UK guidelines

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ABSTRACT

Earlier this year, the Royal College of Physicians in the UK published national guidelines on the management of patients with prolonged disorders of consciousness, updating their 2013 guidance 'particularly in relation to recent developments in assessment and management and … changes in the law governing … the withdrawal of clinically assisted nutrition and hydration'. The report's primary focus is on patients who could live for many years with treatment and care. This update, by a neurologist, an imaging neuroscientist, and a lawyer-ethicist, questions the document's rejection of any significant role for neuroimaging techniques including functional MRI and/or bedside EEG to detect covert consciousness in such patients. We find the reasons for this rejection unconvincing, given (i) the significant advances made in the use of this technology in recent years; and (ii) the wider scope for its use envisaged by the earlier (2018) guidelines issued by the American Academy of Neurology. We suggest that, since around one in five patients diagnosed with prolonged disorders of consciousness are in fact conscious enough to follow commands in a neuroimaging context (i.e. those who are 'covertly conscious' or those with 'cognitive motor dissociation'), and given the clinical, ethical and legal importance of determining whether patients with prolonged disorders of consciousness are legally competent or at least able to express their views and feelings, the guidance from the Royal College of Physicians requires urgent review.

Current UK guidelines on the management of patients with prolonged disorders of consciousness (PDOC) explicitly exclude investigations to detect covert consciousness, contrasting with 2018 US guidance. Scolding et al. argue that, since one in five PDOC patients are in fact conscious, the UK guidance requires urgent review.

Keywords: prolonged disorders of consciousness ; functional imaging ; consciousness ; EEG

Introduction

Earlier this year the Royal College of Physicians (RCP) published national clinical guidelines[1] on prolonged disorders of consciousness (PDOC) (Box 1). The report was the product of a working party charged to update and clarify the RCP's guidance of 2013,[3] 'particularly in relation to recent developments in assessment and management and … changes in the law governing … the withdrawal of clinically assisted nutrition and hydration'. It leans 'substantially' on the 2018 joint RCP and British Medical Association guidance for clinically assisted nutrition and hydration in adults who lack capacity.[4] The report's primary focus is on patients who could live for many years with treatment and

care, and centres on their 'best interests'. (A detailed discussion of 'best interests' is beyond the scope of this article; suffice it to say that the understanding of 'best interests' adopted by the joint guidance has been criticized.[5]) The guidance aims to achieve a more consistent approach to diagnosis and management of patients with PDOC and is scheduled for review in 2025. [AQ2]

This update, by a neurologist (N.S.), an imaging neuroscientist (A.M.O.), and a lawyer-ethicist (J.K.), questions the very limited role envisaged by the guidance for the use of neuroimaging techniques including functional MRI (fMRI) and bedside EEG as diagnostic and prognostic tools for patients with PDOC. We find the guidance's reasons for this limited role unconvincing, not least given (i) the significant advances made in the use of this technology in recent years; and (ii) the wider scope for its use envisaged by the guidelines issued by the American Academy of Neurology (AAN) in 2018.[2] We suggest that, in the light of neuroimaging research indicating that around one in five patients diagnosed with PDOC are in fact conscious enough to follow commands in a neuroimaging context (those who are 'covertly conscious' or those with 'cognitive motor dissociation'[6]) and given the clinical, ethical and legal importance of determining whether patients with PDOC are legally competent or at least able to express their views and feelings, the RCP guidance requires urgent review.

The Royal College of Physicians guidance

The (200-page) RCP guidelines note that the diagnosis of vegetative state (VS) or minimally conscious state (MCS) 'rests on clinical observation of behaviours that may suggest awareness of self and the environment'. They stress that misdiagnosis remains a serious problem, principally because of either diagnostic error or a change in the patient's condition over time. Evaluation is therefore required by a multidisciplinary team of clinicians expert in assessing cognition, communication and motor function in the context of PDOC.

The guidance recommends that a standard clinical evaluation should include a detailed clinical history, a review of medication, and detailed neurological evaluation by an experienced clinician. After the clinical evaluation 'no standard or routine investigations are required for patients in PDOC'. (The general principle espoused is that investigations are only appropriate if the result would alter clinical management and is in the patient's best interests.)

Turning to brain imaging, the RCP states that standard imaging (CT or MRI) undertaken in the acute phase of care should be reviewed to ensure that the nature, extent and location of brain damage are known. However, 'once a patient is in a prolonged DOC … repeat imaging is not routinely required'—scanning is only needed 'to exclude undiagnosed or new specific, structural, operable causes of the state, or if the doctor thinks it justified to determine the extent and location of brain damage for clinical decision-making or to aid in giving a diagnosis'.

The guidance continues that 'more sophisticated imaging techniques such as fMRI and PET scans etc., do not form part of routine clinical evaluation for patients with PDOC'.

The guidance raises seven objections to the use of fMRI:

1. fMRI paradigms are costly to implement and 'not present in most clinical MRI centres';
2. 'The clinical significance of the imagery findings [*sic*] has not yet been established';
3. Particular caution is required when interpreting negative results: about one in five normal volunteers is unable to generate fMRI activity on motor imagery tasks;
4. fMRI is time-consuming;
5. Many patients are unsuitable, including those with implanted non-MRI compatible metal work; patients unable to lie supine for at least an hour; those who require regular suctioning; and those who have involuntary movements such as spasm, teeth grinding or regular head rotation/extension, which have obviously detrimental effects on the quality of data;
6. The prognostic significance of the findings in 'a small cohort of patients who present as VS [who] demonstrate covert responses within an fMRI scanner' is 'as yet unclear', which:
7. raises the ethical dilemma of whether or not and how to disclose this information to clinicians and to patients' families.

The guidance comments that 'passive examinations'—diffusion tensor imaging (DTI) and ^{18}F-fluorodeoxyglucose PET scanning (FDG-PET)—'may have potentially greater clinical application' than activation studies 'because imag-

ing may in future be undertaken in non-research/non-specialist centres, though they are not currently widely available in the UK'.

The guidance concludes that although more advanced brain imaging—and electrophysiology—will continue to be an important focus for research, they cannot yet 'be considered to be part of routine clinical practice'. More work is required to improve our understanding of how these investigations should be interpreted, and whether or how they could contribute to decision-making. At present 'it remains unclear whether they are capable of informing the diagnosis beyond detailed clinical and behavioural assessment over time, and whether they have any prognostic utility in the early stages post-brain-injury' (our emphasis). Currently, therefore, the guidance adds, these more hi-tech investigations do not form part of the standard assessment battery, nor do they represent a 'practicable step' required by section 1(3) of the Mental Capacity Act 2005 to support a person's capacity to make relevant decisions. They should be applied only in the context of a registered research programme.

The American Academy of Neurology guidance

The (11-page) AAN document[2] strikes a different tone from the outset. It rejects the unqualified term 'vegetative state', preferring 'vegetative state/unresponsive wakefulness syndrome' (VS/UWS). It also prefers the adjective 'chronic' to 'permanent' in light of the frequency with which patients recover consciousness, whether after 3 months in cases of non-traumatic VS/UWS or 12 months in patients with traumatic VS/UWS.[7–9]

As with the RCP document, the AAN guidance emphasizes the importance of accurate clinical diagnosis and recommends the use of standardized assessment procedures, such as the Coma Recovery Scale–Revised.[1,2] The American guidance also appears at least superficially to concur with the RCP document in suggesting that 'there is insufficient evidence to confirm or refute the "routine" [our emphasis] clinical use of functional neuroimaging or [sophisticated EEG-based approaches] … to detect conscious awareness in [VS/UWS] patients', and that the 'widespread use of multimodal imaging is unlikely to change the diagnosis in most patients diagnosed with VS/UWS'.

Importantly, however, the AAN guidance breaks new ground in formally recommending fMRI or advanced electrophysiological testing in certain circumstances—'where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioural assessments, or where confounders to a valid clinical diagnostic assessment are identified'. Here, specialized functional imaging or electrophysiological studies may be used to seek 'awareness not identified on neurobehavioural assessment that might prompt consideration of an alternative diagnosis' (Recommendation 2e).[2] No less significantly, the AAN guidance also recommends that in cases where a discrepancy emerges—clinical examination showing no evidence of consciousness but fMRI or electrophysiological testing implying preserved conscious awareness—patient management be altered (Recommendation 2f).[2] Here, frequent neurobehavioural re-evaluations may be conducted, and decisions to reduce rehabilitation treatment may be delayed.

The novel incorporation of these advanced techniques is justified, the document indicates, by the increasing body of research showing that individuals without signs of awareness on behavioural/clinical evaluations may have positive findings using other modalities such as fMRI, PET scans or electrophysiological studies.[10,11] This is at least partly explained by injury sequelae (such as severe spasticity), combined with the inconsistency or subtlety of the behavioural (i.e. clinical) findings, confounding and compromising behavioural assessment. One functional neuroimaging study (the largest) reported that 32% of patients diagnosed as unresponsive on clinical grounds showed brain activity compatible with (minimal) consciousness on at least one functional neuroimaging test and that 69% of these subsequently recovered consciousness.[12] In another study, using high-density EEG, 25 of 75 recordings of patients in VW/UWS were suggestive of MCS, and there was a greater recovery of consciousness among those categorised as MCS than VW/UWS on the EEG.[13] Finally, Claassen et al.[14] recently reported that 16 of 104 (15%) behaviourally non-responsive patients exhibited brain activity that was detectible using EEG at a median of 4 days after injury. While not yet within the window for a diagnosis of PDOC, many of these patients did subsequently pass through that window over the next 12 months during which time seven (44%) recovered to the extent that they were able to function independently for 8 h.

Discussion

The AAN guidance adopts a cautious but clearly more positive stance than the RCP toward the use of neuroimaging in PDOC and has been described as 'a revolution in the practice of neurology that brings such investigations one step closer to incorporation in the routine assessment of DOC patients'.[6]

The seven reasons given in the RCP guidance for its more conservative position seem weak. Although it lists cost first (which we address later), surely the foremost consideration must be clinical value and significance (ii and vi in the list above), which the RCP guidance indicates 'has not been established'. We dispute this and concur with the AAN guidance which—2 years earlier—found the clinical significance of advanced neuroimaging in PDOC to have become increasingly clear. It can, simply, alter the diagnosis.[11]

The RCP assertions that only 'a small cohort' of VS patients have demonstrated covert responses within an fMRI scanner, and that the prognostic significance of these findings is unclear, are difficult to square with the published research. A 2016 systematic review and meta-analysis[15] of 37 studies involving more than a thousand patients showed some 20% to be covertly aware, implying that 'some tens of thousands of patients worldwide have been erroneously assumed to be "awake but unaware", sometimes for decades at a time'.[16] A more recent EEG-based study indicated that 40% of VS/UWS patients were able to follow commands consistently enough to be classified as aware.[17] This is hardly a 'small cohort'.

As for the alleged lack of prognostic value (point vi), we mentioned above some of the evidence cited in the AAN guidance refuting this: over two-thirds of unresponsive individuals in whom functional neuroimaging implied covert consciousness subsequently recovered consciousness.[12] Functional MRI can therefore predict who is most likely to recover.[18] Di et al.[19] reviewed 15 published studies involving 48 patients and found that functional neuroimaging could predict recovery from VS with 93% specificity and 69% sensitivity. The recent EEG-based study showed that 85% of patients identified as capable of an EEG neural command-following task exhibited improvement 3 months later.[17] While it is important not to conflate improvement with recovery, this is nonetheless a statistically significant difference compared to those not showing such covert awareness.

The RCP's view that DTI and FDG-PET may have potentially greater clinical applications than activation studies 'because imaging may in future be undertaken in non-research/non-specialist centres, though they are not currently widely available in the UK' is also difficult to sustain. In fact, almost the opposite is true: PET scanning is now widely available in the UK, but there is no evidence those techniques have any clinical application in the context of PDOC. Further, it is much harder to obtain usable data from DTI than from fMRI.[20] Importantly, it should also be noted that there are more than 400 MRI scanners in the UK alone, and it has been clearly shown that most are capable of performing fMRI.[21]

What of the guidance's concern (point iii) about the risk of false negatives because about one in five normal volunteers are unable to generate fMRI activity on motor imagery tasks? This assertion, unreferenced and unsubstantiated,[1] is questionable. In A.O.'s experience of upwards of 500 healthy individuals scanned, only around 1% fail to 'generate fMRI activity in motor imagery tasks'.[22]

In any event, the risk of false negatives is not an objection to their use: it is positive, not negative, results that influence action. If a scan shows no evidence of consciousness, the patient is no worse off. If, by contrast, a scan would have detected consciousness but is not performed, the patient is significantly worse off.

As for the 'time-consuming' objection (point iv), it is question-begging: the same could be said of many other tests or treatments whose time is warranted by their proven or potential value. Moreover, fMRI motor imagery takes only 5.5 min to generate a meaningful result. And the unsuitability of some patients (point v) is simply irrelevant to the suitability of others (as well as applying to any form of scanning in these patients).

Concerning cost (point i), both fMRI and PET are quite widely available and are not excessively costly, particularly in comparison to the enormous costs of long-term care of patients in PDOC. The EEG-technology used by Pan et al.[6,16] is even more cost-effective than fMRI (arguably the gold standard for detecting covert consciousness) and is portable, meaning it can be deployed at the bedside and/or used for patients with a contraindication for fMRI. The weaknesses of objections i and iv are aggravated by the guidance's underestimate of the potential benefits of neuroimaging: the greater the potential benefit, the more justified the expenditure of time and resources.[23] In most cases the

benefit of assessing DOC patients with investigational neuroimaging would outweigh the costs.[6] Further, the RCP guidance group is not notable for its expertise in health economics; issues of cost and cost-effectiveness in a clinical guidance document aimed primarily at the National Health Service are surely a matter for the National Institute for Health and Care Excellence.

Lastly, the postulated ethical dilemma (point vii)—raised by the (alleged) lack of clarity surrounding the prognostic significance of covert responses—concerning whether and how to disclose this information to clinicians and families, is scarcely an argument against generating the information about the patient's condition and consciousness. This remains the case whether or not the information generated is likely to be clear. The ethical issues relating to fMRI and covert consciousness have in fact been the subject of considerable study.[6,24,25] There are various areas of medicine in which clinicians face the challenge of communicating information which is either unclear or complex, as in genetic counselling. Clinicians have a duty to provide relatives with the available evidence (just as, we may add, they would have a duty to provide a competent patient with that evidence). One of the authors (A.O.) has found that the information has, almost without exception, been received gratefully and with clear understanding. Approaches to imparting complex test results to patients have been developed in other medical situations: 'disclosing investigational neuroimaging data in a way that is responsive to patient values could assist families in finding meaning in the results while also forestalling false hope'.[6]

We now turn, more positively, to several ethical reasons that favour the use of neuroimaging and EEG to determine if patients in PDOC are covertly aware.

First, given the evidence that a substantial minority of patients diagnosed as PDOC—around one in five[10,25,26]—are in fact covertly conscious, if they are autonomous then the ethical principle of respect for autonomy requires clinicians to obtain their informed consent to any treatment. It may of course be very challenging to determine whether a patient in PDOC is autonomous if the patient is capable only of answering 'Yes' or 'No' questions by activating different parts of the brain, but it may not be impossible Box 2). (The ability of 'locked-in' patients to communicate may also be very limited. Indeed, many ordinary patients may signal their consent with rudimentary answers or the silent signing of a form.) This is clearly a difficult issue meriting further reflection. However, even if a patient in PDOC is not autonomous, they may nevertheless be capable of expressing their wishes and feelings, thereby providing useful input to help guide decision-making by clinicians in consultation with relatives.[6]

Second, to fail to test for consciousness by fMRI or EEG is to deprive covertly conscious patients of an important benefit: the opportunity to communicate with their clinical team and relatives and request that life-preserving treatment be maintained and rehabilitation be progressed. Not to scan conscious patients is to abandon them. This abandonment could result in life-preserving treatment and tube-feeding being withdrawn. Accurate prognosis is important, as most decisions to withdraw life-preserving treatment are made within 72 h of injury.[28] Abandonment could also result in condemnation to a life of mental solitude. Is it not unethical, indeed cruel, for clinicians to condemn any patient to the mental equivalent of solitary confinement? To apply the Golden Rule of ethics, would we want, if diagnosed in PDOC, to be deprived of the opportunity to be tested by neuroimaging or EEG for evidence of consciousness?

Third, not only may the use of such technologies be of considerable benefit to a patient, it may also, even if negative, bring relief and reassurance to their relatives. It is sometimes cautioned that disclosing evidence that the patient is conscious will raise false hopes, but this is really an objection to raising false hopes—a risk that applies across medicine—not to disclosing relevant information.[6,29] And, by keeping the information secret, one runs the risk of creating false despair. Communication between doctor, patient and relatives should be candid, not clandestine. The guidance notes that family and friends may be actively involved in assessment and care of the patient and play a key role in the clinical decision-making process as they provide important insights into the character, beliefs and likely wishes of the patient. It adds: 'The provision of timely information, education and support for families, and consultation with them, is therefore a critical factor for successful management and appropriate decision-making regarding care and treatment', and 'all families should be informed about available treatments and investigations'.[1] How can relatives discharge these important roles if they are not informed of the distinct possibility that a scan may show the patient to be fully or partly conscious?

Fourth, not only ethics but also law argues in favour of testing for consciousness. If the patient is in fact legally competent, then they are the appropriate decision-maker. The Mental Capacity Act 2005 (MCA) states that there is a presumption of capacity: a person must be assumed to have capacity unless it is established that they lack capacity.[27] Moreover, a person is not to be treated as unable to make a decision unless 'all practicable steps' to help him do so have been taken [Section 1(3)]. Although the RCP guidance asserts that neuroimaging and electrophysiology are not a practicable step, this assertion is, in the light of our above criticisms, highly questionable. By showing that a patient retains awareness and is able to communicate, albeit in a rudimentary fashion, techniques like fMRI certainly represent practical steps towards helping the patient make a decision and, at the very least, can establish that a patient has potential in this regard. By contrast, failure to use such techniques where they are available not only presumes lack of capacity, but also removes any possibility that some level of residual capacity might be found.

Even if a patient is conscious but not competent, their wishes and feelings are nevertheless relevant. The MCA requires that acts done, or decisions made, for or on behalf of a person who lacks capacity must be done or made in his 'best interests' [Section 1(5)). In determining what is in a patient's best interests the decision-maker must, 'so far as is reasonably practicable', permit and encourage the person to participate, or to improve his ability to participate, as fully as possible in any act done for him and any decision affecting him [Section 4(4)]. The decision-maker must consider 'so far as is reasonably ascertainable' the person's past and present wishes and feelings; the beliefs and values that would be likely to influence his decision if he had capacity, and the other factors he would be likely to consider if able to do so [Section 4(6)]. The Supreme Court has indicated that decision-makers should consider the particular patient at the particular time and try to put themselves in the patient's place to determine what the patient's attitude would likely be[30] UKSC 67, 2013).

A good case can therefore surely be made that neuroimaging is, at least in some if not all cases, a practicable step to determine whether an individual in PDOC is competent and, if they are not competent, that it is nevertheless a reasonably practicable means of permitting or encouraging the patient to participate in decision-making, and of ascertaining his or her wishes and feelings.

Finally, there are human rights implications of not scanning those in PDOC. The withdrawal of life-sustaining treatment and care from patients who, if scanned and found conscious, would have wanted to have their treatment and care continued, may breach their right to life under Article 2 of the European Convention on Human Rights. Moreover, States Parties to the UN Convention on the Rights of Persons with Disabilities (a Convention that the UK has ratified) undertake to ensure and protect the full realization of all human rights and fundamental freedoms for all persons with disabilities[31] without discrimination of any kind on the basis of disability (Article 4.1), including the effective enjoyment of the right to life on an equal basis with others (Article 10); the right not to be subjected to cruel, inhuman or degrading treatment (Article 15), and the right to enjoyment of the highest standard of health without discrimination on the basis of disability (Article 25). States Parties also undertake to prevent discriminatory denial of health care or health services or food and fluids on the basis of disability [Article 25(f)); to take appropriate measures to provide access by persons with disabilities to the support they may require to exercise their legal capacity (Article 12.3); to promote the development, availability and use of new technologies, including information and communication technologies suitable for persons with disabilities [Article 4.1(g)], and to promote the availability and use of assistive devices and technologies, designed for persons with disabilities, as they relate to habilitation and rehabilitation (Article 26.3).

The weakness of the RCP's assessment of the potential value of neuroimaging may reflect the under-representation in its guideline-development group of neuroscientists and, in particular, of experts in neuroimaging. Whatever the explanation, its views on the value of neuroimaging and EEG in PDOC merit urgent reconsideration. Whilst research into this area is continuing apace, we believe there is already sufficient evidence to warrant a revision of the UK guidance so as to bring it into closer alignment with the US guidance.

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Competing interests

The authors report no competing interests.

Box 1 Definitions[1,2]

Prolonged Disorders Of Consciousness[1]: Defined in the guidance as 'any disorder of consciousness that has continued for at least four weeks following sudden onset brain injury'.

Vegetative[a] State[1]: 'A state of wakefulness without awareness in which there is preserved capacity for spontaneous or stimulus-induced arousal—evidenced by sleep-wake cycles and a range of reflexive and spontaneous behaviours'.

Minimally Conscious State[1]: 'A state of severely altered consciousness in which minimal but clearly discernable behavioural evidence of self or environmental awareness is demonstrated.' Since 2013 the word 'persistent' VS or MCS has been replaced by 'continuing'. 'Permanent'[b] VS or MCS may be diagnosed only after the patient has been in VS or MCS for at least 6 months and when the recovery of consciousness has become highly improbable.

VS/UWS (Vegetative State or Unresponsive Wakefulness Syndrome)[2]: The AAN-preferred acronym, rather than 'VS' alone.

[a]The AAN also rejected the adjective 'permanent' and proposed instead that 'chronic' was more accurate. The AAN's substantial evidence-based review found evidence that, even looking at a 12 month cut-off (note that the UK document uses 6 months for 'permanent'), 'a substantial minority will recover consciousness beyond this time frame'; they therefore conclude that 'continued use of the term permanent VS is not justified'—further evidence that the UK guidance appears behind the step of the science.

[b]The RCP guidance defends the use of the adjective 'vegetative', despite noting a growing sense of discomfort because the word is thought to connote being a vegetable, observing that the notion has its origins with Aristotle who distinguished between vegetative and higher functions. However, the origin of the notion is no answer to the charge that the term is understandably perceived as derogatory by many relatives, whether schooled in classical philosophy or not. Is it an answer to offence caused by 'negro' that it originates from the Latin for 'black'?

Box 2 Capacity

The Mental Capacity Act 2005[27] defines incapacity in section 3(1). Section 3(2) provides: 'A person is not to be regarded as unable to understand the information relevant to a decision if he is able to understand an explanation of it given to him in a way that is appropriate to his circumstances (using simple language, visual aids *or any other means*[a]).'

Section 3(1) provides that a person is unable to make a decision if he is unable inter alia to communicate his decision '(whether by talking, using sign language *or by any other means*[a])'.

(Fans of *Star Trek* will recall the episode *The Menagerie: Part II* in which Captain Pike signals his wishes by one beep for 'Yes' and two for 'No'.)

[a]Our emphasis.

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AAN =	American Academy of Neurology
fMRI =	functional MRI
(P)DOC =	(prolonged) disorders of consciousness
RCP =	Royal College of Physicians
UWS =	unresponsive wakefulness syndrome
VS =	vegetative state

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Query: AQ6: Please provide abbreviated journal title, volume number and page range for reference 5.
Author Response: This is a web-only journal, article is accessible at http://www.bailii.org/uk/other/journals/WebJCLI/1999/issue4/keown4.html[accessed 27-02-2020

Query: AQ7: Please provide volume number and page range for reference 23.
Author Response: Available at https://www.researchgate.net/publication/348635149_What_Justifies_the_Allocation_of_Health_Care_Resources_to_Patients_with_Disorders_of_Consciousness(yet to receive page numbers]

Query: AQ8: Please provide accessed date for reference 30.
Author Response: Acessed 27 - 02 - 2021

Query: AQ9: Please provide publisher details for reference 31.

Author Response: Published by the UNUnited Nations and 2008 are both repeated and one of each needs deleting, please