



Alive inside

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Abstract

This article provides an ethical analysis of the U.S. practice guideline update on disorders of consciousness. Our analysis focuses on the guideline's recommendations regarding the use of investigational neuroimaging methods to assess brain-injured patients. Complex and multifaceted ethical issues have emerged because these methods alter the clinical understanding of consciousness. We address issues of false hope, patient suffering, and cost. We argue that, in spite of these concerns, there is significant benefit to using neuroimaging to assess brain-injured patients in most cases.

KEYWORDS

consciousness, disorders of consciousness, minimally conscious state, neuroethics, neuroimaging, neurology, vegetative state

1 | MR. R

Five days before Christmas in 1999, Mr. R, a 26-year-old graduate of the University of Waterloo with a promising career in robotics, and his girlfriend drove away from his grandfather's house in Sarnia, Ontario.¹ At once, an otherwise normal day in the holiday season became a catastrophe. Their car was struck by a police vehicle responding to an emergency call. The police officer and Mr. R's girlfriend suffered minor

injuries, but Mr. R's injuries were devastating. Neuroimaging showed herniation, bleeding, and contusions in his left parietal and temporal lobes. In the days to follow, he was unable to open his eyes or produce sound. Mr. R. remained in the hospital for 1 month and was then discharged into the care of his parents to recover at home.

In the ensuing 12 years, Mr. R was assessed regularly by neurologists. They diagnosed him as being in a vegetative state, a condition of wakeful unresponsiveness.² Their clinical exams, using techniques such as the JFK Coma Recovery Scale-Revised, demonstrated that Mr. R had semi-regular sleep-wake cycles but no awareness of himself or his environment. Between 2012 and 2013, 20 clinical exams were performed by specialized healthcare professionals. Each exam

¹Case adapted from: Fernández-Espejo, D., & Owen, A. M. (2013). Detecting awareness after severe brain injury. *Nature Reviews Neuroscience*, 14(11), 801–809; Owen A. M. (2017). *How science found a way to help coma patients communicate*. Retrieved from <https://www.theguardian.com/news/2017/sep/05/how-science-found-a-way-to-help-coma-patients-communicate>; BBC Panorama. (2012). *The mind reader: Unlocking my voice*. Retrieved from <https://www.bbc.co.uk/programmes/b01ny377>. All information is publicly available. Detailed clinical information regarding Mr. R's condition and assessment can be found in the supplementary material of Fernández-Espejo & Owen, *op. cit.*

²Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state: Parts I and II. *NEJM*, 330(21), 1499–1508, 1572–1579.

produced the same results. Mr. R showed no behavioral responses to commands—such as “raise your right arm”—and no behavioral responses to visual, tactile, auditory, or noxious stimuli. His condition differed from that of the minimally conscious state. Patients in the minimally conscious state have semi-regular sleep-wake cycles, as Mr. R did, but, unlike him, they display intermittent behavioral evidence of awareness.³

In February 2012, Mr. R.'s parents enrolled him in a study at the University of Western Ontario to discover whether functional neuroimaging could detect awareness in persons with catastrophic brain injuries. While lying in the scanner, he was instructed to imagine one of two activities—playing tennis or visiting the rooms of his home—for repeated 30-second intervals. In fully conscious persons, imagining these activities preferentially activates different brain structures. The finding of sustained and predictable brain activity in these regions is interpreted as a proxy for behavioral command-following.⁴ Remarkably, Mr. R.'s brain activity matched that of fully conscious persons, suggesting that he was aware of his surroundings.

Investigators then adapted this method to assess whether Mr. R. could communicate. They asked a series of yes/no questions. To answer “yes,” Mr. R was asked to imagine playing tennis. To answer “no,” he was asked to imagine visiting the rooms of his home. Mr. R correctly answered questions regarding his name, the name of his support worker (whom he had met following his injury), the date, and his location. Additionally, Mr. R. was asked whether he still enjoyed watching ice hockey on the television, an activity that he had enjoyed prior to his accident. He was even asked twice whether he was in physical pain, to which, each time, he replied “no.”

These results were revolutionary. They demonstrated that, despite being consistently diagnosed as being in the vegetative state for 12 years, Mr. R. was conscious. Mr. R was alive inside.

The recently issued U.S. practice guideline update for disorders of consciousness (DoC) aims to improve the care and management of patients like Mr. R.⁵ This joint effort by the American Academy of Neurology, the American Congress of Rehabilitation Medicine, and the National Institute on Disability, Independent Living, and Rehabilitation Research recommends how clinicians can use advancements in neuroscience to improve the care of their patients. The guideline is the product of a multi-year consensus process and evidence-based review, derived from the 2011 American Academy of Neurology process manual.⁶ To ensure that recommendations re-

flect the highest degree of analytical rigor, the manual specifies strict inclusion criteria for studies.⁷

The standard method of diagnosis of DoC patients is the clinical exam. Clinicians use one of several neurobehavioral scales to elicit the following behaviors: reproducible responses to visual, auditory, or noxious stimuli; object recognition and use; command-following; or communication.⁸ Evidence of one or more of these behaviors is regarded as a marker of consciousness and diagnostic of the minimally conscious state. There is not, however, consensus internationally regarding scale standardization. Variation persists regarding which scale should be used, the optimal frequency of clinical examination, and the training needed to use a scale correctly.

This has led to two serious diagnostic problems. The first is misdiagnosis due to human error. Although there are discrepancies regarding the rate of clinical misdiagnosis,⁹ one of the most extensive studies of this problem found that as many as 41% of patients diagnosed as being in the vegetative state according to an unstandardized method—diagnosis by consensus among the clinical team—could be misclassified. When examined with the clinically validated JFK Coma Recovery Scale-Revised, these patients were reclassified as minimally conscious.¹⁰ This suggests that use of unstandardized, non-clinically validated methods could lead clinicians to underestimate the presence of consciousness in nearly half of patients thought to be in a vegetative state.

Second, there is a proportion of DoC patients in whom standardized neurobehavioral scales are insensitive to preserved consciousness. These patients, like Mr. R, are consistently diagnosed as being in a vegetative state according to rigorous clinical examination, but they are demonstrably conscious when assessed with neuroimaging or electroencephalography (EEG). A meta-analysis of six studies using the methods applied to Mr. R demonstrated that 42 of 292 DoC patients (14.4%) who were entirely unresponsive at the bedside could modulate their brain activity to command.¹¹ These patients are variously referred to as “covertly conscious”¹² or as having “cognitive-motor dissociation.”¹³ Their consciousness is

³Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., ..., Zasler, N. D. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, 58(3), 349–353.

⁴Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, 313(5792), 1402.

⁵Giacino, J. T., Katz, D. I., Schiff, N. D., Whyte, J., Ashman, E. J., Ashwal, S., ... Armstrong, M. J. (2018). Practice guideline update recommendations summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology*, 91(10), 450–460.

⁶Gronseth G. S., Woodroffe, L. M., & Getchius, T. S. (2011). *American Academy of Neurology clinical practice guideline process manual*. Retrieved from <http://tools.aan.com/globals/axon/assets/9023.pdf>.

⁷Giacino, J. T., Katz, D. I., Schiff, N. D., Whyte, J., Ashman, E. J., Ashwal, S., ... Armstrong, M. J. (2018). Comprehensive systematic review update summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Archives of physical medicine and rehabilitation*. *Neurology*, 99(9), 461–470.

⁸For an extensive review of variations in methods of assessment, see Seel, R. T., Sherer, M., Whyte, J., Katz, D. I., Giacino, J. T., Rosenbaum, A. M., ... Zasler N. D. (2010). Assessment scales for disorders of consciousness: Evidence-based recommendations for clinical practice and research. *Archives of Physical Medicine and Rehabilitation*, 91(12), 1795–1813.

⁹Wade, D. T. (2018). How often is the diagnosis of the permanent vegetative state incorrect? A review of the evidence. *European Journal of Neurology*, 25(4), 619–625.

¹⁰Schnakers, C., Vanhaudenhuyse, A., Giacino, J. T., Ventura, M., Boly, M., Majerus, S., ... Laureys, S. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, 9(35), 1–5.

¹¹Kondziella, D., Friberg, C. K., Frokjaer, V. G., Fabricius, M., & Møller, K. (2016). Preserved consciousness in vegetative and minimal conscious states: Systematic review and meta-analysis. *JNNP*, 87(5), 485–492.

¹²Peterson, A., & Bayne, T. (2018). Post-comatose disorders of consciousness. In R. Gennaro (Ed.), *The Routledge handbook of consciousness* (pp. 351–365). New York, NY: Routledge.

¹³Schiff, N. D. (2015). Cognitive motor dissociation following severe brain injuries. *JAMA Neurology*, 72(12), 1413–1415.

manifest in brain activity, not in overt behavior, and neuroimaging or EEG are the only methods by which their consciousness is revealed.

The guideline includes ambitious recommendations to address these problems. Not only does the guideline recommend using standardized, clinically validated scales for diagnosis, but it also describes when neuroimaging and EEG methods may be used to complement clinical assessment. For example: recommendation 2e states that investigational neuroimaging and EEG methods may be used when serial clinical exams yield “inconclusive findings;” recommendation 2f states that such methods may be used to justify the continuation of “active rehabilitation management;” and recommendation 5 states that such methods may be used for prognosis.

These recommendations represent a revolution in the practice of neurology and rehabilitation medicine. Although standardized neurobehavioral scales are still regarded as the gold standard for diagnosis, they are no longer considered the *sole* window into a patient’s consciousness. Instead, investigational methods that measure consciousness directly from the brain are now one step closer to being incorporated in the routine assessment of DoC patients. These methods could substantially improve clinical decision-making, pain management, and rehabilitation.

The guideline’s endorsement of neuroimaging methods presents an opportunity to revisit perennial ethical concerns associated with DoC patients and the nuances of translating these investigational methods into clinical practice. Evidence of consciousness following brain injury can inform ethically fraught decisions, such as whether to continue artificial nutrition, hydration, and mechanical ventilation, or how to treat complications such as pneumonia or sepsis years after injury. Owing to their relatively nascent evidence base, however, the guideline qualifies the use of neuroimaging and EEG: they may be used only if they have a favorable harm–benefit ratio and a favorable cost–benefit ratio.¹⁴ But how should clinicians, families, or other stakeholders interpret this qualification? In this article, we build on previous work¹⁵ by providing an ethical analysis of the use of investigational neuroimaging in DoC patients. We put to one side harms normally associated with neuroimaging, such as a reaction to contrast agents, or blood pressure changes associated with a prone scanning posture. Instead, we focus on broader ethical issues associated with how investigational neuroimaging and EEG might come to alter the clinical understanding of consciousness.

We begin with a brief overview of the neuroimaging methods highlighted in the guideline. We introduce several conceptual

distinctions to categorize these methods based on their task design and the underlying theory that supports the ascription of consciousness to a patient from measured brain activity. We then address three ethical issues: false hope, patient suffering, and cost. Our frame of reference for engaging these issues is a North American perspective. Nevertheless, these issues touch deep conceptual puzzles that are not unique to any particular jurisdiction or healthcare system. Rather, they turn on how investigational neuroimaging is beginning to revolutionize our very understanding of consciousness. We defend the use of investigational neuroimaging methods against these concerns and introduce a number of practical recommendations to mitigate harms and costs, where present. For clarity, our analysis focuses on the use of investigational neuroimaging, as these methods currently have a stronger evidence base than that of EEG methods. However, the arguments developed below are intended to apply to both neuroimaging and EEG (as well as to other modalities).

2 | THE VALUE OF USING NEUROIMAGING TO ASSESS DOC PATIENTS

Investigational neuroimaging methods used to assess DoC patients fit into one of two categories: active paradigms and passive paradigms.¹⁶ Active paradigms involve a study design that requires participants to engage in a mental task. These methods, like the clinical exam, assume that agency is a marker of consciousness.¹⁷ Just as raising one’s arm in response to a command is believed to be strong evidence of consciousness, so too is willful brain modulation. The representation of consciousness in active paradigms is thus similar to that of clinical exams. A patient is regarded as conscious because she is behaving, albeit only mentally, in a way that requires consciousness. Her mental behavior is not regarded as a reflex.

The most intensely studied active paradigm highlighted in the guideline is the functional magnetic resonance imaging (fMRI) mental imagery task. As described in the case of Mr. R, the mental imagery task requires participants to imagine activities for repeated and sustained 30-second intervals, interspersed with periods of rest. Imagining playing tennis activates the supplementary motor area, while imagining visiting the rooms of a home activates the parahippocampal gyrus, posterior parietal lobe, and lateral premotor cortex. These networks are anatomically distinct and their activation patterns are easily observed and differentiated. Two of the broadest fMRI mental imagery task studies to date found that as many as 17% of participants clinically diagnosed as being in a vegetative state could willfully modulate their brain activity to command.¹⁸ The

¹⁴Giacino et al., op. cit. note 5, table 1 legend. These qualifications also extend to other health interventions described in the guideline.

¹⁵Fins, J. J., & Bernat, J. L. (2018). Ethical, palliative, and policy considerations in disorders of consciousness. *Neurology*, 91(10), 471–475; Fins J. J., Illes, J., Bernat, J. L., Hirsch, J., Laureys, S., & Murphy, E. (2008). Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *AJOB*, 8(9), 3–12; Weijer, C., Peterson, A., Webster, F., Graham, M., Cruse, D., Fernández-Espejo, D., ... Owen, A.M. (2014). The ethics of neuroimaging after serious brain injury. *BMC Medical Ethics*, 15(41), 1–13; Jox, R. J., Bernat, J. L., Laureys, S., & Racine, E. (2012). Disorders of consciousness: Responding to requests for novel diagnostic and therapeutic interventions. *Lancet Neurology*, 11(8), 732–738; Kaal, K. J., Harrison, M., Whitehurst, D. G., Townson, A., Dance, D., Stoessel A. J., & Illes, J. (2018). Operationalizing neuroimaging for disorders of consciousness in the Canadian context. *Canadian Journal of Neurological Sciences*, 45(6), 633–635.

¹⁶Peterson & Bayne, op. cit. note 12.

¹⁷Bayne, T. (2013). Agency as a marker of consciousness. In A. Clark, J. Kiverstein & T. Vierkant (Eds.), *Decomposing the will* (pp. 160–180). Oxford, U.K.: Oxford University Press.

¹⁸Monti, M. M., Vanhaudenhuyse, A., Coleman, M. R., Boly, M., Pickard, J. D., Tshibanda, L., ... Laureys, S. (2010). Willful modulation of brain activity in disorders of consciousness. *NEJM*, 362(7), 579–589; Stender, J., Gosseries, O., Bruno, M. A., Charland-Verville, V., Vanhaudenhuyse, A., Demertzi, A., Chatelle, C., ... Laureys, S. (2014). Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: A clinical validation study. *Lancet*, 384(9942), 514–522.

mental imagery task has also been successfully adapted to incorporate different imagined activities, such as rock climbing and swimming,¹⁹ and has been applied with both fMRI and high-density EEG.²⁰

Although the mental imagery task is broadly regarded as the gold standard for investigational neuroimaging assessment of DoC patients, the task's cognitive demands could increase the likelihood of false negatives. For example, Monti and colleagues (2010) found that only 1 of 31 minimally conscious-state patients enrolled in their study could perform the task, and Stender and colleagues (2014) had similar difficulties in eliciting positive results from participants known to be conscious through clinical measures. To address this issue, investigators have modified active paradigms to reduce their cognitive demands and minimize the possibility of a false negative result. Naci and colleagues (2013) observed that requiring participants to selectively attend to an auditory stimulus, such as instances of their own name, enhanced the neuronal representation of attention, which could serve as a proxy for mental imagery in patients with impaired cognition. A study involving 15 healthy participants and 3 DoC patients demonstrated that all participants could modulate a canonical attention network when counting the number of times they heard their own name.²¹ Importantly, the guideline does not reference this investigational method, as the study's sample size does not meet the inclusion criteria for the evidence-based review. Nevertheless, this study highlights the diligence of clinical researchers in optimizing active paradigms for the clinic.

A second investigational method utilizes a 'passive' neuroimaging paradigm. Passive paradigms measure brain activity as participants are at rest or passively exposed to a stimulus. Passive paradigms turn on a distinct assumption about the relationship between brain activity and consciousness. Whereas active paradigms are designed to elicit evidence of agency, passive paradigms are designed to elicit brain activity that is believed to be closely associated with a conscious state (e.g., being awake, asleep, or under general anesthesia) or a circumscribed feature of conscious processing (e.g., conscious visual processing).²² The representation of consciousness through passive paradigms thus requires investigators to accept certain background assumptions. Much like a biomarker of disease, one must accept that there is a correlational, if not a causal, relationship between consciousness and the neuronal mechanism measured.

One passive paradigm highlighted in the guideline uses ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG PET) to measure cortical metabolism in DoC patients. The whole-brain metabolic rate for DoC patients is between 42% and 55% of normal, and differences in metabolic rates between patients clinically diagnosed as vegetative and minimally conscious are observed in the frontoparietal associative cortices.²³ These findings are consistent with frontoparietal hypometabolism observed in healthy individuals under general anesthesia or in deep sleep. In a clinical validation study involving 126 DoC patients, Stender and colleagues observed that FDG PET had high overall congruence with the JFK Coma Recovery Scale–Revised and high sensitivity to the clinical diagnosis of the minimally conscious state.²⁴ Moreover, changes in cortical metabolism also tracked patient outcome 12 months after assessment. Preserved frontoparietal metabolism was correlated with positive outcomes, while frontoparietal hypometabolism was correlated with negative outcomes.

The above-reviewed methods are still regarded as investigational, yet their continued success in detecting consciousness in DoC patients suggests that they could benefit the care of patients. First, these methods could improve diagnostic accuracy. Neurological conditions secondary to the loss of consciousness, such as hypertonia, might prevent accurate assessment with neurobehavioral scales. Hypertonia causes muscle tightness, which can prevent a patient from complying with behavioral commands even if she is otherwise conscious. In other DoC patients, like Mr. R, damage to corticothalamic pathways could prevent motor output altogether. Investigational neuroimaging methods could improve diagnostic accuracy in both such patient subgroups.

Second, investigational neuroimaging could also improve prognostication. Predicting outcome following brain injury is difficult. DoC patients who have suffered a cardiac arrest are unlikely to recover if they lack pupillary reflexes and somatosensory evoked potentials bilaterally, and their EEG voltage is below 20 μ V.²⁵ Outcome associated with traumatic etiology, however, is variable, and some patients can recover years after injury. Accurate prognosis is important as most decisions to withdraw life-sustaining therapies, which are informed by clinical exams, occur within the first 72 hours of injury.²⁶ Recommendation 5 of the guideline suggests that neuroimaging assessment of a patient's auditory processing 2 to 3 months after injury could be predictive of recovery.²⁷ Likewise, measurement of

¹⁹Bardin, J. C., Fins, J. J., Katz, D. I., Hersh, J., Heier, L. A., ... Voss, H. U. (2011). Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. *Brain*, 134(3), 769–782.

²⁰Goldfine, A. M., Victor, J. D., Conte, M. M., Bardin, J. C., & Schiff, N. D. (2011). Determination of awareness in patients with severe brain injury using EEG power spectral analysis. *Clinical Neurophysiology*, 122(11), 2157–2168; Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., ...Owen, A. M. (2011). Bedside detection of awareness in the vegetative state: A cohort study. *Lancet*, 378(9809), 2088–2094; Claassen, J., Doyle, K., Matory, A., Couch, C., Burger, K. M., Velazquez, A., ...Roh, D. (2019). Detection of brain activation in unresponsive patients with acute brain injury. *New England Journal of Medicine*, 380(26), 2497–2505.

²¹Naci, L., & Owen, A. M. (2013). Making every word count for nonresponsive patients. *JAMA Neurology*, 70(10), 1235–1241.

²²Bayne, T., & Hohwy, J. (2014). Global disorders of consciousness. *WIREs Cognitive Science*, 5(2), 129–138.

²³Stender, J., Kupers, R., Rodell, A., Thibaut, A., Chatelle, C., Bruno, M.A., ... Gjedde, A. (2014). Quantitative rates of brain glucose metabolism distinguish minimally conscious from vegetative state patients. *Journal of Cerebral Blood Flow & Metabolism*, 35(1), 58–65. <https://www.sciencedirect.com/science/article/pii/S0140673614600428>

²⁴Stender, J., et al., op. cit. note 23.

²⁵Weijer, C., Bruni, T., Gofton, T., Young, G. B., Norton, L., A. Peterson, & Owen, A. M. (2016). Ethical considerations in functional magnetic resonance imaging research in acutely comatose patients. *Brain*, 139(1), 292–299.

²⁶Turgeon, A. F., Lauzier, F., Simard, J. F., Scales, D. C., Burns, K. E. A., Moore, L., ..., Fergusson, D. (2011). Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: A Canadian multi-centre cohort study. *CMAJ*, 183(14), 1581–1588.

²⁷Coleman, M. R., Davis, M. H., Rodd, J. M., Robson, T., Ali, A., Owen, A. M., & Pickard, J. D. (2009). Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain*, 123(9), 2541–2552.

cortical metabolism could also predict positive from poor outcomes, or serve to gatekeep active rehabilitation management.

Third, neuroimaging assessment might also be therapeutic. Although not discussed in the guideline, it is possible that, in the future, these techniques could be used as cognitive prosthetics. The mental imagery task can be adapted for yes/no communication. To date, at least three DoC patients have communicated with this method.²⁸ This application requires further technical refinement, but it shows promise. Some theorists have considered whether DoC patients might participate in some medical decisions that impact their quality of life.²⁹ The fact that a patient can communicate with the aid of neuroimaging does not imply that she has decision-making capacity. Nevertheless, opening a channel of communication raises this possibility. The increase in agency afforded to DoC patients could be beneficial to them, or to surrogates and clinicians who might wish for patient input while making clinical decisions.

The potential benefits of investigational neuroimaging must be tempered by considering how the results might be understood by decision-makers. Active paradigms and passive paradigms represent consciousness differently, and this complicates whether and how consciousness can be inferred from the data. Active paradigms are conceptually similar to clinical exams in that they are designed to elicit behaviors that require consciousness. Passive paradigms represent consciousness differently. For passive paradigms, the ascription of consciousness hinges entirely on assumptions regarding the association between consciousness and a neuronal mechanism. This inference might be difficult for decision-makers to comprehend. A patient's family might be told that she is aware because her cortical metabolism is consistent with that of the minimally conscious state, but without other familiar evidence of consciousness, the value of this information might not be fully appreciated.

To sharpen this point, consider the broadly influential legal case involving Terri Schiavo.³⁰ Suppose that investigational neuroimaging methods were available to inform the legal dispute between Ms. Schiavo's family and husband over the removal of life-sustaining therapies. Ms. Schiavo's husband, Michael Schiavo, petitioned the courts to remove her feeding tube so that she would be allowed to die, but her parents, Robert and Mary Schindler, objected to this petition, arguing that their daughter was conscious and that the removal of food and fluids was inconsistent with her Roman Catholic

values. Although it is unlikely that Ms. Schiavo would have been responsive to these methods given what is known from autopsy findings, the prospect of using them in similar cases raises several important questions. Would a positive response to neuroimaging have had any influence? Would Ms. Schiavo's husband have reconsidered his decision to withdraw life-sustaining therapies if FDG PET had revealed that her cortical metabolism was consistent with that of the minimally conscious state? Further, how would the court have interpreted this information? Suppose Ms. Schiavo had performed the mental imagery task but showed no behavioral evidence of awareness. Would the court have then been inclined to support her parents wish to continue life-sustaining therapies? These questions suggest that the translation of these methods to clinical services will likely have complex implications for decision-makers. Not only is it unclear how decision-makers would interpret these findings, but it is also unclear whether these methods should inform all, or only some, clinical decisions.

Investigational neuroimaging methods also raise complex issues regarding validity.³¹ As reviewed above, the mental imagery task is cognitively demanding. This raises questions regarding false negative results. Investigators observe that FDG PET is more sensitive to preserved consciousness than the mental imagery task, but this claim may fail to account for the underlying theoretical differences between active and passive paradigms. FDG PET may indeed be more sensitive to consciousness, but this assertion requires one to presume that cortical metabolism of a particular kind is demonstrative of consciousness. This presumption is in tension with the orthodox clinical view that agency—not cortical metabolism—is a marker of consciousness.³² These considerations suggest that, like clinical exams, investigational neuroimaging methods might also be subject to error. Ethical guidance in thinking about DoCs under conditions of uncertainty could assist decision-makers as they interpret neuroimaging data.³³

Should investigational neuroimaging methods be used to assess patients like Mr. R? We think so. But we acknowledge that the benefit of these methods must be weighed against potential harms and costs. How, then, should clinicians, families, and other stakeholders decide when the value of investigational neuroimaging is worth these harms and costs? And how might we mitigate potential harms associated with the complexity of neuroimaging data? We address these questions below by outlining three perennial ethical concerns raised in cases like that of Mr. R. We argue that—at least, in most cases—the benefit of assessing DoC patients with investigational neuroimaging would outweigh potential harms and costs.

²⁸Monti, M. et al., op. cit. note 22; Naci & Owen 2013, op. cit. note 27; Fernández-Espejo & Owen 2013, op. cit. note 1.

²⁹Peterson, A., Naci, L., Weijer, C., Cruse, D., Fernández-Espejo, D., Graham, M., & Owen, A. M. (2013). Assessing decision-making capacity in the behaviorally nonresponsive patient with residual covert awareness. *AJOB-Neuroscience*, 4(4), 3–14; Fins, J. J. (2018). Mosaic decisionmaking and reemergent agency after severe brain injury. *Cambridge Quarterly of Healthcare Ethics*, 27(1), 163–174; Peterson, A. (2019). A critical analysis of Joseph Fins' mosaic decisionmaking: A response to "mosaic decisionmaking and reemergent agency after severe brain injury". *Cambridge Quarterly of Healthcare Ethics*, 28, 725–736; Glannon, W. (2016). Brain-computer interfaces in end-of-life decision-making. *Brain-Computer Interfaces*, 3(3) 133–139; Bendtsen, K. (2013). Communicating with the minimally conscious: Ethical implications in end-of-life care. *AJOB-Neuroscience*, 4(1), 46–51; Cairncross, M., Peterson, A., Lazosky, A., Gofton, T., & Weijer, C. (2016). Assessing decision-making capacity in patients with communication impairments: A case study. *Cambridge Quarterly of Healthcare Ethics*, 25(4), 691–699.

³⁰Quill, T. E. (2005). Terri Schiavo—a tragedy compounded. *NEJM*, 352(16), 1630–1633.

³¹Peterson, A., Cruse, D., Naci, L., Weijer, C., & Owen, A. M. (2015). Risk, diagnostic error, and the clinical science of consciousness. *NeuroImage: Clinical*, 7, 588–597.

³²Peterson, A. (2016). Consilience, clinical validation, and global disorders of consciousness. *Neuroscience of Consciousness*, 1(1), 1–9.

³³Johnson, L. S., & Lazaridis, C. (2018). The sources of uncertainty in disorders of consciousness. *AJOB-Neuroscience*, 9(2), 76–82; Lazaridis, C. (2019). Withdrawal of life-sustaining treatments in perceived devastating brain injury: The key role of uncertainty. *Neurocritical Care*, 30(1), 33–41.

3 | WOULD NEUROIMAGING ASSESSMENT OF MR. R LEAD TO FALSE HOPE?

A first ethical concern is that investigational neuroimaging could lead to false hope. False hope occurs when a person believes in a positive clinical outcome, but this belief is inconsistent with the clinical facts. False hope could occur as a result of therapeutic misconception.³⁴ The guideline acknowledges that these neuroimaging methods are transitioning from the investigational setting to clinical practice, yet their evidence base still requires time to mature. Patients' families might not appreciate the liminal state of the science and might be inclined to reason beyond the evidence. Families might also be aware of media reports, which in some cases may embellish the strength of neuroimaging in detecting covert consciousness or provide a misleading representation of the quality of preserved consciousness in brain-injured patients.³⁵ This could be harmful to both families and patients. It could be harmful to families in that they might already be emotionally vulnerable, and false beliefs could compound this vulnerability. False hope could likewise harm a patient in that the decision to withdraw life-sustaining therapies might be delayed based on the false belief that a patient will recover.³⁶

Investigational neuroimaging data are complex, and disclosure to patients' families could result in a misappreciation of the results. The fact that any neuroimaging method demonstrates preserved consciousness in a DoC patient does not imply that she retains a full suite of cognitive capacities, nor does it guarantee that she will recover these capacities in the future. Additionally, failure to appreciate underlying theories of consciousness, or the relative validity of different methods, might also facilitate false hope. Misappreciation of these facts can impair decision-making and lead to harm.

Although investigational neuroimaging raises legitimate worries about the appreciation of results, it is far from obvious that disclosure of neuroimaging data would necessarily lead to false hope. There are currently no systematic studies on how patients' families might interpret investigational neuroimaging data. Thus, while false hope could result from disclosure, it is equally plausible that disclosure could have no influence at all. In a study examining family beliefs regarding DoC patients, Tresch and colleagues observed that, of 33 family caregivers for patients clinically diagnosed as being in a vegetative state, 90% of patients were regarded by caregivers as conscious even after the caregivers had been informed of the clinical diagnosis.³⁷ These findings suggest that families might have strong beliefs regarding preserved consciousness in DoC patients and that these beliefs might not be influenced by new information.

Nevertheless, clinicians might still adopt precautionary measures to mitigate false hope, where present.³⁸ For example, there are currently no best practices for disclosing investigational neuroimaging results to patients' families. Recommendations 8 and 15 of the guideline describe the importance of counseling patients' families with realistic expectations and evidence-based language, but these recommendations do not provide specific guidance with regard to investigational neuroimaging. One approach to developing best practices might be to borrow methods for disclosing neuroimaging data in other neurological populations. Harkins and colleagues developed best practices for disclosing investigational amyloid imaging results to cognitively healthy adults by using a modified Delphi method.³⁹ The Delphi process revealed several key insights for disclosure, including the recommendation that: (1) participants should receive sufficient information about neuroimaging; (2) participants should be screened for emotional distress; (3) a skilled communicator should disclose the results; (4) disclosure should occur in person with time for discussion; and (5) periodic follow-up consultations should occur. Replicating this process within the DoC research community could be an important first step in identifying best practices for disclosure.

Guidance for disclosure might also be taken from discussion of genetic biomarker assessment for neurodegenerative diseases. In these circumstances, a genetic counselor might discuss a common genetic risk factor for Alzheimer's disease, apolipoprotein E, in the context of pre-clinical imaging results or tau protein accumulation. Genetic counselors are trained to translate this complex clinical information for nonexperts. This can allow patients or families to envision the scope of possible results and therapies, and it can enhance autonomous and authentic choice.

A member of the clinical team who is designated and trained to disclose investigational neuroimaging results could, by the same token, facilitate appreciation of the data. Such an individual might also be skilled in disclosing data in a way that reflects patient and family values. Recommendation 11 of the guideline states that, for chronic DoCs, clinicians should become familiar with patient and family preferences to help guide clinical decisions. Some DoC patients might develop complications years after injury, and families might need to choose between therapy and palliation. 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.

More empirical work is needed to determine whether disclosure of investigational neuroimaging results would lead to false hope. If it does, more work is also required to determine whether the development of best practices for disclosure or the designation of a family liaison similar to that of a genetic counselor would mitigate false hope,

³⁴Fins, J. J. (2016). Neuroethics and disorders of consciousness: Discerning brain states in clinical practice and research. *AMA Journal of Ethics*, 18(12), 1182–1191.

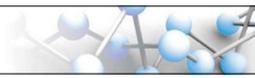
³⁵Samuel, G., & Kitzinger, J. (2013). Reporting consciousness in coma: Media framing of neuro-scientific research, hope, and the response of families with relatives in vegetative and minimally conscious states. *JOME Journal*, 3, 1–5.

³⁶Kitzinger, J., & Kitzinger, C. (2013). The 'window of opportunity' for death after severe brain injury: Family experiences. *Sociology of Health & Illness*, 35(7), 1095–1112.

³⁷Tresch, D. D., Sims, F. H., Duthie E. H., & Goldstein, M. D. (1991). Patients in a persistent vegetative state attitudes and reactions of family members. *Journal of the American Geriatrics Society*, 39(1), 17–21.

³⁸Graham, M., Weijer, C., Peterson, A., Naci, L., Cruse, D., Fernández-Espejo, D., ... Owen, A. M. (2015). Acknowledging awareness: Informing families of individual research results for patients in the vegetative state. *Journal of Medical Ethics*, 41(7), 534–538.

³⁹Harkins, K., Sankar, P., Sperling, R., Grill, J. D., Green, R. C., Johnson K. A., ..., Karlawish, J. (2015). Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimer's Research & Therapy*, 7(1), 26.



where present. Until these data are available, however, developing and adopting best practices for disclosure might reasonably improve a family's appreciation of neuroimaging results and avoid potential harms.

4 | IS MR. R'S LIFE WORTH LIVING?

A second ethical concern is that, even if families accurately appreciate investigational neuroimaging data, patients like Mr. R might be suffering intolerably. The use of investigational neuroimaging would not have any extant benefit. Rather, neuroimaging would only serve to keep patients like Mr. R alive, and this is inherently harmful.

This ethical concern stems from a technical philosophical argument regarding the moral status of DoC patients.⁴⁰ A being has moral status if and only if it is owed moral consideration for its own sake. A stone lacks moral status. It makes no moral difference to the stone if one maliciously kicks it or throws it into the Thames River. A person, by contrast, does have moral status, for it does make a moral difference to *her* if she is maliciously kicked or thrown into the Thames. Lack of moral consideration for this person results in harm, whereas no such harm occurs to the stone.

Consciousness plays a role in the ascription of moral status to a being. That a being is conscious implies that it might have the capacity to suffer, or to have pleasurable experiences, along with a range of other plausible capacities. With these capacities comes a range of moral duties. The fact that a being can suffer suggests that we might have a duty to prevent it from suffering, and to increase its chances of having pleasurable experiences. Some theorists argue further that beings can fall on a spectrum of moral status, according to which some enjoy full moral status and others do not.⁴¹ To have full moral status, a being must not only be conscious, but it must also have sophisticated cognitive capacities that allow it to value its own life. These capacities include a sense of self over time and the capacity to develop life plans. Without these capacities, the continuation or cessation of life does not matter to the being. Although we may have a moral duty to consider the welfare of the being, it does not follow that we must also respect its right to life, especially if it is suffering.

DoC patients for whom investigational neuroimaging is required to detect consciousness might lack the sophisticated cognitive capacities to value their own lives. It follows, according to this view, that they might also lack full moral status. Although it is important to consider their welfare, there is no moral duty to keep these patients alive, for the continuation or cessation of their lives does *not matter to them*. Some argue further that the welfare of

these patients is also very poor; so poor in fact that their condition has been likened to a state that is "far worse than that of someone in the worst form of solitary confinement," even worse than death itself.⁴² Withdrawal of life-sustaining therapies, or a do-not-resuscitate (DNR) order, is not only permissible but morally required to prevent further suffering.

This argument is consistent with the findings of several interview studies assessing clinician, scientist, and family attitudes toward end-of-life decisions in DoC patients.⁴³ Respondents consistently report that they would recommend withdrawal of life-sustaining therapies for others and themselves, particularly in the case of the vegetative state. Jox and colleagues also observed that of the 44 family caregivers they interviewed, 85% reported that they considered limiting treatment because of patient quality of life. The above-reviewed argument thus reflects real attitudes of real DoC stakeholders. How should we respond to these concerns?

We think that there are good reasons to be skeptical of this argument, as do other theorists working on this problem.⁴⁴ First, it is unclear whether we ought to accept the presumption of a conceptual relationship between full moral status and the capacities involved in valuing one's own life. Theorists generally agree that consciousness plays a role in the ascription of moral status, but there is currently no consensus regarding *which* role, nor which capacities should be regarded as morally relevant. This is reflected in the way that we treat other cognitively impaired patients. There are many patients who lack the cognitive capacities necessary for valuing their own lives, yet we still treat them as though they have full moral status. By the moderate to severe stage of dementia caused by Alzheimer's disease, patients lack the capacity to generate and carry out life plans. Should we therefore regard these patients as lacking a right to life? On the contrary, these patients still remain the focus of care and consideration from their families and clinical teams.

Second, even if we are inclined to accept the presumption of a relationship between full moral status and the capacities to value one's own life, it is simply very hard to determine whether those capacities are present in any given DoC patient. Indeed, the guideline explicitly states that preservation of cognitive capacities in DoC

⁴² Kahane & Savulescu, *op. cit.* note 54.

⁴³ Demertzi, A., Ledoux, D., Bruno, M. A., Vanhauzenhuyse, A., Gosseries, O., Soddu, A., ... Laureys, S. (2011). Attitudes towards end-of-life issues in disorders of consciousness: A European survey. *Journal of Neurology*, 258(6), 1058–1065; Gipson, J., Kahane, G., & Savulescu, J. (2014). Attitudes of lay people to withdrawal of treatment in brain damaged patients. *Neuroethics*, 1(7), 1–9; Kuehlmeier, K., Palmour, N., Riopelle, R.J., Bernat, J. L., Jox, R. J., & Racine, E. (2014). Physicians' attitudes toward medical and ethical challenges for patients in the vegetative state: Comparing Canadian and German perspectives in a vignette survey. *BMC Neurology*, 14(1), 119; Jox, R. J., Kuehlmeier, K., Klein, A. M., Herzog, J., Schaupp, M., Nowak D. A., ..., Bender A. (2015). Diagnosis and decision making for patients with disorders of consciousness: A survey among family members. *Archives of Physical Medicine and Rehabilitation*, 96(2), 323–330

⁴⁴ Braddock, M. (2017). Should we treat vegetative and minimally conscious patients as persons? *Neuroethics*, 10(2), 267–280; Graham, M. (2017). A fate worse than death? The well-being of patients diagnosed as vegetative with covert awareness. *Ethical Theory and Moral Practice*, 20(5), 1005–1020; Johnson, L. S. (2013). Can they suffer? The ethical priority of quality of life research in disorders of consciousness. *Bioethica Forum*, 6(4), 129–136; Graham, M., Weijer, C., Cruse, D., Fernandez-Espejo, D., Gofton, T., Gonzalez-Lara, L. E., ..., Owen A. M. (2015). An ethics of welfare for patients diagnosed as vegetative with covert awareness. *AJOB-Neuroscience*, 6(2), 31–41.

⁴⁰ Kahane, G., & Savulescu, J. (2009). Brain damage and the moral significance of consciousness. *Journal of Medicine and Philosophy*, 34(1), 6–26; Levy, N., & Savulescu, J. (2009). Moral significance of phenomenal consciousness. *Progress in Brain Research*, 177, 361–370.

⁴¹ McMahan, J. (2002). *The ethics of killing: problems at the margins of life*. Oxford, U.K.: Oxford University Press.



patients is variable, and that recovery can occur years after injury.⁴⁵ Thus, from a strictly empirical vantagepoint, it is doubtful whether we could discriminate with high confidence which DoC patients lack these cognitive capacities, and which do not.

Third, it is unclear whether the welfare of DoC patients is so poor that we are morally required to withdraw life-sustaining therapy or stipulate a DNR order. To date, there are no data on the subjective quality of life of DoC patients. However, interview studies with analogous clinical populations suggest that some neurological patients might not have the poor quality of life that we assume. In fact, it might be the opposite. A 2013 study examining 19 locked-in-syndrome patients with vascular etiologies or end-stage amyotrophic lateral sclerosis and 20 healthy participants found comparable reports of wellbeing.⁴⁶ Quality of life was assessed with the McGill Quality of Life Single Item Scale (MQOL-SIS). Results showed no significant difference in MQOL-SIS scores between patients and healthy participants.

A 6-year follow-up study of the quality of life of locked-in-syndrome patients also demonstrated that their wellbeing remained stable over time.⁴⁷ Thirty-nine locked-in-syndrome patients with vascular etiologies completed baseline measure with the Anamnestic Comparative Self-Assessment (ACSA), which measures an individual's global assessment of quality of life. These data were compared 6 years later with ACSA scores and the French Reintegration to Normal Living Index. Seventy percent of respondents ($n = 21$) reported either stable or improved quality of life. Surprisingly, self-reported wellbeing was not correlated with gradual increases in disability. Respondents who had more complications still reported stable or improved quality of life.

Caution should be taken when interpreting these results. The experience of locked-in-syndrome patients is likely very different from that of DoC patients, not least in the capacity to be aware of one's condition, make sense of it, adapt, and communicate. Moreover, it is also plausible that some locked-in-syndrome patients *do* find their lives intolerable. After all, 30% of participants *did not* report stable or improved quality of life at 6-year follow-up. Nonetheless, these findings highlight two important facts. First, it may be problematic to make claims about the quality of life of DoC patients from the frame of reference of able-bodied people. Making such claims results in a well-known disability paradox, according to which the wellbeing of persons with disabilities is drastically underestimated by able-bodied individuals.⁴⁸ This provides good reason to be skeptical of claims made from the philosophical armchair regarding the quality of life of DoC patients.

Second, presumptions about negative quality of life in DoC patients might not account for potential response shifts. A response shift is a change in an individual's internal standards of quality of life in response to changes in health status.⁴⁹ Prior to brain injury, an individual might intuit that she would not want to live in a state of profound disability. Yet after injury she might find that her experience contradicts her pre-injury intuitions. She may, in fact, be able to carry out new life goals and plans.

To be sure, these insights must be tempered by their implications for advance directives. If the data suggest that people are generally bad at forecasting the kind of life they would value, is this reason enough to doubt the very legitimacy of advance directives? A thorough answer to this question is beyond the scope of this article, and several other theorists have explored this topic in detail.⁵⁰ Nevertheless, we would argue that, notwithstanding this conceptual puzzle, a genuine understanding of how DoC patients are faring and what clinical decisions they might favor requires that we understand their condition *from their point of view*. Developing methods for assessing the subjective quality of life of DoC patients could shed light on this issue in the future.

Suppose, however, that the quality of life of most—if not all—DoC patients is in fact poor. Is this reason enough to presume that the lives of DoC patients are not worth living and that the use of investigational neuroimaging in these patients is inherently harmful? We think not. Although some will think that clinical decisions for DoC patients should turn primarily, if not exclusively, on quality-of-life considerations, we think that focusing narrowly on these issues overshadows the variety of reasons that families, clinicians, or other stakeholders may have for recommending continuation—or cessation—of life-sustaining therapies. These reasons might stem from religious beliefs regarding the intrinsic value of life or suffering. Conversely, stakeholders might also conclude that care should be withdrawn, but not because a patient lacks moral status. Rather, it is precisely because a family and clinical team regard a patient as a moral person that her wish to die—expressed either presently or in an advance directive—ought to be respected.

What is apparent is that families are likely to make decisions that best reflect patient values only if all clinical information is made available to them, that they are sufficiently counseled, and that their views are respected. (In jurisdictions in which clinicians assume decision-making roles, neuroimaging information would likely also be helpful as it would allow clinicians to personalize treatment plans or to increase confidence in recommending withdrawal of care.) Unsurprisingly, this sentiment is consistent with the guideline's recommendations, which place families at the center of the decision-making process. The information garnered from investigational neuroimaging would not deter from this process. Rather, it would enhance it.

⁴⁵Estraneo, A., Moretta, P., Loreto, V., Lanzillo, B., Santoro, L., & Trojano, L. (2010). Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. *Neurology*, 75(3), 239–245.

⁴⁶Rousseau, M. C., Pietra, S., Nadjji, M., & de Villemeur, T. B. (2013). Evaluation of quality of life in complete locked-in syndrome patients. *Journal of Palliative Medicine*, 16(11), 1455–1458.

⁴⁷Rousseau, M. C., Baumstarck, K., Alessandrini, M., Blandin, V., de Villemeur, T. B., & Auquier, P. (2015). Quality of life in patients with locked-in syndrome: Evolution over a 6-year period. *Orphanet Journal of Rare Diseases*, 10(1), 88.

⁴⁸Albrecht, G. L., & Devlieger, P. J. (2009). The disability paradox: High quality of life against all odds. *Social Science & Medicine*, 48(8), 977–988.

⁴⁹Schwartz, C. E., Bode, R., Repucci, N., Becker, J., Sprangers, M. A. G., & Fayers, P. M. (2006). The clinical significance of adaptation to changing health: A meta-analysis of response shift. *Quality of Life Research*, 15(9), 1533–1550.

⁵⁰Spelley, R. (2003). Reviving Ulysses contracts. *Kennedy Institute of Ethics Journal*, 13(4), 373–392.

5 | IS ASSESSING MR. R WITH NEUROIMAGING WORTH THE COST?

A third ethical concern is that investigational neuroimaging is not worth the cost. The methods outlined in the guideline are consistent with the U.S. Clinical Laboratory Improvement Act, which mandates costly neuroimaging infrastructures and personnel. Transportation of patients to a scanning unit could further compound these costs. Efforts have been made to translate neuroimaging methods to clinical scanners with some success,⁵¹ but the extent to which all recommended methods could be translated is unknown. Investigational neuroimaging tasks have also been adapted to high-density EEG. EEG is less expensive than neuroimaging, yet it raises several other technical obstacles, such as decreased spatial resolution and susceptibility to movement artifacts. These issues raise not only ethical concerns about cost, but also practical concerns about feasibility, as not all healthcare facilities are capable of providing these services.

Long-term care for DoC patients also raises cost concerns. Globally, it is estimated that 50 to 60 million traumatic brain injury cases occur annually, with an estimated international cost burden of U.S.\$400 billion. In the U.S. alone, the annual cost of traumatic brain injury is estimated at U.S.\$76.5 billion, and patients who require hospitalization account for 90% of these healthcare costs.⁵² DoC patients raise further resource allocation considerations, as they often require prolonged care or specialized rehabilitation.⁵³

Long-term care for DoC patients also raises complex jurisdiction-specific policy issues. In nations without mandated healthcare coverage, access to long-term care could be impacted by the often circuitous recovery pattern of DoC patients.⁵⁴ Likewise, in nations with mandated healthcare coverage, long-term care of DoC patients could raise concerns about allocation of costly resources in contexts of resource scarcity. Even if the benefit of investigational methods is worth the initial cost, downstream auxiliary healthcare costs might still be difficult to justify.

A thorough analysis of the cost of investigational neuroimaging and long-term care for DoC patients is beyond the scope of this article. Still, concerns about cost might be addressed by one of several preliminary considerations. First, it is plausible that investigational neuroimaging would result in cost-savings. These cost-savings could extend to both immediate clinical care and long-term management.

For example, a 2004 study, which compared immediate versus delayed computed tomography (CT) assessment for acute stroke, showed that accurate early diagnosis by immediate CT scans increased patient survival and reduced healthcare costs.⁵⁵ The guideline outlines a similar argument to justify the use of the consciousness modulating drug, Amantadine. Recommendation 14 states that faster recovery from brain injury with the aid of Amantadine “reduces the burden of disability, lessens health care costs, and minimizes psychosocial stressors in patients and caregivers.”⁵⁶ Using investigational neuroimaging to improve prognostic accuracy or to gatekeep rehabilitation could have a similar result.

Second, the cost of investigational neuroimaging might also be mitigated by “piggy backing” investigational techniques on clinically indicated scans. For example, Weijer and colleagues argue that, to adequately mitigate potential risks of neuroimaging research involving acutely comatose patients, piggy backing an investigational study on a clinically indicated structural scan can decrease overall scanning time, decrease the amount of personnel required for scanning, and decrease the likelihood of serious adverse events while transporting participants to the scanning unit.⁵⁷ Not only does this technique proportionally balance potential risks and benefits of research, but it also provides a plausible approach to combining treatments to reduce auxiliary healthcare costs.

Third, promising scientific developments in the use of high-density EEG to assess DoC patients might serve as a screening measure for more expensive investigational methods.⁵⁸ Edlow observes that assessment of DoC patients might be organized into a series of hierarchical screening measures: first, a patient is assessed with a standardized clinical exam; second, a patient is assessed with high-density EEG; and third, a patient is assessed with costly investigational neuroimaging.⁵⁹ This approach would allow clinicians to screen out patients for whom investigational neuroimaging is likely to be unsuccessful. EEG is far less expensive than neuroimaging, and can be brought to the patient's bedside, which could increase access and feasibility.

The above-reviewed considerations might assist clinicians as they consider the immediate use of investigational neuroimaging in the clinical setting. However, investigational neuroimaging methods for DoC patients—in addition to other novel therapies—also raise deeper conceptual puzzles regarding their cost-effectiveness.

⁵¹Fernandez-Espejo, D., Norton, L., & Owen, A. M. (2014) The clinical utility of fMRI for identifying covert awareness in the vegetative state: A comparison of sensitivity between 3T and 1.5T. *PLoS One*, 9(4), e95082.

⁵²Coronado, V. G., McGuire, L. C., Faul, M. F., Sugarman, D. E., & Pearson, W. S. (2012). Traumatic brain injury epidemiology and public health issues. In N. D. Zasler, D. I. Katz & R. D. Zafonte (Eds.), *Brain injury medicine: Principles and practice* (2nd ed.), (pp. 84–100). New York, NY: Demos Medical Publishing.

⁵³Members of the consensus conference on the rehabilitation of persons with traumatic brain injury; NIH Consensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury. (1999). *JAMA*, 282, 974–983.

⁵⁴Fins, J. J., Wright, M. S., Kraft, C., Rogers, A., Romani, M. B., Godwin, S., & Ulrich, M. R. (2016). Whither the ‘improvement standard’? Coverage for severe brain injury after *Jimmo v. Sebelius*. *Journal of Law, Medicine & Ethics*, 44(1), 182–193; Wright, M. S., Varsava, N., Ramirez, J., Edwards, K., Guevermont, N., Ezer, T., & Fins J. J. (2017). Severe brain injury, disability, and the law: Achieving justice for a marginalized population. *Florida State University Law Review*, 45, 313–382.

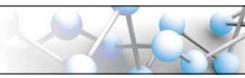
⁵⁵Wardlaw, J. M., Seymour, J., Cairns, J., Keir, S., Lewis, S., & Sandercock, P. (2004). Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke*, 35(11), 2477–2483.

⁵⁶Giacino et al., op. cit. note 5, p. 456.

⁵⁷Weijer et al., op. cit. note 31.

⁵⁸Curley, W. H., Forgacs, P. B., Voss, H. U., Conte, M. M., & Schiff, N. D. (2018). Characterization of EEG signals revealing covert cognition in the injured brain. *Brain*, 141(5), 1404–1421; Sekar, K., Schiff, N. D., Labar, D., & Forgacs, P. B. (2019). Spectral content of electroencephalographic burst-suppression patterns may reflect neuronal recovery in comatose post-cardiac arrest patients. *Journal of Clinical Neurophysiology*, 36(2), 119–126; Braiman, C., Fridman, E. A., Conte, M. M., Voss, H. U., Reichenbach, C. S., Reichenbach, T., & Schiff, N. D. (2018). Cortical response to the natural speech envelope correlates with neuroimaging evidence of cognition in severe brain injury. *Current Biology*, 28(23), 3833–3839.

⁵⁹Owen, A. M., Coleman, M. R., Menon, D. K., Berry, E. L., Johnsrude, I. S., Rodd, J. M., ..., Pickard, J. D. (2005). Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. *Progress in Brain Research*, 150, 457–608.



Cost-effectiveness analyses estimate the value of alleviating disease burden by comparing changes in quality-of-life against the price of the healthcare intervention.⁶⁰ Thus, for example, the cost of investigational neuroimaging might be justified by estimating the quality-of-life units gained from any given method relative to its cost. But this raises a puzzle. As we have argued in Section 4, determining the quality of life of DoC patients is difficult, and there are reasons to believe that we might underestimate their welfare. This technical difficulty might bias estimation of quality of life units, and negatively influence the validity of cost-effectiveness analyses for this population. More broadly, cost-effectiveness analyses themselves contain controversial assumptions about the relevance of welfare to healthcare policy. Why should improvement in quality of life be the central consideration for determining the cost-effectiveness of investigational neuroimaging—or any novel therapy, for that matter—in DoC patients?

One alternative to a welfare-based approach to justifying the cost of investigational neuroimaging is instead to evaluate the method's capacity to facilitate access to opportunity.⁶¹ Interventions that facilitate access to opportunity allow patients to pursue their own conception of the good. This approach is attractive because it leaves a patient's conception of the good unanalyzed. A healthcare intervention's capacity to improve quality of life might satisfy the conception of the good for some patients. But an intervention might equally inform clinical decisions that support patient values that are orthogonal to standard views of quality of life, such as continuing treatment in a DoC patient for religious reasons. The cost of investigational neuroimaging could be justified by an opportunity-based framework in both such cases.

We think that investigational neuroimaging could facilitate access to opportunity for DoC patients. As the guideline highlights, investigational neuroimaging could function as a gatekeeper for continued rehabilitation, and it might also be used as a neural prosthetic, based on future technical improvements. Neuroimaging assessment could also inform clinical decisions that best reflect a patient's values, even if pursuing those values are inconsistent with standard notions of quality of life. Opportunity-based frameworks for healthcare justice still require conceptual refinement, and further work needs to be done to thoroughly apply such a framework to the DoC context. However, we believe that this is a promising avenue of future research to explicate the justice claims that DoC patients (or other disabled populations) have to investigational neuroimaging and other novel therapies.

6 | CONCLUSION

In this article, we have provided an ethical analysis of the benefits, harms, and costs of using investigational neuroimaging to assess DoC patients, consistent with the practice guideline update on DoCs. Our

analysis is intended to highlight how changes in the clinical understanding of consciousness can lead to complex and multifaceted ethical issues that cut across jurisdictions and healthcare systems. We have argued that, in spite of these ethical concerns, the benefits of investigational neuroimaging assessment likely outweigh potential harms and costs in most cases. Further, we have identified areas of future empirical and conceptual research, which could assist clinicians and theorists in addressing these issues, particularly as investigational neuroimaging methods transition from the research setting to clinical practice.

To be sure, there will be cases in which the harms or costs of investigational neuroimaging outweigh benefits. Transporting a critically ill patient to an alternative medical facility for the sole purpose of investigational neuroimaging assessment, which may in the end be clinically uninformative, would likely not be justified; the patient could die and there is no extant benefit to neuroimaging assessment. Similarly, continued assessment of a patient with investigational methods despite consistent negative—or uninformative—results might not be justified, for there is also no extant benefit to the continued cost of assessment. Nonetheless, for the majority of medically stable DoC patients, particularly patients like Mr. R for whom these methods are feasible, there seems to be a clear benefit to using investigational neuroimaging despite perennial ethical concerns. For these patients, investigational neuroimaging could make a significant difference in the accuracy of diagnosis and prognosis, and that can inform consequential long-term care decisions.

The practice guideline update is a milestone in the history of neurology. Recommendations to use investigational neuroimaging methods are but one aspect of the guideline, and there is a need for further normative analysis of its rich content. We encourage continued debate on these issues. Bringing clarity to the underlying ethics of caring for brain-injured patients can assist clinicians and healthcare institutions as they incorporate the guideline in clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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⁶⁰Sassi, F. (2006). Calculating QALYs, comparing QALY and DALY calculations. *Health Policy and Planning*, 21(5), 402–408.

⁶¹Daniels, N. (2007). *Just health*. New York, NY: Cambridge University Press; Hausman, D. M. (2015). *Valuing health: Well-being, freedom, and suffering*. Oxford, U.K.: Oxford University Press.



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