

The ethics of psychedelic research in disorders of consciousness

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Abstract

This article provides an ethical analysis of psychedelic research involving disorders of consciousness patients. We apply two internationally accepted approaches for analyzing the ethics of human research, the Value-Validity Framework and Component Analysis, to a research program recently proposed by Scott and Carhart-Harris. We focus on Scott and Carhart-Harris's proposal, but the ethical frameworks outlined are applicable to other novel research protocols in the science of consciousness.

Key words: disorders of consciousness; pharmacology; methodology; psychedelics; research ethics; psilocybin

A man goes to knowledge as he goes to war: wide-awake, with fear, with respect, and with absolute assurance. Going to knowledge or going to war in any other manner is a mistake.

Carlos Castaneda
The Teachings of Don Juan: A Yaqui Way of Knowledge

Introduction

Scott and Carhart-Harris (2019) recently proposed the investigational administration of the natural serotonergic psychedelic, psilocybin, to disorders of consciousness (DoC) patients. Their research program outlines healthy participant trials to investigate psilocybin's capacity to modulate consciousness. These experiments involve psilocybin administration while healthy participants are under sedation or in non-REM sleep (Scott and Carhart-Harris 2019, 5–6). Once efficacy and safety are established, they propose an adaptive trial involving DoC patients.

Neuroimaging and electrophysiological (EEG) studies—either alone or in combination with transcranial magnetic stimulation (TMS)—demonstrate a strong association between brain complexity and the preservation of consciousness (Casali et al. 2013; Sitt et al. 2014). At least one study has shown an increase in brain complexity associated with psilocybin administration in healthy participants (Schartner et al. 2017). Scott and Carhart-Harris reason that the administration of psilocybin to DoC patients might also increase brain complexity and hasten recovery. This would place psilocybin among a limited range of “awakening drugs” for DoC patients, such as Amantadine and Zolpidem, that complement other rehabilitation efforts in this population (Giacino et al. 2012; Thonnard et al. 2013).

We applaud Scott and Carhart-Harris for seeking out innovative therapies for DoC patients. Treatment of DoC patients is challenging, and the development of new, cost-effective therapies could revolutionize clinical care and rehabilitation.

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Nevertheless, caution must be taken when involving this population in clinical research. Scott and Carhart-Harris justify their proposal by arguing that it is “ethically proportionate” where proportionate is understood as an adequate balance of the risks and benefits of research (Scott and Carhart-Harris 2019, 4). This intuition is correct, but the generality of this claim obscures several complex issues that are relevant to a rigorous ethical analysis of psychedelic research involving DoC patients.

In this article, we pose a series of questions (Table 1) to assist researchers in understanding how ethicists would analyze a psilocybin trial involving DoC patients. We focus on Scott and Carhart-Harris’s proposed research program, but the conceptual frameworks we apply—the Value-Validity Framework (Binik and Hey 2019) and Component Analysis (Weijer and Miller 2004)—are internationally accepted approaches for ethical analysis and can be readily used to evaluate other research protocols in the science of consciousness (cf. Weijer et al. 2016).

Psychedelic Research in DoC

DoC are neurological conditions in which consciousness is globally impaired for an extended period of time (Peterson and Bayne 2018). Following a period of coma due to traumatic or anoxic brain injury, a proportion of brain-injured patients may recover, whereas others may enter into a vegetative state (VS), minimally conscious state (MCS), or die (Jennett 2002). The VS is characterized by wakeful unresponsiveness, consistent with recovery of the reticular activating system (Jennett and Plum 1972). VS patients will open their eyes spontaneously and have semiregular sleep patterns but will display no evidence of awareness of self or environment. MCS patients, in contrast, show limited but discernable evidence of awareness, including the capacities to follow commands, recognize and use objects, respond appropriately to painful stimuli, or communicate (Giacino et al. 2002). Patients who recover from an MCS with aggressive rehabilitation may transition into an emergence from minimally conscious state (EMCS; Nakase-Richardson et al. 2012). EMCS patients show improved communication and cognitive function but are confused or lack situational orientation

(Nakase-Richardson et al. 2009). Patients who do not recover may remain in a VS or MCS indefinitely, or they may die as a result of withdrawal of care or medical complications secondary to their condition.

A precise mechanistic link between the loss of consciousness and brain injury has not yet been formulated. However, several hypotheses—including the mesocircuit hypothesis (Schiff 2010) and global workspace theory (Dehaene et al. 2011)—could have clinical value. One promising area of research involves the assessment of informational dynamics to determine whether a patient’s brain retains the capacity to integrate information, and whether this integration is associated with the modulation of consciousness. Casali et al. (2013) refined this technique by devising a novel index that represents the degree to which TMS perturbation can alter a large set of integrated brain regions over time. EEG recordings of a “TMS echo” can be expressed as a linear value, or perturbation complexity index (PCI), which tracks the degree to which a patient’s brain integrates information. High PCI values correlate with healthy, wakeful consciousness, whereas low PCI values correlate with impaired consciousness in clinically diagnosed VS and MCS patients. This complexity-based metric could improve prognostication and diagnostic accuracy in DoC patients who appear unresponsive at the bedside.

The success of complexity-based metrics in discriminating levels of consciousness in brain-injured patients has motivated researchers to refine these indices (Sitt et al. 2014; Schartner et al. 2015; Hudetz et al. 2016) as well as to identify interventions that might therapeutically modulate brain complexity. Controlled doses of psilocybin, as proposed by Scott and Carhart-Harris (2019), might be one pharmacological intervention that could increase brain complexity and potentially hasten recovery in VS, MCS, and EMCS patients.

Psilocybin is a serotonin 2A receptor agonist. Serotonin 2A receptor agonism, Scott and Carhart-Harris report, is “associated with enhanced cognitive flexibility [and] cortical neural plasticity” in animal models, whereas serotonin 2A receptor antagonism “is associated with reduced cognitive flexibility and slow-wave sleep” in humans (Zhang and Stackman 2015;

Table 1. Guiding ethical questions for conducting a psilocybin trial in DoC patients

Research ethics question	Description
Does a psilocybin trial involving DoC patients have clinical or social value?	Clinical value concerns whether a trial’s hypothesis is relevant to answering a pressing clinical question. Social value concerns the relevance of a trial’s hypothesis in addressing an important scientific or social problem.
Is the proposed psilocybin trial scientifically valid?	A protocol is valid if the study design is appropriate to answer the research question. The use of inappropriate or unreliable methods undermines the study’s potential to produce knowledge of clinical or social value.
Is psilocybin administration a therapeutic or nontherapeutic procedure?	Therapeutic procedures have an evidence base sufficient to justify the belief that they may be of direct benefit to research participants. Nontherapeutic procedures are used solely to answer a scientific question. Distinguishing therapeutic from nontherapeutic procedures allows for an accurate risk-benefit analysis of a trial.
Does psilocybin administration in DoC patients pose no more than a minor increase over minimal risk?	A key protection for vulnerable participants is the limit set on the risks to which they may permissibly be exposed for scientific purposes. This limit is universally recognized as the minimal risk threshold. It is unethical to apply nontherapeutic procedures in vulnerable participants that exceed this risk threshold.
Will research participants be selected fairly?	Fair selection of research participants ensures that the benefits and burdens of research participation are distributed equitably.
Will valid surrogate consent be sought for research participation?	Surrogate consent for research is permissible. Safeguards should be put in place to prevent therapeutic misconception or to address the possibility that a participant might regain consent capacity during the trial.

Carhart-Harris and Nutt 2017; Ly et al. 2018; Scott and Carhart-Harris 2019, 3). These cognitive changes are notable as serotonin 2A receptors are densest in structures associated with the default-mode network—an intrinsic cortical network associated with consciousness—and are predominately expressed postsynaptically on pyramidal cells with dendrites that span, and potentially integrate, all layers of the cortex. Preliminary neuroimaging studies support a potential relationship between psilocybin administration and increased brain complexity (Schartner et al. 2017) and, as Scott and Carhart-Harris note, “this finding has been replicated using a variety of complexity measures and measurement tools” (Carhart-Harris 2018; Scott and Carhart-Harris 2019, 3). These findings motivate Scott and Carhart-Harris’s hypothesis: if clinically meaningful changes in consciousness are closely associated with brain complexity, and brain complexity might be improved with psilocybin, then psilocybin might result in clinically meaningful improvements in consciousness among VS, MCS, and EMCS patients.

In what follows, we critically analyze this proposal through the lens of research ethics. We identify particular details in Scott and Carhart-Harris’s proposal, charitably interrogate their epistemic and ethical merit, and raise a number of practical suggestions that might assist researchers who are interested in proposing a psilocybin trial involving DoC patients.

Does a psilocybin trial involving DoC patients have clinical or social value?

New drug trials expose participants to risk and are resource intensive. These burdens may be justified, but only if the trial has sufficient clinical or social value. The Value-Validity Framework is a method for evaluating whether a trial’s burdens are justified by determining whether the underlying research question has clinical or social value (Binik and Hey 2019). Clinical value concerns whether a trial’s research question is relevant to answering a pressing clinical hypothesis, whereas social value concerns the relevance of the research question in addressing an important scientific or social problem. Ensuring that a trial’s research question has value promotes public trust in the scientific enterprise.

The research question encapsulated by Scott and Carhart-Harris’s proposal is whether psilocybin can modulate consciousness and hasten recovery in DoC patients. This research question has clinical value. Incidence of the VS in North America and Europe is estimated to be between 5 and 25 per million population (Beaumont and Kenealy 2005). Currently, there are few pharmacological treatments for these patients. Several drugs have been tested—Amantadine and Zolpidem are among the most promising—but results are mixed, and Amantadine has only just recently been recommended for clinical practice in the US practice guideline update on DoC (Giacino et al. 2018). In addition, the pharmacological mechanisms of these drugs differ from that of psilocybin. Psilocybin would thus be in a new category of agents, serotonin 2A receptor agonists, that could hasten recovery following brain injury.

The proposed research question also has scientific and social value. In the USA, 3.5 million traumatic brain injuries occur annually with a cost-burden of at least \$76.5 billion (Maas et al. 2017). The lifetime-care costs for DoC patients are further compounded by the need for long-term care and access to multidisciplinary rehabilitation (NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury 1999). In addition, determining how the brain produces consciousness remains one of the most important questions of modern science. Psilocybin trials in healthy participants have already yielded

important information regarding brain complexity and changes in states of consciousness. Application of psilocybin in DoC patients could further advance this knowledge.

Researchers interested in conducting a psilocybin trial involving DoC patients should emphasize the clinical and social value of this research. This value explains, in part, why conducting such a trial would be justified.

Is the proposed psilocybin trial scientifically valid?

A research protocol is scientifically valid if the trial design is appropriate to answer the proposed research question (Binik and Hey 2019). A protocol that lacks scientific validity would fail to justify the burdens placed on research participants even if the research question is socially or clinically valuable.

Scott and Carhart-Harris describe a research program involving healthy participant trials and adaptive trials for DoC patients. This research program is distinct from a specific trial design, so it is difficult to determine whether a psilocybin trial involving DoC patients would be scientifically valid. Nevertheless, one feature of their proposed research program requires careful scrutiny.

Scott and Carhart-Harris suggest that improvements in consciousness are closely associated with a participant’s brain complexity. They represent brain complexity as a Lempel-Ziv Complexity (LZC), which is an index of information “compressibility” (Sitt et al. 2014; Scott and Carhart-Harris 2019, 3). An LZC value can be calculated from either resting-state EEG, or from a PCI. “LZC-based values of spontaneous EEG,” Scott and Carhart-Harris observe, “reliably discriminate vegetative state from minimally conscious state patients and values increase monotonically with patients’ conscious level” (Scott and Carhart-Harris 2019, 3).

Scott and Carhart-Harris describe that the end-point measure of improvements in consciousness following psilocybin administration would be an LZC value. They note further that clinically validated neurobehavioral scales (e.g. the JFK-Coma Recovery Scale-Revised or the Wessex Head Injury Matrix) would be incorporated, where feasible (Scott and Carhart-Harris 2019, 6). But why should we believe that an LZC value will predict recovery absent of verification from clinically validated scales? Scott and Carhart-Harris review compelling evidence of the power of LZC values in discriminating conscious from unconscious DoC patients. Yet, to our knowledge, an LZC value is not a clinically-validated index for classifying DoC patients. The validity of a psilocybin trial would thus hang on the strength of associations between an LZC value and a clinical diagnosis. This feature of the trial design could be challenged. An LZC value might be used in phase II trials, but more pragmatic evaluations of clinical outcomes would be needed in later trials.

Complexity-based metrics used to assess improvements in consciousness might also be complicated by evidence showing that brain complexity can increase, rather than decrease, when a participant is unconscious. Schartner et al. (2017) recently demonstrated that subanesthetic doses of ketamine are associated with increases in LZC values. Yet, in contrast, an increase in PCI values has also been elicited in participants with anesthetic doses of ketamine, which render participants entirely unresponsive (Sarasso et al. 2015). To be sure, PCI values and LZC values represent different cortical functions associated with complexity. This might explain these opposite trends during ketamine induction. Nevertheless, different neurobiological mechanisms underlying the loss of consciousness in healthy participants (e.g. dissociation vs. increased inhibition) can yield

opposite results with complexity-based metrics. This raises the question as to whether a reliable baseline complexity-based metric can even be established to assess the effect of a drug.

We suggest that researchers interested in conducting a psilocybin trial involving DoC patients consider assessing participants with neurobehavioral scales as a complementary extension of complexity-based metrics. Researchers might begin a trial with LZC values as end-point measures, but more pragmatic, longitudinal assessment will likely be required as proof of the drug's efficacy as the research program matures.

Is psilocybin administration a therapeutic or nontherapeutic procedure?

Once it is established that a trial is valuable and scientifically valid, researchers may proceed to a risk-benefit analysis of the trial's procedures. Component analysis is an internationally accepted approach for judging the proportionality of a trial's risks and benefits (Weijer and Miller 2004). This method systematically disambiguates the risks associated with different trial procedures and identifies areas where safeguards could mitigate risk, consistent with valid scientific design.

Component analysis begins by asking which trial procedures are therapeutic and which are nontherapeutic. Therapeutic procedures are interventions that have an evidence base sufficient to justify the belief that they may be of direct benefit to research participants, whereas nontherapeutic procedures are used to solely answer a scientific question (Weijer and Miller 2004, 570). Distinguishing therapeutic from nontherapeutic procedures allows researchers to analyze their risks and benefits independently.

In the translational trajectory of drug development, a pharmacological intervention will predictably transition from a nontherapeutic procedure to a therapeutic procedure as its evidence base matures. Several trials must be conducted—in both healthy and clinical populations—before there is an evidence base sufficient to justify the drug's therapeutic benefit. We think that, early in its translational trajectory, psilocybin should be regarded as a nontherapeutic procedure for DoC patients. Scott and Carhart-Harris outline several important studies that demonstrate the effect of psilocybin on brain complexity (Schartner et al. 2017), and the relationship between brain complexity and consciousness (Wu et al. 2011; Casali et al. 2013; Sitt et al. 2014). But these studies do not make a direct connection between the administration of psilocybin and clinically valuable improvements in consciousness. The hypothesis that psilocybin might hasten recovery in DoC patients is thus contingent on a particular background theory regarding the relationship between brain complexity and consciousness (Tononi et al. 1994).

To be sure, Scott and Carhart-Harris acknowledge that brain complexity need not “be the cause of conscious awareness,” only that it is an “explanatory correlate of the neural processes intimately related to conscious awareness” for their hypothesis to be plausible (Scott and Carhart-Harris 2019, 3). Nevertheless, other competing theories of the neural mechanisms that are correlated with consciousness in DoC patients—the mesocircuit hypothesis and the global workspace theory—might also have clinical value (Schiff 2010; Dehaene et al. 2011). This tension among underlying theories tempers the idea that, without further evidence, psilocybin ought to be regarded as a therapeutic procedure.

Notwithstanding these theoretical concerns, the experimental evidence presented to justify psilocybin's therapeutic benefit might also be called into question. Scott and Carhart-Harris reference two historical studies involving the administration of another serotonin 2A agonist (Lysergic acid diethylamide or

LSD) while healthy participants were in non-REM sleep (Muzio et al. 1966; Torda 1968). Administration of LSD induced transient episodes of rapid-eye movement, which likely represented an improvement in consciousness. These studies are relevant for understanding the potential association between serotonin 2A agonists and consciousness. However, even if these studies were adequately replicated, it is unclear why changes in consciousness in healthy participants during non-REM sleep should be regarded as an experimental proxy for DoC patients. The mechanisms that underly changes in consciousness during sleep in healthy participants are likely radically different than those affected by severe brain injury.

In addition, to our knowledge, psilocybin has only just received “Breakthrough Therapy” designation from the U.S. Food and Drug Administration for trials involving patients with treatment-resistant depression (<https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment-resistant-depression/>). “Breakthrough Therapy” designation is an important step in advancing clinical research involving psilocybin, but such a designation is not transferable between clinical populations. The fact that there is promising—albeit preliminary—evidence of safety and tolerability of psilocybin in a psychiatric population does not itself warrant research involving DoC patients. Unlike psychiatric patients, DoC patients often sustain multiple injuries, are chronically or critically ill, and might be on other medications that could interact adversely with psilocybin. Moreover, to our knowledge, psilocybin has not been approved for any clinical use. This sets psilocybin apart from other pharmacological interventions in DoC patients, which have already been approved for other clinical applications.

Scott and Carhart-Harris propose conducting several experiments in healthy participants before implementing psilocybin in DoC patients. We commend Scott and Carhart-Harris for focusing first on studies involving healthy participants, as results from these studies could support claims regarding the drug's therapeutic benefit. However, in demonstrating the potential therapeutic benefit of psilocybin, we suggest that researchers carefully identify similarities and differences between control conditions (e.g. healthy participants in non-REM sleep or under sedation) and the neurological dysfunction characteristic of DoC patients. The mechanisms underlying the loss of consciousness in the former are likely to be distinct from those affected in the latter.

Does psilocybin administration pose no more than a minor increase over minimal risk?

Once a trial's procedures have been identified as either therapeutic or nontherapeutic, researchers can evaluate their respective risks and benefits. One approach to evaluating risks and benefits—as Scott and Carhart-Harris suggest (Scott and Carhart-Harris 2019, 4)—is to determine whether the total magnitude of the potential benefits is proportionate to the potential risks. Thus, in this case, it might be reasoned that the potential benefits of psilocybin to DoC patients, who may have no other therapeutic options, clearly outweigh any potential risks; DoC patients have nothing to lose and everything to gain.

We think that this approach is wrong for two reasons. First, focusing narrowly on risk-benefit proportionality ignores the potential vulnerability of research participants. Vulnerable participants are defined as those individuals who are at an increased likelihood of being wronged (Hurst 2008). Vulnerable participants might be unable to provide consent, be subject to coercion, or be members of a marginalized community. Examples of vulnerable

participants include children, prisoners, pregnant individuals, and people with cognitive disabilities. Ignoring the vulnerability of research participants can result in the attitude that some individuals are beyond harm or, in the extreme case, that they lack moral standing. We think this attitude should be resisted. The very fact that we regard DoC patients as individuals who have the potential to recover, rather than mere corpses, suggests that they do have moral standing and that the harms of research participation should be taken seriously (Peterson et al. 2019). Moreover, a vulnerable participant, precisely in virtue of her vulnerability, has far more to lose than a healthy individual if things go wrong during the research intervention.

Second, the presumption that risk-benefit proportionality is sufficient to justify research participation is inconsistent with national and international policies on research involving vulnerable participants (COIMS 2016). A key protection for vulnerable participants is the limit set on the risks to which they may permissibly be exposed for scientific purposes. The Declaration of Helsinki, which has been continually endorsed by the World Medical Association since its drafting in 1964, explicitly states that vulnerable participants “must not be included in a research study that has no likelihood of benefit for them unless [...] the research entails only minimal risk and minimal burden” (WMA 2013, Paragraph 28). DoC patients are vulnerable participants. They are, therefore, entitled to this minimal risk protection.

A standard interpretation of minimal risk is that it is the risk encountered in daily life; however, there is considerable debate in the literature regarding whose daily life this should be: a healthy individual or a clinical participant? The relevant issue for researchers proposing a psilocybin trial involving DoC patients is to consider whether the risk of psilocybin administration would exceed this threshold in either case.

To address this, Scott and Carhart-Harris describe a phase II psilocybin trial involving patients with treatment-resistant depression (Carhart-Harris et al. 2016; Carhart-Harris et al. 2018). They observe that, in this trial, “administration of oral psilocybin was well-tolerated [...], with the most common adverse events being mild transient anxiety just prior to as well as during drug onset” (Scott and Carhart-Harris 2019, 5). They also note that psilocybin has the potential to induce a transient unpleasant state of deep anxiety (or “bad trip”), although the frequency of this adverse psychological event is difficult to estimate.

To mitigate these risks, Scott and Carhart-Harris propose an adaptive trial design with dose escalation, beginning at very small dosages. They also propose adopting procedures from psychiatric trials, including drug administration in a familiar environment and ensuring that people who can provide psychological support are present (Scott and Carhart-Harris 2019, 5). These procedures are consistent with previous safety guidelines for human psychedelic research (Johnson et al. 2008).

We think that a more careful analysis of the potential risks of psilocybin administration in DoC patients is needed. We agree with Scott and Carhart-Harris that assumptions about the long-term negative psychological effects of psilocybin are largely unfounded (cf. Krebs and Johansen 2013; Johansen and Krebs 2015). Nevertheless, the possibility that adverse psychological events could result from a nontherapeutic procedure in a vulnerable population is cause for concern.

First, the risk mitigation procedures borrowed from trials in psychiatric populations might be insufficient for the variation and complexity of risk profiles in DoC patients. Risk mitigation in DoC patients presents a puzzle: different categories of DoC patients—VS, MCS, and EMCS—have variations in preserved

cognitive function that may, or may not, leave them susceptible to risks at the beginning of a trial. However, if psilocybin is successful, this may change a participant’s risk profile as the trial progresses. VS patients are not conscious and thus—at least, initially—would not be at risk of adverse psychological events, whereas EMCS patients are conscious and may be susceptible to pre-administration- or drug-onset-anxiety. Yet, if psilocybin was effective in a VS patient, this would change her risk profile; she would become susceptible to risks that she would not otherwise be subject to if she were unconscious. This raises complex questions regarding the probability of adverse psychological events, as the probability appears to be linked to, and changes with, the effectiveness of the drug and a participant’s diagnosis at enrollment. Ongoing risk assessment and mitigation that tracks the modulation of consciousness throughout a trial might be one way to resolve this problem.

Second, adverse psychological events might be compounded by the cognitive changes that occur when patients emerge from unconsciousness. The posttraumatic confusional state is a well-documented clinical phenomenon that occurs in EMCS patients. Posttraumatic confusion is characterized by sleep disturbances, psychotic episodes, and delirium (Sherer et al. 2005, 2014). This state is not itself a risk of research participation. The condition can be medically managed and, generally speaking, it is an indicator of a positive outcome of an intervention intended to hasten recovery. Nevertheless, the fact that posttraumatic confusion could be exacerbated by an adverse psychological event associated with psilocybin is cause for concern. A brain-injured patient might experience a “nightmarish” awakening rather than a smooth transition into consciousness. Administration of psilocybin in a familiar environment and providing psychological support could mitigate this risk, but these procedures might also be insufficient to address this unique clinical phenomenon.

Third, the fact that some DoC patients might be unable to communicate whether they are experiencing an adverse psychological event suggests that researchers are unlikely to know if such events are occurring. If psilocybin interacts with another medication causing the participant to become hypotensive, this could readily be detected with clinical monitoring equipment. Yet the detection of an adverse psychological event in DoC patients is not straightforward. VS patients cannot communicate, whereas MCS patients may or may not have preserved functional communication. Meanwhile, EMCS patients can communicate, but the range of their verbal repertoire is often limited to “yes” or “no” responses and they could lack situational awareness (Nakase-Richardson et al. 2009). These limitations could prevent DoC patients from immediately communicating their anxiety or efforts to seek psychological support. Proxy measures of anxiety, such as heart rate, perspiration, or respiration monitoring, combined with the proposed adaptive trial design could mitigate this risk, but only to the extent that researchers can reasonably know when things are going badly. Not knowing that a participant is experiencing an adverse psychological event makes this risk worse.

Finally, concerns could be raised about the use of TMS while DoC patients are under the influence of psilocybin. Magnetic perturbation of the cortex during increased cortical excitability of pyramidal cells could lead to unknown risks. These risks could also be compounded by changes in seizure thresholds following brain injury. This, again, points to complications in relying on a complexity-based metric as the sole end-point measure of a psilocybin trial. Deriving an LZC value from resting-state EEG, rather than a PCI, is likely the safest option for this clinical population.

Scott and Carhart-Harris defend the ethical legitimacy of their proposed trial by comparing psilocybin to other investigational interventions used in DoC patients. They note that “the invasive surgical implantation of Deep Brain Stimulation (DBS) electrodes has been carried out for 50 years, despite a lack of consistent evidence of benefits for improving conscious awareness” (Scott and Carhart-Harris 2019, 5). If such procedures were deemed ethical in the past, they reason, then surely psilocybin should be too.

This is a bad argument, for it assumes that the investigational implantation of DBS electrodes in DoC patients is, in fact, ethical. To be convincing, Scott and Carhart-Harris need to argue that DBS is ethical before comparing it to psilocybin administration. This concern notwithstanding, we think that discussion of DBS should not be a central consideration for justifying a psilocybin trial involving DoC patients. Ethics committees might appeal to past precedent when evaluating a novel trial, but past precedent alone is insufficient to justify a current trial’s ethical permissibility.

If researchers are interested in proposing a psilocybin trial involving DoC patients, they should clearly demonstrate how administration poses no more than a minor increase over minimal risk, and how the proposed risk mitigation procedures are commensurate with the unique challenges posed by this clinical population. For example, a risk management protocol for psilocybin-induced anxiety could help researchers address these challenges as they arise. The protocol might specify when researchers should block the acute influence of psilocybin with a 2A receptor antagonist, reduce anxiety with pharmacological sedation, or use a combination of both.

Will research participants be selected fairly?

The ethical principle of justice requires that research participants be selected fairly. Fair selection ensures that the benefits and burdens of research participation are distributed equitably (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; WMA 2013; COIMS 2016).

A long-standing heuristic in research ethics is that recruitment of research participants should proceed from the least vulnerable to the most vulnerable, provided that the research can be carried out equally as well in either population (cf. COIMS 2002, Guideline 13). Application of this heuristic in a proposed psilocybin trial bears on the question of scientific validity. Who should be recruited for a psilocybin trial to ensure scientific validity and satisfaction of the principle of justice? Should researchers transition directly from healthy participant trials to studies involving noncommunicative DoC patients? Or should there be intermediary steps in participant selection?

Scott and Carhart-Harris state that the initial “patient inclusion criteria and recruitment protocol would be similar to previous early-phase pharmacology studies in [DoC patients]” (Scott and Carhart-Harris 2019, 5). What do these inclusion criteria look like? One early-phase trial of Amantadine recruited DoC patients 4–16 weeks after traumatic brain injury (Giacino et al. 2012). This ensured that participants were medically stable, but still early enough in their recovery that pharmacological intervention might yield measurable results. In addition, previous pharmacological trials have either excluded patients with nontraumatic etiologies (Giacino et al. 2012) or used mixed samples of traumatic and nontraumatic patients (Thonnard et al. 2013).

Early recruitment of DoC patients raises several questions. Such patients might still be comatose, and may be receiving other treatments that compete with psilocybin. For example, ketanserin, which is used as either an anti-hypertensive or to

reduce shivering in the operating room, might be indicated after severe brain injury (Leslie and Sessler 2003). But this drug is also a 2A receptor antagonist and is known to block the effects of psilocybin. Would a trial require that patients forgo this medication? If so, would this be justified? Further, if some patients are recruited early in recovery, they might still be hospitalized in an intensive care unit. Research involving patients in intensive care is ethically complicated (Truog 2005). Participation in a trial could impede the individualized care that DoC patients need in the early stages of recovery. This would be difficult to justify if the trial’s procedures are nontherapeutic.

We think that a plausible approach to recruitment is to begin with healthy participants and then progress to clinical populations with incrementally worse cognitive impairment. This would allow researchers to determine safety, tolerability, and dosing in healthy and medically stable clinical participants who can communicate (e.g. EMCS patients) prior to application in noncommunicative patients (e.g. VS or comatose patients). Not only would this allow for accurate identification of adverse psychological events, but it would also ensure that the most vulnerable brain-injured patients are not disproportionately burdened by research participation.

Will valid surrogate consent be sought for research participation?

The ethical principle of respect for persons requires that researchers seek the consent of participants for research participation (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; WMA 2013; COIMS 2016).

Some research participants lack the capacity to consent (e.g. people with cognitive disabilities or children). However, clinical research in these populations could be valuable and most jurisdictions agree that surrogate consent for research is authorized.

DoC patients require surrogate consent for research participation. There are several ethical issues that researchers should be sensitive to when seeking surrogate consent. First, the surrogates of DoC patients—usually next of kin—might misunderstand the research or overestimate the therapeutic value of the intervention. Safeguards should be put in place to ensure that this misunderstanding does not occur (Bruni et al. 2019). Researchers should first clear the consent procedure with the clinical team. The clinical team will have the strongest sense of a family’s attitudes toward research participation. In addition, consent should be sought in a private space where the surrogate can adequately process the risks of psilocybin administration. The consent form should be short, be written at a level that can be understood by the surrogate, and be explicit as to whether psilocybin administration is a therapeutic or nontherapeutic procedure (Nishimura et al. 2013). These safeguards will help surrogates understand the research protocol and current knowledge regarding the therapeutic benefit of the drug.

In addition, it is also plausible that, if psilocybin is effective at hastening recovery, some participants may regain the capacity to voice their preferences regarding continued participation in the trial. Researchers should prepare for this by incorporating ongoing evaluation of decision-making capacity in the trial. This could involve a modified capacity assessment for people with communication impairments (Cairncross et al. 2016), or an assent-dissent model similar to that used in research involving children (Levy et al. 2003).

Conclusion

This article provided an ethical analysis of psychedelic research involving DoC patients. We focused on Scott and Carhart-Harris's proposal, but the ethical frameworks described are applicable to other research protocols in the science of consciousness. We encourage researchers to use these frameworks when proposing new studies involving DoC patients. The frameworks support the overall strength of the scientific enterprise and assure ethics committees that researchers are taking the protection of vulnerable participants seriously.

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References

- Beaumont JG, Kenealy PM. Incidence and prevalence of the vegetative and minimally conscious states. *Neuropsychol Rehabil* 2005;15:184–9.
- Binik A, Hey SP. A framework for assessing scientific merit in ethical review of clinical research. *Ethics Human Res* 2019;41:2–13.
- Bruni T, Graham M, Norton L, et al. Informed consent for functional MRI research on comatose patients following severe brain injury: balancing the social benefits of research against patient autonomy. *J Med Ethics* 2019;45:299–303.
- Cairncross M, Peterson A, Lazosky A, et al. Assessing decision-making capacity in patients with communication impairments: a case study. *Cambridge Q Healthcare Ethics* 2016;25:691–9.
- Carhart-Harris RL. The entropic brain-revisited. *Neuropharmacology* 2018;142:167–78.
- Carhart-Harris RL, Bolstridge M, Day CM, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology* 2018;235:399–408.
- Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 2016;3:619–27.
- Carhart-Harris RL, Nutt DJ. Serotonin and brain function: a tale of two receptors. *J Psychopharmacol* 2017;31:1091–120.
- Casali AG, Gosseries O, Rosanova M, et al. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med* 2013;5:198ra105.
- Council for International Organizations of Medical Sciences (COIMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: World Health Organization, 2002.
- Council for International Organizations of Medical Sciences (COIMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: World Health Organization, 2016.
- Dehaene S, Changeux JP, Naccache L. The global neuronal workspace model of conscious access: from neuronal architectures to clinical applications. In: Dehaene S, Christen Y (eds), *Characterizing Consciousness: From Cognition to the Clinic?* Berlin: Springer, 2011, 55–84.
- Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002;58:349–53.
- Giacino JT, Katz DI, Schiff ND, et al. 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. *Arch Phys Med Rehabil* 2018;99:1699–709.
- Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012;366:819–26.
- Hudetz AG, Liu X, Pillay S, et al. Propofol anesthesia reduces Lempel-Ziv complexity of spontaneous brain activity in rats. *Neurosci Lett* 2016;628:132–5.
- Hurst SA. Vulnerability in research and health care; describing the elephant in the room? *Bioethics* 2008;22:191–202.
- Jennett B. The vegetative state. *J Neurol Neurosurg Psychiatry* 2002;73:355–7.
- Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. *Lancet* 1972;299:734–7.
- Johansen PØ, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. *J Psychopharmacol* 2015;29:270–9.
- Johnson MW, Richards WA, Griffiths RR. Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 2008;22:603–20.
- Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. *PLoS One* 2013;8:e63972.
- Leslie K, Sessler DI. Perioperative hypothermia in the high-risk surgical patient. *Best Pract Res Clin Anaesthesiol* 2003;17:485–98.
- Levy MD, Larcher V, Kurz R. Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). *Eur J Pediatr* 2003;162:629–33.
- Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. *Cell Rep* 2018;23:3170–82.
- Maas AI, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017;16:987–1048.
- Muzio JN, Roffwarg HP, Kaufman E. Alterations in the nocturnal sleep cycle resulting from LSD. *Electroencephalogr Clin Neurophysiol* 1966;21:313–24.
- Nakase-Richardson R, Whyte J, Giacino JT, et al. Longitudinal outcome of patients with disordered consciousness in the NIDRR TBI Model Systems Programs. *J Neurotrauma* 2012;29:59–65.
- Nakase-Richardson R, Yablon SA, Sherer M, et al. Emergence from minimally conscious state: insights from evaluation of posttraumatic confusion. *Neurology* 2009;73:1120–6.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research*. Washington, DC: Government Printing Office, 1979.
- NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. Rehabilitation of persons with traumatic brain injury. *JAMA* 1999;282:974–983.
- Nishimura A, Carey J, Erwin PJ, et al. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Med Ethics* 2013;14:28.
- Peterson A, Bayne T. Post-comatose disorders of consciousness. In: Gennaro R (ed.), *The Routledge Handbook of Consciousness*. New York: Routledge, 2018, 351–365.

- Peterson A, Owen AM, Karlawish J. Alive inside. *Bioethics*, 2019; doi: 10.1111/bioe.12678.
- Sarasso S, Boly M, Napolitani M, et al. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. *Curr Biol* 2015;25:3099–105.
- Schartner M, Seth A, Noirhomme Q, et al. Complexity of multidimensional spontaneous EEG decreases during propofol induced general anaesthesia. *PLoS One* 2015;10:e0133532.
- Schartner MM, Carhart-Harris RL, Barrett AB, et al. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. *Sci Rep* 2017;7:46421.
- Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci* 2010;33:1–9.
- Scott G, Carhart-Harris RL. Psychedelics as a treatment for disorders of consciousness. *Neurosci Conscious* 2019;2019:niz003.
- Sherer M, Nakase-Thompson R, Yablon SA, et al. Multidimensional assessment of acute confusion after traumatic brain injury. *Arch Phys Med Rehabil* 2005;86:896–904.
- Sherer M, Yablon SA, Nick TG. Psychotic symptoms as manifestations of the Posttraumatic Confusional State: prevalence, risk factors, and association with outcome. *J Head Trauma Rehabil* 2014;29:E11–8.
- Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain* 2014;137:2258–70.
- Thonnard M, Gosseries O, Demertzi A, et al. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. *Funct Neurol* 2013;28:259.
- Tononi G, Sporns O, Edelman GM. A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci USA* 1994;91:5033–7.
- Torda C. Contribution to serotonin theory of dreaming (LSD infusion). *N Y State J Med* 1968;68:1135–8.
- Truog RD. Will ethical requirements bring critical care research to a halt? *Intensive Care Med* 2005;31:338–44.
- Weijer C, Bruni T, Gofton T, et al. Ethical considerations in functional magnetic resonance imaging research in acutely comatose patients. *Brain* 2016;139:292.
- Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? *Nat Med* 2004;10:570.
- World Medical Association (WMA). *Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects*. WMA, October, 2013. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (20 July 2019, date last accessed).
- Wu DY, Cai G, Yuan Y, et al. Application of nonlinear dynamics analysis in assessing unconsciousness: a preliminary study. *Clin Neurophysiol* 2011;122:490–8.
- Zhang G, Stackman RW Jr. The role of serotonin 5-HT_{2A} receptors in memory and cognition. *Front Pharmacol* 2015;6:225.