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Neuroimaging Research into Disorders of Consciousness

Moral Imperative or Ethical and Legal Failure?

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ABSTRACT

This article explores the ethical and legal implications of enrolling individuals with disorders of consciousness (DOC) in neuroimaging research studies. Many scientists have strongly emphasized the need for additional neuroimaging research into DOC, characterizing the conduct of such studies as morally imperative. On the other hand, institutional review boards charged with approving research protocols, scientific journals deciding whether to publish study results, and federal agencies that disburse grant money have limited the conduct, publication, and funding of consciousness investigations based on ethical and legal concerns. Following a detailed examination of the risks and benefits of neuroimaging research involving individuals with DOC, the author urges IRBs, scientific journals, and funding agencies to no longer stall the conduct, publication, and funding of neuroimaging research into DOC if certain criteria designed to protect the health and safety of individuals with DOC are satisfied.

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I. INTRODUCTION

¶ 1 For centuries, disorders of consciousness[1] have captured the attention of

[1] The nature of consciousness is widely debated and difficult to define. *See, e.g.*, TORIN ALTER & SVEN WALTER, PHENOMENAL CONCEPTS AND PHENOMENAL KNOWLEDGE: NEW ESSAYS ON CONSCIOUSNESS AND PHYSICALISM (2006) (examining the nature of consciousness); Michel Jouvet, *Coma and Other Disorders of Consciousness*, *in* 3 HANDBOOK OF CLINICAL NEUROLOGY 116 (P. J. Vinken & G. W. Bruyn eds., 1969) ("[C]onsciousness is very difficult to define."). In this article, I adopt a clinical neuroscience approach and use the word "consciousness" to refer to two elements: an individual's wakefulness and her awareness of self and environment. *See, e.g.*, Steven Laureys et al., *Self-Consciousness in Non-Communicative Patients*, 16 CONSCIOUSNESS & COGNITION (forthcoming) ("For the purposes of clinical neurosciences, consciousness consists of two basis elements: *arousal* (*i.e.*, wakefulness, vigilance or level of consciousness) and *awareness of environment and of self* (*i.e.*, content of consciousness)."); Steven Laureys, *The Neural Correlate of (Un)awareness: Lessons from the Vegetative State*, 9 TRENDS COGNITIVE SCIENCES 556, 556 (2005) ("Consciousness has two main components: wakefulness and awareness."). I use the phrase "disorders of consciousness" to refer to coma, the vegetative state, and the minimally conscious state. THE MOHONK REPORT, A REPORT TO CONGRESS: DISORDERS OF CONSCIOUSNESS: ASSESSMENT, TREATMENT, AND RESEARCH NEEDS 6, *available at* http://www.nbirtt.org/resources/Mohonk_Report_Press_V2.pdf (last visited July 19, 2007) [hereinafter, MOHONK REPORT] (defining disorders of consciousness, including coma, vegetative state, and minimally conscious state). *See infra* Part I(A) for relevant definitions and diagnostic criteria.

physicians, scientists, philosophers, lawyers, and families.[2] When an individual partially or completely loses consciousness, the answers to questions such as "Can she hear me?" "Does he understand me?" "Is she suffering?" and "Will he get better?" can have profound clinical, ethical, legal, and social consequences.[3] In this article, I explore the ethical and legal implications of enrolling individuals with disorders of consciousness in neuroimaging research studies.

¶ 2 Since the middle of the nineteenth century, physicians have used the traditional neurological examination to diagnose disorders that we now classify as coma, vegetative state, and minimally conscious state.[4] Although coma can be diagnosed with relative ease, the differential diagnosis of the vegetative and minimally conscious states can be challenging.[5] In addition, clinicians presently know of no medications or surgical interventions that will definitively reduce the length of an individual's impaired consciousness.[6]

¶ 3 Over the past decade, however, scientists have used various functional neuroimaging technologies to better understand disorders of consciousness, improve differential diagnoses, predict short-term improvement, and lay the foundation for future studies that may, someday, identify methods of communicating and treating individuals with disorders of consciousness.[7] During the past four years, scientists have made a

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[2] *See* GERMAN E. BERRIOS, THE HISTORY OF MENTAL SYMPTOMS: DESCRIPTIVE PSYCHOPATHOLOGY SINCE THE NINETEENTH CENTURY (1996) (surveying the history of mental disorders, including disorders of consciousness, from the nineteenth century to the present).

[3] *See* Laureys, *Neural Correlate*, *supra* note 1, at 557 (asking, "Do patients in a vegetative state feel or hear anything?"); Joy Hirsch et al., *fMRI Reveals Intact Cognitive Systems in Two Minimally Conscious Patients*, SOC'Y FOR NEUROSCIENCE (2001), *available at* http://fmri.org/pdfs/NS2001.pdf (last visited July 9, 2007) (asking these questions); Joseph J. Fins, *Rethinking Disorders of Consciousness*, HASTINGS CENTER REPORT, May 31, 2005, at 22-24 (examining how functional neuroimaging study results are used to cast doubt on the ethical propriety of withholding and withdrawing life-sustaining treatment); MOHONK REPORT, *supra* note 1, at 17 ("Disorders of consciousness have profound social, ethical, and economic consequences.").

[4] Very generally, a neurological examination is the clinical assessment of a patient by a physician to determine, among other things, the patient's responsiveness to external stimuli. *See, e.g.*, Roger A. Barker, *The Neurological Assessment of Patients in Vegetative and Minimally Conscious States*, 15 NEUROPSYCHOLOGICAL REHABILITATION 214, 214 (2005) (describing the neurological assessment of patients in the vegetative and minimally conscious states). The modern neurological examination evolved between 1850 and 1914. B.M. Patten, *The History of the Neurological Examination*, 1 J. HIST. NEUROSCIENCE 3, 3 (1992).

[5] Lawrence R. Huntoon, *The Perilous Vegetative State*, 10(2) J. AM. PHYSICIANS & SURGEONS 35, 35 (2005) (recognizing the difficulty of differentially diagnosing the vegetative and minimally conscious states); Roxanne Pickett Hauber, *Better Care for Low-Level Brain-Injured Patients and Their Families*, J. NEUROSCIENCE NURSING, Feb. 1, 2002, ("While the state of coma is relatively easy to diagnose, differential diagnosis of other states of reduced consciousness, such as the vegetative and minimally conscious states, have proven to be much more difficult.").

[6] *See, e.g.*, Steven Laureys et al., *How Should Functional Imaging of Patients with Disorders of Consciousness Contribute to Their Clinical Rehabilitation Needs?*,19 CURRENT OPINION NEUROLOGY 520, 520 (2006) ("No treatment has been proven to alter the course of recovery from [vegetative state] or [minimally conscious state].").

[7] *See, e.g.*, *infra* notes 8-10. *See generally* Joseph T. Giacino et al., *Functional Neuroimaging Applications for Assessment and Rehabilitation Planning in Patients with Disorders of Consciousness*, 87 ARCHIVES PHYSICAL MED. REHABILITATION S67, S67 (2006) (reviewing the use of fMRI to "characterize the integrity

number of important findings. In a 2005 study, several American scientists found that some individuals in the minimally conscious state may retain widely distributed cortical systems that have potential for cognitive and sensory function.[8] In a 2006 study, several European scientists concluded that functional neuroimaging might be a means by which individuals with disorders of consciousness can use their residual cognitive capabilities to communicate their thoughts to those around them.[9] And, in a 2007 study, scientists from China and Belgium suggested that traditional behavioral assessments can miss cerebral processing that might herald short-term improvement.[10]

¶ 4 In light of these findings, many scientists have strongly emphasized the need for additional neuroimaging research into disorders of consciousness,[11] characterizing the conduct of such studies as morally imperative.[12] On the other hand, institutional review boards (IRBs) charged with approving research protocols, scientific journals deciding whether to publish study results, and federal agencies that disburse grant money have limited the conduct, publication, and funding of consciousness investigations based on ethical and legal concerns.[13] Although several issues have been raised, perhaps the two most prominent relate to the relationship between informed consent and neuroimaging

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of residual cortical networks and . . . search for neural evidence of cognitive function in patients with disorders of consciousness.”).

[8] Nicholas D. Schiff et al., *fMRI Reveals Large Scale Activation in Minimally Conscious Patients*, 64 NEUROLOGY 514, 514 (2005).

[9] Adrian M. Owen et al., *Detecting Awareness in the Vegetative State*, 313 SCIENCE 1402, 1402 (2006).

[10] H.B. Di et al., *Cerebral Response to Patient’s Own Name in the Vegetative and Minimally Conscious States*, 68 NEUROLOGY 895, 898 (2007).

[11] *See, e.g.*, Joy Hirsch, *Raising Consciousness*, 115 J. CLINICAL INVESTIGATION 1102, 1103 (2005) (“[A]ccelerated research efforts focused on both investigations of consciousness and disorders of consciousness, as well as resolution of the many obstacles to performing the research, could bring about a ‘quantum leap’ in advantages for informed clinical practice serving severely brain-injured patients.”); Steven Laureys et al., *Brain Function in Coma, Vegetative State, and Related Disorders*, 3 LANCET NEUROLOGY 537, 544 (2004) (“Severe brain damage represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious, and locked-in patients deserve special procedural protections. However, it is important to stress that they are also at risk of being denied therapy that may be life-saving if clinical research cannot be done on these patient groups.”); *see also* Steven Laureys, *Eyes Open, Brain Shut*, SCIENTIFIC AMERICAN, May 2007, at 32, 37 (“We have learned much from new imaging techniques that measure neural activity in brain-damaged patients, but more research is needed before scientists can use functional neuroimaging to confirm a diagnosis of the vegetative state and to help in the prognosis and treatment of this devastating medical condition.”).

[12] Douglas Steinberg, *Consciousness Is Missing—and So Is Research*, 6 EMBO Rep. 1009, 1011 (2005) (“Therefore, some observers see a moral imperative, not just an ethical trap, in the study of consciousness disorders.”). *See also* Benedict Carey, *Signs of Awareness Seen in Brain-Injured Patients*, N.Y. TIMES, Feb. 8, 2005 (quoting Columbia neurologist Joy Hirsch’s statement that the failure to conduct additional neuroimaging research is “unconscionable”).

[13] Steinberg, *supra* note 12, at 1009 (identifying several legal and ethical concerns); Laureys et al., *Brain Function*, *supra* note 11, at 544 (“Nonetheless, researchers studying these patients have been refused grants, ethics committee approval, and research publication; these decisions tend to be made on the basis that studies of patients who cannot provide consent are unethical.”). *See generally* Marcia Angell, *Editorial Responsibility: Protecting Human Rights by Restricting Publication of Unethical Research in* THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 276, 281 (George J. Annas & Michael A. Grodin eds. 1992) (discussing the emerging consensus that editors of scientific journals should not publish clearly unethical research).

risks and benefits.[14] Some believe that functional neuroimaging studies do not directly benefit individuals with disorders of consciousness, which may cause legal risks-to-benefits balancing tests[15] to balance in favor of no research.[16] Others focus on the inability of individuals with disorders of consciousness to consent to their own research participation, thus implicating ethical and legal principles relating to voluntary and informed consent.[17]

¶ 5 To further confuse matters, the proper interpretation of relevant ethical and legal principles, including the relationship between neuroimaging research risks and benefits and surrogate consent to research involving adults, is not clear. In the United States, neither federal nor most state laws provide a nuanced definition of "research benefit."[18] When we balance research risks and benefits, do we consider only long-term, grand-scale therapeutic benefits? What about short-term clinical improvements, such as a change from the vegetative to the minimally conscious state? What about the benefit of diagnostic clarity? Federal law also does not specifically address the issue of consent to research on behalf of adults with disorders of consciousness (or even adults with other decisional impairments, including severe psychiatric conditions and developmental disabilities),[19] and state law in this area varies, if it exists at all.[20] The lack of federal

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[14] *See infra* Part I(E) (discussing these concerns in more detail).

[15] 45 C.F.R. § 46.111(a)(2) (2007) (requiring the risks of human subjects research to be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.").

[16] Steinberg, *supra* note 12, at 1009. See *infra* Part I(E), for a brief discussion of the legal and ethical concerns frequently raised by institutional review boards, scientific journals, and funding agencies, and *infra* Part III, for an analysis of these issues.

[17] 45 C.F.R. § 46.111(a)(4) (2007) (requiring scientists conducting human subjects research to seek informed consent from each prospective subject or the subject's legally authorized representative); *id*. § 46.116 ("Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.").

[18] *See* 45 C.F.R. § 46.102 (2007) (the definition section of the Common Rule, which does not define the word benefit); *id*. § 46.111(a)(2) (stating simply that research risks must be reasonable in relation to "anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.)"; Nancy M. P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J. L MED. & ETHICS 332, 332 (2000) ("The Common Rule actually doesn't say much about benefit."); Jonathan Moreno, *Regulation of Research on the Decisionally Impaired: History and Gaps in the Current Regulatory System*, 1 J. HEALTH CARE L. & POL'Y 1, 15 (1998) ("The [National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's] recommendations were virtually silent about what constitutes 'benefit' to the subject . . . ").

[19] A decisional impairment may manifest itself for one or more reasons, including a psychiatric condition, developmental disability, dementia, use of drugs and alcohol, and severe illness, just to name a few. The law tends to refer to individuals with decisional impairments as "incompetent" or "incapacitated." In this Article, I will use the phrase "decisional impairment" as opposed to "incompetence" or "incapacity" because decisional impairment is the reason why a particular individual might not be. *See generally infra* Part II(D) (examining the development of federal law governing human subjects research and explaining its failure to address research involving adults with decisional impairments).

[20] *See* Moreno, *supra* note 18, at 14 ("The states are a crazy quilt of regulation in this area, with most having no rules that clearly apply to this group while some are quite restrictive."); *infra* Part II(E) (examining the development of state law governing human subjects research).

guidance and the patchwork of state law can make it difficult for American scientists, IRBs, scientific journals, and funding agencies to agree on an applicable regulatory framework, especially when the research may be conducted in a laboratory located in one city but will draw patients who are residents of neighboring states.[21]

¶ 6 The result of this confusion is a chasm, or perhaps a perceived chasm, between scientists, who may appear to be overstepping ethical and legal boundaries in their pursuit of knowledge and diagnostic clarity even though they have expressly considered the ethical and legal implications of their work,[22] and ethics committees, scientific journals, and funding agencies, which are charged with protecting human subjects and publishing and funding only ethical and legal protocols but do not have black-and-white rules to guide their efforts.[23] This article attempts to bridge this chasm. Because I think that this chasm (real or perceived) lacks balance and subtlety, I attempt to interpret neuroimaging research, ethics, and law in the same dimension, rather than assuming that neuroimaging research, ethics, and law are necessarily in conflict.[24]

¶ 7 In Part I, I will introduce the use of functional magnetic resonance imaging as a tool in the investigation of disorders of consciousness and examine three neuroimaging research protocols involving individuals in vegetative and minimally conscious states.[25] My aim is to familiarize the reader with the ways in which scientists use functional neuroimaging to study disorders of consciousness, the knowledge that is expected to result from these studies, the benefits (if any) that may accrue to the research subjects, the persons who consent to research participation on behalf of the subjects, the process for obtaining consent, and any specific procedures that may have been established to protect the subjects' safety and welfare during their research participation. As you read Part I, think about any tensions, real or perceived, between the scientific goals of pursuing knowledge, obtaining diagnostic clarity, and predicting short-term clinical improvement and society's need to protect the health and welfare of human subjects, especially subjects who may not be able to protect themselves.

¶ 8 In Part II, I provide an abbreviated history of human subjects research involving individuals with decisional impairments as well as the development of relevant American[26] ethical and legal human-subjects protections. These protections emerged after it was discovered that scientists recruited individuals with psychiatric disorders and

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[21] *See, e.g.*, Steinberg, *supra* note 12, at 1010 (describing an institutional review board's attempt to stop a research protocol involving individuals with disorders of consciousness because the individuals could not consent to their own research participation, as well as the scientist's successful defense, which was that the patients resided in states that permit proxy consent).

[22] *See, e.g.*, Fins, *supra* note 3, at 23 ("bioethicists need to grapple with the imponderables, both theoretical and practical, that attend to disorders of consciousness.").

[23] *See infra* Part II(D) (discussing the lack of federal guidance with respect to research involving adults with decisional impairments).

[24] *See* Chris Gastmans, *Introduction*, *in* BETWEEN TECHNOLOGY AND HUMANITY: THE IMPACT OF TECHNOLOGY ON HEALTH CARE ETHICS 9 (2002) (taking a similar approach to the perceived relationship between technology and health care).

[25] *See infra* Part I.

[26] A cross-country comparison of human subjects protections is worthwhile although beyond the scope of this Article.

developmental disabilities into risky experiments unrelated to their conditions.[27] As you read Part II, think about whether protections developed as a result of ethically questionable studies involving individuals with psychiatric conditions and developmental disabilities are, or should be, applicable to studies involving patients in the vegetative and minimally conscious states.

¶ 9 In Part III, I examine whether additional neuroimaging research into disorders of consciousness is a moral imperative or an ethical and legal failure. I analyze in detail the relationship between and among the risks of neuroimaging research in a consciously disordered population, the reported therapeutic and diagnostic benefits, and the knowledge that may be expected to result. I conclude by calling for a federal regulation (or, barring a federal regulation, uniform state laws) that addresses surrogate consent to human subjects research involving individuals with decisional impairments.

¶ 10 A note about my language choices in this article: The use of words and phrases in particular orders can reflect negative and disparaging attitudes about individuals with physical and mental disabilities.[28] For decades, society has referred to individuals with disabilities by their disability first and their individuality second.[29] One guiding principle to maintain the integrity of individuals as whole human beings is to avoid language that implies that a person as a whole is disabled by identifying the individual first, then her condition. "An individual with a disability," "an individual with a disorder of consciousness," or "an individual in the vegetative state" is preferable to "a disabled individual," "a consciously disordered individual," or "a vegetative individual," although the latter phrases are less bulky. I have made a concerted effort to adhere to these principles, although I do use four acronyms, including disorder of consciousness (DOC), locked-in syndrome (LIS), minimally conscious state (MCS), and vegetative state (VS) to streamline my sentences. In addition, it is technically correct to refer to "a patient who has a DOC," "a patient who has LIS," "a patient who is in the MCS," and "a patient who is in the VS"; however, I will delete the phrases "who has" and "who is in the" and just use "a patient with DOC," "a patient with LIS," "a patient in MCS," and "a patient in VS" to further streamline my sentences.

II. NEUROIMAGING RESEARCH INTO DISORDERS OF CONSCIOUSNESS

A. Functional Neuroimaging and Disorders of Consciousness: An Overview

¶ 11 One of the fastest growing scientific fields in terms of the numbers of scientists and the knowledge being gained is neuroscience.[30] Neuroscience is devoted to the scientific study of the nervous system, including its structure, function, development,

[27] *See infra* Parts II(A)-(C).
[28] *See, e.g.*, American Psychiatric Association, Committee on Disability Issues in Psychology, Guidelines for Non-Handicapping Language in APA Journals, http://apastyle.apa.org/disabilities.html (last visited July 16, 2007).
[29] *Id.*
[30] JONATHAN D. MORENO, MIND WARS: BRAIN RESEARCH AND NATIONAL DEFENSE 3 (2006).

genetics, biochemistry, physiology, pharmacology, and pathology.[31] "In recent years, both the scope of neuroscience and the methodologies employed by neuroscientists have broadly expanded, from biochemical and genetic analysis of dynamics of individual nerve cells and their molecular constituents to the imaging of both brain structure and function."[32] Some believe that the ability of modern neuroimaging techniques to image brain structure and function is one of the most significant neuroscientific achievements in recent history.[33] This article focuses on neuroscientific investigations involving one particular type of functional neuroimaging technology—functional magnetic resonance imaging (fMRI)—to image the brain function of individuals with DOCs.

¶ 12 Although fMRI is in only its second decade, scientists already have conducted tens of thousands of human subjects research studies using the technology, which identifies localized changes in blood oxygenation that occur in the brain when an individual performs an active or a passive mental task.[34] Scientists use fMRI not only to map sensory, motor, and cognitive function but also to study the neural correlates of a range of physical and mental conditions, behaviors, characteristics, and preferences.[35] Because fMRI is a powerful method of imaging human brain function, especially impaired brain function,[36] many scientists are interested in imaging the brains of individuals with DOCs.[37]

¶ 13 In a typical fMRI experiment, scientists assign subjects one or more active or passive control and experimental tasks and scan their brains during the performance of such tasks.[38] fMRI captures in images the different blood-oxygenation-level-dependent (BOLD) contrasts that result from the control and experimental tasks.[39] By subtracting the control images from the experimental images, scientists create "maps" of the brain

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[31] *See id*. at 17.

[32] *Id*. *See also* Peter Woodruff, *Imaging the Brain: Clinical and Research Implications for Neuropsychiatry*, *in* BETWEEN TECHNOLOGY AND HUMANITY: THE IMPACT OF TECHNOLOGY ON HEALTH CARE ETHICS 145, 147-50 (Chris Gastmans ed., 2002) (providing an overview of structural and functional imaging of the brain).

[33] WALTER GLANNON, BIOETHICS AND THE BRAIN 45 (2007).

[34] David G. Norris, *Principles of Magnetic Resonance Assessment of Brain Function*, 23 J. MAGNETIC RESONANCE IMAGING 794, 794-95 (2006); David Dobbs, *Hard Science or "Technicolor Phrenology?": The Controversy over fMRI*, SCIENTIFIC AMERICAN MIND, Apr. 2005, *available at* http://daviddobbs.net/page2/page6/page6.html (last visited July 9, 2007). *See generally* Stacey A. Tovino, *Functional Neuroimaging Information: A Case for Neuro Exceptionalism?* 34 FLA. ST. U. L. REV. 415, Parts II and III (2007) (thoroughly reviewing the history of fMRI and its current clinical, research, and social applications).

[35] *See* Tovino, *supra* note 34, at n.198-226; MORENO, *supra* note 30, at 98 ("Many . . . projects make use of functional magnetic resonance imaging (fMRI), one of the most exciting windows into the black box.").

[36] *See, e.g.*, Judy Illes et al., *Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging*, 3 BRAIN & COGNITION 358, 358 (2002); Judy Illes, Ethical Issues at the Intersection of Imaging and Genomics, Presentation at the Princeton University Symposium: Politics of Biomedical Research: Issues, Information and Policy Decision-Making (Mar. 28, 2003).

[37] Laureys et al., *Brain Function*, *supra* note 11, at 537 (noting the frequency with which functional neuroimaging is providing new insights into cerebral activity in patients with severe brain damage).

[38] Judy Illes & Eric Racine, *Imaging or Imagining? A Neuroethics Challenge Informed by Genetics*, 5 AM. J. BIOETHICS 2, 5, 7. In the case of patients with disorders of consciousness, the tasks assigned are passive stimulations. Giacino et al., *supra* note 7, at S70.

[39] *See* Illes & Racine, *supra* note 38.

showing the areas to which a surplus of oxygenated blood flowed in response to the performance of the experimental tasks.[40] Scientists then interpret these maps as revealing which parts of the brain are implicated by the performance of particular mental tasks or the presentation of particular stimuli.

¶ 14 One area of fMRI research involves the study of DOCs that may follow a stroke, head trauma, or other complex injury to the central nervous system.[41] The meaning of "consciousness" (and, hence, "DOCs") is widely debated.[42] In this article, I adopt a clinical neuroscience approach and use the word "consciousness" to refer to an individual's wakefulness and her awareness of self and environment.[43] Individuals who have disordered consciousness may lack any evidence of consciousness, as in coma, or may exhibit limited or inconsistent consciousness, as in the MCS.[44] A brief review of three disorders of consciousness (coma, VS, and MCS) as well as the LIS is necessary before proceeding.[45]

¶ 15 A coma is a state of sustained pathologic unconsciousness in which an individual's eyes remain closed and the individual cannot be aroused.[46] Individuals in a coma display no evidence of awareness of themselves or their environment, no purposeful motor activity, no behavioral response to command, and no evidence of language comprehension or expression.[47] Individuals in a coma usually transition to the VS or the MCS within two to four weeks.[48]

¶ 16 The VS is a clinical condition of complete unawareness of the self and

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[40] *Id.*; Jeffrey R. Binder & Stephen M. Rao, *Human Brain Mapping with Functional Magnetic Resonance Imaging*, *in* LOCALIZATION AND NEUROIMAGING IN NEUROPSYCHOLOGY 185, 193 (Andrew Kertesz ed., 1994); Donald Kennedy, *Neuroimaging: Revolutionary Research Tool or a Post-Modern Phrenology?* AM. J. BIOETHICS, Mar.-Apr. 2005, at 19.

[41] Hirsch et al., *supra* note 3. *See generally* Stacey Tovino & William J. Winslade, *A Primer on the Law and Ethics of Treatment, Research, and Public Policy in the Context of Severe Traumatic Brain Injury*, 14 ANNALS HEALTH L. 1, Part II (2005) (examining disorders of consciousness that may follow traumatic brain injury).

[42] *See supra* note 1 and accompanying text.

[43] There is no shortage of definitions of the word *consciousness* in the scientific, philosophical, and law literatures. *See, e.g.*, Laureys et al., *Self-Consciousness*, *supra* note 1 at 2 ("There is at present no satisfactory, universally accepted definition of human consciousness. . . . For the purposes of clinical neurosciences, consciousness consists of two basis elements: *arousal* (i.e., wakefulness, vigilance or level of consciousness) and *awareness of environment and of self* (i.e., content of consciousness)."); Laureys, *Neural Correlate*, *supra* note 1, at 556 ("Consciousness has two main components: wakefulness and awareness."). *See generally* Alain Morin, *Levels of Consciousness and Self-Awareness: A Comparison and Integration of Various Views*, *available at* http://www.societyofrobots.com/robottheory/self-awareness_review.pdf (last visited July 10, 2007) (comparing and integrating a number of views regarding consciousness and self-awareness).

[44] *See* MOHONK REPORT, *supra* note 1, at 6.

[45] *See generally* Laureys et al., *Brain Function*, *supra* note 11, at 537-46 (reviewing the nosological criteria and functional neuroanatomical basis for brain death, coma, vegetative state, minimally conscious state, and locked-in state).

[46] Joseph D. Giacino, *Disorders of Consciousness, Recent Scientific Advances and Ethical Implications*, PowerPoint Presentation, Slide 7, 2nd TBI Interagency Conference, Bethesda, Maryland, Mar. 9, 2006, *available at* http://www.tbi-interagency.org/pdf/jgiacino_disorders.pdf (last visited July 10, 2007).

[47] *Id*. at Slide 8.

[48] *Id.*

environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic functions.[49] Diagnostic criteria for VS thus include no evidence of awareness of self or environment; no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; and no evidence of language comprehension or expression.[50] Scientists often state that the diagnosis of VS relies on the absence of behaviors that typically accompany conscious awareness.[51] Individuals in VS do, however, show intermittent wakefulness manifested by the presence of sleep-wake cycles,[52] sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with some medical and nursing care but usually without mechanical respiration,[53] and variably preserved cranial nerve (pupillary, oculocephalic, corneal, vestibulo-ocular, gag) and spinal reflexes.[54]

¶ 17 The MCS is "a condition of severely altered consciousness" in which an individual demonstrates "minimal but definite behavioral evidence of self or environmental awareness."[55] Diagnostic criteria for MCS thus include the demonstration of limited but clearly discernible evidence of self or environmental awareness by one or more of the following four behaviors: (1) following simple commands; (2) gesturing or verbally responding "yes" or "no," regardless of accuracy; (3) intelligible verbalization; or (4) purposeful behavior, including movements or behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity.[56] Examples of qualifying purposeful behavior include appropriate smiling or crying in response to linguistic or visual content, eye movement that follows a moving object, and reaching for objects.[57] These behaviors may occur inconsistently, but they would need to be reproducible or sustained long enough to be differentiated from reflexive behavior.[58] Unlike the diagnosis of VS, which is based on the absence of evidence of consciousness, the diagnosis of MCS is based on the presence of specific behavioral manifestations of

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[49] American Academy of Neurology, *Practice Parameters: Assessment and Management of Patients in the Persistent Vegetative State*, 45 NEUROLOGY 1015, 1015 (1995). A VS may be classified as persistent when it is present at one month after acute traumatic or nontraumatic brain injury and present for at least one month in degenerative or metabolic disorders or developmental malformations. *Id*. A VS may be classified as permanent when it lasts twelve or more months after a traumatic injury or three or more months after a nontraumatic injury. Giacino, *supra* note 46, at Slide 13. An individual who is permanently vegetative is said to have an "exceedingly rare" chance of regaining consciousness. American Academy of Neurology at 1015. Many scientists suggest avoidance of the *persistent* and *permanent* vegetative classifications and, instead, suggest the phrase *vegetative state* accompanied by a description of the cause of injury and the length of time since onset. Giacino, *supra* note 46, at Slide 12. I will follow this suggestion here.
[50] Hirsch, *supra* note 11, at 1102; American Academy of Neurology, *supra* note 49, at 1015.
[51] Hirsch, *supra* note 11, at 1102.
[52] *Id.*
[53] *Id.*
[54] American Academy of Neurology, *supra* note 49, at 1015.
[55] Joseph D. Giacino, *The Minimally Conscious State: Definition and Diagnostic Criteria*, 58 NEUROLOGY 349, 350-51 (2002).
[56] *Id.* at 351.
[57] *Id.*
[58] *Id.*

conscious awareness.[59] Patients who are in the upper boundary of MCS may say words or phrases and gesture and may show evidence of memory, attention, and intention.[60] Only when a patient reliably and consistently communicates, however, will the patient be considered to have emerged from MCS to consciousness.[61]

¶ 18 Finally, LIS is a condition in which individuals are aware and conscious but cannot produce speech, limb, or large-scale facial movements.[62] Diagnostic criteria for LIS include: (i) the presence of sustained eye opening; (ii) preserved basic cognitive abilities; (iii) aphonia or severe hypophonia; (iv) quadriplegia or quadriparesis; and (v) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid.[63] One of the most famous individuals diagnosed with LIS is Jean Dominique Bauby, the French editor in chief of *Elle* magazine who, in 1995, suffered a stroke and fell into a coma.[64] When Bauby woke up twenty days later, he was mentally aware of his surroundings but physically paralyzed except for his ability to move his left eyelid.[65] Bauby raised his left eyelid to communicate with his family, friends, caregivers, and editor through a "blinking code," which became his sole means of communication.[66] Bauby used this blinking code to dictate his memoir, which was published three days prior to his death in 1997.[67]

¶ 19 The ability to differentially diagnose VS, MCS, and LIS is important. The diagnosis of LIS is necessary to prevent conscious individuals who are physically paralyzed from being treated as though they are unaware of themselves or their environment.[68] Many scientists believe that differentially diagnosing the VS and the MCS is also important because patients in MCS may respond better to therapy and may have a better clinical outcome than patients who remain in VS.[69] Although physicians can diagnose coma with relative ease due to the eyes-shut presentation of the patient,[70] the differential diagnoses of VS, MCS, and LIS have been described as more difficult, more subjective, and more dependent on the skill and experience of the examining physician, the amount of time the physician spends observing the behavior of the patient,

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[59] Hirsch, *supra* note 11, at 1102.
[60] Fins, *supra* note 3, at 22-24.
[61] *Id.*
[62] Steven Laureys et al., *The Locked-In Syndrome: What Is It Like to be Conscious but Paralyzed and Voiceless?*, 150 PROGRESS BRAIN RESEARCH 495, 495 (2005).
[63] *Id.* at 497-98. *See also* Eimear Smith & Mark Delargy, *Locked-In Syndrome*, 330 BRITISH MED. J. 406, 406 (2005) (providing additional definitions and diagnostic criteria).
[64] JEAN DOMINIQUE BAUBY, THE DIVING BELL AND THE BUTTERFLY: A MEMOIR OF LIFE IN DEATH (1998) (chronicling Bauby's thoughts on his locked-in state and hospital stay, as well as his family life and career before his stroke).
[65] *Id.*
[66] *Id.*
[67] *Id.*
[68] *See, e.g.*, Laureys et al., *supra* note 62, at 499 ("[T]he [LIS] diagnosis may be missed and the patient may erroneously be considered as being in a coma, vegetative state, or akinetic mustism . . . . Most distressingly, the time elapsed between brain insult and LIS diagnosis was on average 2.5 months (78 days). Several patients were not diagnosed for more than 4 years.") (internal references omitted).
[69] Huntoon, *supra* note 5, at 35; Douglas I. Katz, *Minimally Conscious State*, KURZWEILAI.NET, *available at* http://www.kurzweilai.net/meme/frame.html?main=/articles/art0161.html (last visited July 16, 2007).
[70] Pickett Hauber, *supra* note 5.

the physical ability of the patient to respond to a particular stimulus, and a number of other factors.[71] LIS, for example, can be difficult to diagnose because patients may emerge to LIS from coma after variable and substantial delays.[72] VS and MCS can be difficult to distinguish due to the subjectivity traditionally involved in determining whether there is some evidence of self- or environmental awareness.[73]

¶ 20 Because of these and other challenges, scientists have been studying whether fMRI and other functional neuroimaging technologies can provide evidence of cerebral networks or an internal form of "awareness" that is not externally observable.[74] To illustrate these efforts, I review three fMRI studies the results of which have been published in peer-reviewed scientific journals during the past four years. The first study involves individuals in MCS, the second study involves individuals in VS, and the third study involves individuals in both VS and MCS.

B. fMRI Study 1: Large-Scale Network Activation in Patients in MCS

¶ 21 In one fMRI study published in *Neurology* in February 2005, scientists at Cornell University, Columbia University, Georgetown University Medical Center, and the JFK Johnson Rehabilitation Institute hypothesized that patients in MCS may retain active cerebral networks that underlie cognitive function (hereinafter, fMRI Study 1).[75] To test their hypothesis, the scientists used fMRI to scan the brains of two adult patients who had severe brain injuries that led to MCS and the brains of seven healthy adult volunteers.[76] The first patient in MCS had experienced a spontaneous bleed in the left temporoparietal region of his brain.[77] The highest-level behavioral responses that physicians observed for this patient included one-step command following, inconsistent identification of objects through eye gaze, and intelligible single-word verbalizations.[78] The second patient in MCS had experienced a blunt trauma to the right frontal region of his brain.[79] The highest-level behavioral responses that physicians observed for the second patient included occasional verbalization and an inconsistent ability to follow

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[71] Huntoon, *supra* note 5, at 35; Katz, *supra* note 69.
[72] *See* Smith & Delargy, *supra* note 63, at 407.
[73] *See, e.g.*, Laureys et al., *supra* note 6, at 521 ("Movements that appear to be volitional may actually be reflexive in nature and vice versa. Complicating matters further, patients may exhibit behavioral signs of awareness during one examination and fail to do so on the next."). *See generally* Calixto Machado, *The Minimally Conscious State: Definition and Diagnostic Criteria*, NEUROLOGY, June 24, 2002, *available at* http://neurology.org/cgi/eletters/58/3/3 (last visited July 16, 2007) (noting the philosophical impossibility of detecting the subjective dimension of awareness).
[74] *See, e.g.*, Di et al., *supra* note 10, at 895 ("A challenge in the management of severely brain-damaged patients with altered states of consciousness is the differential diagnosis between the vegetative state (VS) and the minimally conscious state (MCS), especially for the gray zone separating these clinical entities. . . . [Our studies showed that] [t]he cerebral responses to patient's own name spoken by a familiar voice as measured by fMRI might be a useful tool to preclinically distinguish minimally conscious state–like cognitive processing in some patients behaviorally classified as vegetative."); Huntoon, *supra* note 5, at 35.
[75] Schiff et al., *supra* note 8, at 514-15.
[76] *Id.*
[77] *Id.* at 515.
[78] *Id.*
[79] *Id.*

complex commands.[80]

¶ 22 By definition, the two patients in MCS were unable to consent to their own research participation.[81] The scientists obtained informed consent to the patients' research participation from surrogates: "Legally authorized surrogates for both patients were contacted by medical personnel not directly involved in the current studies. Informed consent was obtained according to institutional guidelines on two occasions, allowing for a period of evaluation and opportunity for additional information."[82]

¶ 23 During the study, the scientists used fMRI to scan the patients' brains while conducting three different passive stimulation activities. First, the scientists gently rubbed the patients' palms and fingers with a coarse-textured plastic surface, an activity selected because of the patients' inflexible hand positions.[83] Second, the scientists placed headphones on the patients and played an audio narrative of familiar events spoken by persons familiar to the patients.[84] Third, the scientists played through the same headphones the same audio narrative, but this time in reverse. Here, it was assumed that the backwards statements would be recognizable as speech but that the linguistic content of the speech would not be recognizable.[85] The scientists performed each activity twice for a total of six passive stimulations per patient in MCS.[86]

¶ 24 The scientists found that the forward playing of the audio narratives elicited activity in regions of the brains (the superior and middle temporal gyrus) of the two patients in MCS and that the seven healthy volunteers demonstrated similar activations when comparably stimulated.[87] When the scientists played the audio narratives in reverse, however, they found "markedly reduced" responses in the brains of the two patients in MCS as compared with the brains of the seven healthy volunteers.[88] The scientists suggested, therefore, that the two patients in MCS had "reduced engagement for linguistically meaningless stimuli."[89] After stating that they had presented the first fMRI maps of neural responses to tactile stimulation and language processing of individuals in MCS,[90] the scientists further suggested that individuals in MCS may retain widely distributed cortical systems with potential for cognitive and sensory function despite the individuals' inability to follow simple instructions or communicate reliably.[91]

¶ 25 The same day the study was published in *Neurology*, *New York Times* reporter Benedict Carey suggested to millions of readers that patients in MCS may be, literally and in the lay sense of the word, "aware" of what goes on around them: "Thousands of

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[80] *Id.*
[81] *Id.*
[82] *Id.*
[83] *Id.*
[84] *Id.*
[85] *Id.*
[86] *Id.*
[87] *Id.*
[88] *Id.* at 514, 516-17.
[89] *Id.*
[90] *Id.* at 514.
[91] *Id.*

brain-damaged people who are treated as if they are almost completely unaware may in fact hear and register what is going on around them but be unable to respond, a new brain-imaging study suggests."[92] Carey also quoted the opinion of one of the study authors that it was "morally imperative" to pursue fMRI research involving individuals in MCS:

> The most consequential thing about this is that we have opened a door, we have found an objective voice for these patients, which tells us they have some cognitive ability in a way they cannot tell us themselves. . . . [The patients are] more human than we imagined in the past, and it is unconscionable not to aggressively pursue research efforts to evaluate them and develop therapeutic techniques.[93]

Following the publication of the study, many other scientists agreed that the study findings warranted further research in this area.[94] Others, however, found the study to be more suggestive than conclusive and clarified that the results did not mean that patients in MCS were likely to recover or that treatment was possible.[95]

C. fMRI Study 2: Detecting Awareness in the VS

¶ 26 In a second fMRI study published in *Science* in September 2006, scientists at the University of Cambridge and University of Liège went one step further by hypothesizing that fMRI might provide a means for detecting not only preserved brain function but also conscious awareness in individuals diagnosed as vegetative using standard clinical testing (hereinafter, fMRI Study 2).[96] To test their hypothesis, the scientists proposed to use fMRI to scan the brain of a twenty-three-year-old woman who had suffered a severe traumatic brain injury and whom a multidisciplinary clinical team had subsequently diagnosed as vegetative.[97] Because the woman could not consent to her own research participation, the scientists obtained consent to the woman's research participation from her next of kin.[98]

¶ 27 During the study, the scientists gave the woman spoken instructions to perform

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[92] Carey, *supra* note 12.
[93] *Id.*
[94] *See, e.g.*, Chad H. Moritz, *fMRI Reveals Large-Scale Activation in Minimally Conscious Patients*, NEUROLOGY, May 3, 2005, *available at* http://www.neurology.org/cgi/eletters/64/3/514#2651 (last visited July 12, 2007).
[95] Carey, *supra* note 12. Following the study's publication, disability advocates from the Not Dead Yet organization also referred to the study in their public cry for a nationwide moratorium on the withholding and withdrawal of life-sustaining treatment from individuals in VS. The theory behind the moratorium is that physicians should not withhold or withdraw nutrition, hydration, and other therapies from individuals who are, in the organization's own words, not dead yet. *See How Much More Evidence Do We Need? Disability Activists Call for Moratorium on Starvation and Dehydration*, NOT DEAD YET, Feb. 14, 2005, *available at* http://www.notdeadyet.org/docs/moratoriumPR021405.html (last visited July 9, 2007).
[96] Owen et al., *supra* note 9, at 1402.
[97] *Id.*; Adrian M. Owen, *Summary: Detecting Awareness in the Vegetative State*, http://www.mrc-cbu.cam.ac.uk/~adrian/Site/Summary.html (last visited July 12, 2007).
[98] E-mail from Dr. Martin Coleman, MRC Cognition and Brain Sciences Unit, to Stacey Tovino (July 13, 2007, 03:42 A.M. CST) (on file with author).

two mental imagery tasks.[99] The first instruction was to imagine playing a game of tennis.[100] The second instruction was to imagine visiting all of the rooms of her house, starting from the front door.[101] During the periods when the scientists asked the woman to imagine playing tennis, they observed significant activity in an area of her brain known as the supplemental motor area.[102] During the periods when the scientists asked the woman to imagine herself walking through her home, they observed significant activity in different regions of the brain, including the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex.[103] When the scientists compared the woman's neural responses with the responses of healthy volunteers who performed the same imagery tasks, the responses were indistinguishable.[104] The scientists concluded that although the woman fulfilled the traditional clinical criteria for VS, she was, in scientific terms, consciously aware of herself and her surroundings:

> [T]his patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement. Moreover, her decision to cooperate with the authors by imagining particular tasks when asked to do so represents a clear act of intention, which confirmed beyond any doubt that she was consciously aware of herself and her surroundings.[105]

The scientists also stated that fMRI might be a method by which other patients in VS and MCS could "use their residual cognitive capabilities to communicate their thoughts to those around them by modulating their own neural activity."[106]

¶ 28 Again writing for the *New York Times*, although this time on page A1, Benedict Carey reported, "A severely brain-damaged woman in an unresponsive, vegetative state showed clear signs of conscious awareness on brain imaging tests."[107] Carey quoted a Cornell scientist, who was not involved in the study, as stating that the study provided "'knock-down, drag-out' evidence for conscious activity, but that it was not clear 'whether we'll see this in one out of 100 vegetative patients, or one out of 1,000, or ever again.'"[108] The *Times* write-up included other, more cautious quotations:

> The imaging techniques used in the new study could help identify which patients are most likely to emerge—once the tests are studied in larger

[99] Owen et al., *supra* note 9, at 1402.
[100] *Id.*
[101] *Id.*
[102] *Id.*
[103] *Id.*
[104] *Id.*
[105] *Id.*
[106] *Id. See also Patient in Vegetative State Plays Tennis in Her Head*, MRC PRESS RELEASE, Sept. 8, 2006, *available at* http://www.mrc.ac.uk/NewsViewsAndEvents/News/MRC002623 (last visited July 9, 2007) ("This technique may allow us to identify which patients have some level of awareness. . . . Future work will investigate whether the technique can be used more widely in these patients and whether this discovery could lead to a way of communicating with some patients who may be aware, but unable to move or speak.").
[107] Benedict Carey, *Vegetative Patient Shows Signs of Awareness, Study Says*, N.Y. TIMES, Sept. 7, 2006, at A1.
[108] *Id.*

> numbers of unconscious people. . . . "For now I think what this study does is to create another shade of gray in the understanding of gray matter."[109]

Other scientists were less impressed with the study authors' conclusions, calling them far fetched[110] and warning of their ethical, social, and other implications: "The question of conscious awareness in the vegetative state has relevance far beyond the limits of the neuroscience community, with an impact on individual lives that is hard to calculate. . . . [I]t is imperative that alternative data interpretations be carefully considered before making radical inferences."[111]

D. fMRI Study 3: Cerebral Responses to Patient's Own Name

¶ 29 Scientists continue to use fMRI to study disorders of consciousness. In a third fMRI study published in *Neurology* in March 2007, scientists from China and Belgium hypothesized that fMRI might be useful to preclinically distinguish VS and MCS (hereinafter, fMRI Study 3).[112] (Remember, some scientists believe that patients in MCS may respond better to therapy and ultimately may have a better clinical outcome than patients who remain in VS.[113] Reports of patients in MCS but misdiagnosed as VS for almost twenty years add fuel to the desire for more accurate diagnoses.[114]) To test their hypothesis, the scientists used fMRI to scan and compare the brain activations of seven patients in VS and four patients in MCS, all but two of whom had experienced traumatic brain injury.[115] Due to the importance of their initial diagnoses, the scientists used extensive and repeated clinical testing, including five different validated behavioral scales, to arrive at an initial diagnosis of VS or MCS for each patient.[116] Because the patients were unable to consent to their own research participation, "[i]nformed written consent was obtained from the families of all patients, and the study was approved by the Ethics Committee of Zhejiang University School of Medicine."[117]

¶ 30 After obtaining family consent, the scientists used headphones to deliver to each patient a digital recording of the patient's own name spoken by a familial voice (SON-FV), which in this case happened to be a voice of a first-degree family member.[118] The scientists chose SON-FV, a powerful "emotionally laden auditory stimuli," with the hope of maximizing their chances of detecting residual brain function.[119] During the study, the scientists scanned the patients' brains using a block design that incorporated six active

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[109] *Id.*
[110] Parashkev Nachev & Masud Husain, *Comment on "Detecting Awareness in the Vegetative State,"* SCIENCE, Mar. 2, 2007, at 1221a.
[111] *Id.*
[112] Di et al., *supra* note 10, at 895.
[113] Huntoon, *supra* note 5, at 35.
[114] GLANNON, *supra* note 33, at 158-59 (discussing the case of Arkansas resident Terry Wallis who was misdiagnosed as VS for nineteen years).
[115] The scientists initially enrolled five patients in MCS but had to exclude one patient's data due to her head movement. Di et al., *supra* note 10, at 896.
[116] *Id.*
[117] *Id.*
[118] *Id.*
[119] *Id.* at 895-96.

blocks (during each of which seven SON-FVs were presented) and seven baseline blocks (during which only the noise of the MRI machine was available).[120] Because accurate MRI scanning requires the patient to lie still, and because patients in VS and MCS have reflexive and uncontrolled body movements that tend to increase with the noise of the magnet in the MRI machine, the scientists used special headphones and placed homemade head-fixation devices on each patient.[121]

¶ 31 The scientists found that two of the patients in VS failed to show any significant cerebral activation, three of the patients in VS showed SON-FV-induced activation within the primary auditory cortex, and two of the patients in VS and all four of the patients in MCS showed activation not only in the primary auditory cortex but also in hierarchically higher-order associative temporal areas.[122] The scientists conducted additional behavioral testing at one, two, and three months post-study to examine the prognostic value of the study[123] and found that the two patients in VS who showed the most widespread activation actually had improved to MCS.[124] The scientists opined that traditional behavioral assessments (assessments without scanning) can miss cerebral processing that might herald short-term improvement:

> In our opinion, these two patients were already with MCS during fMRI scanning but behavioral signs of consciousness could (even using the best clinical assessments available) only be shown 3 months later. This interpretation is in line with previous reports showing unusual activation of higher order areas (using respectively presentation of familiar faces and verbal stimuli) followed by clinical recovery some months later. Hence, fMRI seems to offer a higher sensitivity to identify cognitive processing in patients emerging from a VS compared to bedside clinical tools.[125]

¶ 32 The scientists concluded that using fMRI to measure cerebral responses to a patient's own name spoken by a familial voice might be a useful method of preclinically identifying some patients with "minimally conscious state–like cognitive processing."[126]

¶ 33 Several scientists who commented on the published study agreed that it added to the evidence that the brains of some individuals in VS support more cerebral processing of external stimuli than their behavioral state suggests and that such processing portends better short-term prognosis.[127] They also emphasized, however, that patients with "minimally conscious–like processing" were still "cognitively devastated" and that end-of-life decision making, including decisions to withhold and withdraw life-sustaining treatment, should not be altered.[128] One commentator stated more directly: "None of this

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[120] *Id.* at 896.
[121] *Id.* at 897.
[122] *Id.* at 897, 898.
[123] *Id.* at 896.
[124] *Id.* at 897.
[125] *Id.* at 898 (internal references omitted).
[126] *Id.* at 895.
[127] Thomas I. Cochrane, *Is fMRI a Useful Prognostic Tool in Early Vegetative State?*, JOURNAL WATCH NEUROLOGY, May 15, 2007.
[128] *Id.*

changes the fact however that most people wouldn't want to be kept alive artificially in a MCS either and going from a [persistent] VS to an MCS is no real improvement in the big scheme of things."[129]

E. Practical, Legal, and Ethical Limitations

¶ 34 Throughout this part, I have briefly introduced a few hurdles posed by fMRI research involving individuals with DOC, including their inability to consent to their own research participation and their inability to follow instructions to hold still in an MRI scanner. I would like to expand on these hurdles and introduce a few additional practical, ethical, legal, and social obstacles to neuroimaging research involving individuals with DOC. These obstacles include, but certainly are not limited to, the cost of and lack of funding for neuroimaging studies, the absence of a federal law and a patchwork of state laws governing surrogate consent for individuals with DOC, and the communication barriers between and among scientists, reporters, lawyers, ethicists, and other stakeholders.

¶ 35 Neuroimaging research involving individuals with DOC is costly. Imagine a research project that involves only healthy volunteers who transport themselves to a research laboratory or other test site, unaccompanied by healthcare personnel, to take a written psychological test. The healthy volunteers walk, drive, or use public transportation to transport themselves to the test site; read and complete the written test under the supervision of the scientists, their study coordinators, graduate students, or other test proctors; and then transport themselves home. Not all, but certainly some, research protocols are this easy to coordinate and are relatively inexpensive. But when a research project involves a patient with DOC, some of whom may be residents of rehabilitation hospitals or other long-term care facilities, the scientists must arrange and pay for the safe transport of the patient from the facility to the laboratory, which may include an ambulance, and must provide any medical support needed by the patient, which may include monitoring by an intensive care physician during the study.[130]

¶ 36 Neuroimaging research involving patients with DOC also can be time consuming and generate a fair amount of unusable data. As mentioned in fMRI Study 3, many patients in VS and MCS have reflexive and uncontrolled body movements that increase with the noise of the magnet that lies within the MRI machine.[131] Because accurate MRI results require patients to lie still during the scanning procedure, scientists may place special noise-reduction headphones and head-fixation devices on their subjects.[132] Even with these devices, some subjects still move their heads too much. In fMRI Study 3, for example, the scientists initially enrolled seven patients in VS and five patients in MCS, although they were subsequently forced to exclude data relating to one patient in MCS who moved her head too much in synchronization with the auditory

[129] Drew Rosielle, *fMRI & the PVS; Opioids and Respiratory Depression*, PALLIMED: A HOSPICE AND PALLIATIVE MEDICINE BLOG, *available at* http://www.pallimed.org/2007/04/fmri-pvs-opioids-respiratory-depression.html (last visited July 9, 2007).
[130] Steinberg, *supra* note 12, at 1009.
[131] Di et al., *supra* note 10, at 897.
[132] *Id.*

stimuli while she was in the scanner.[133] The data had to be thrown away because it was impossible for the scientists to separate the neural responses that were due to the stimuli (the audio recording of the patient's own name spoken by a familial voice) versus the movement of the patient's head.[134] Other scientists conducting neuroimaging studies have experienced a failure rate of up to two out of every three patients in MCS who are scanned.[135]

¶ 37 Traditional government funding usually does not cover all or even some of these costs of neuroimaging research in consciously disordered populations. In the United States, the National Institutes of Health (NIH), the National Science Foundation (NSF), and other federal agencies do not grant significant funds for the study of DOC.[136] Knowing this, some American scientists request funds not from the NIH or NSF but from disability-based agencies, such as the U.S. Department of Education's National Institute on Disability and Rehabilitation Research, which has separate funding for traumatic-brain-injury research.[137] European scientists also report difficulty obtaining funding for their consciousness studies, especially in comparison to their investigations of Parkinson's disease and other, more traditional, degenerative neurological conditions.[138]

¶ 38 Legal and ethical concerns, typically raised by IRBs charged with approving research protocols, scientific journals deciding whether to publish study results, and government funding agencies, further limit the conduct and publication of consciousness investigations.[139] In particular, IRBs, scientific journals, and funding agencies are concerned (1) that neuroimaging studies do not directly benefit research subjects, which may cause the risk-to-benefits balancing test[140] to balance in favor of no research; (2) that some functional neuroimaging studies pose more than a minimal risk of injury to subjects;[141] and (3) about the inability of patients with DOC to consent to their own research participation, which implicates ethical and legal principles relating to voluntary and informed consent.[142] Although fMRI generally is considered minimal risk, other functional neuroimaging technologies, including positron emission tomography (PET),

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[133] *Id.* at 897-98.
[134] *Id.* at 896.
[135] Steinberg, *supra* note 12, at 1009.
[136] *Id.*
[137] *Id.*
[138] *Id.*
[139] *Id.*
[140] 45 C.F.R. § 46.111(a)(2) (2007) (requiring human subjects research projects to meet certain criteria, including the criterion that "[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result").
[141] Steinberg, *supra* note 12, at 1009.
[142] 45 C.F.R. § 46.111(a)(4) (2007) (requiring human subjects research projects to meet certain criteria, including the criterion that "[i]nformed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116."); *id.* § 46.116 ("Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."). *See generally* Richard Smith, *Should the BMJ Reject All Studies that Do Not Include Informed Consent?*, 314 BRITISH MED. J. 1059, 1059 (1997) (illustrating the role ethical concerns play in publication decisions made by scientific journals).

do require the injection of radioactive tracers that are considered riskier.[143]

¶ 39 "Whether or not these arguments are raised depends on the institution, locality and country in which a particular study is being evaluated."[144] Some scientists experience few ethical and legal obstacles in the conduct of their research, while other scientists encounter them frequently. An IRB reportedly tried to stop the research of Columbia neurologist Joy Hirsch, one of the authors of fMRI Study 1, two different times.[145] In one of these cases, the IRB reportedly told her that she could not obtain surrogate (or proxy) consent to the research participation of an individual in VS or MCS.[146] Dr. Hirsch was able to continue her research by proving that her subjects were residents of states that permit proxy consent.[147] But her defense highlights a related issue, which is that federal law does not specifically address consent to research on behalf of adults with decisional impairments,[148] and state law in this area varies, if it exists at all.[149] The lack of federal guidance and the patchwork of state law can make it difficult for scientists and their IRBs to agree on an applicable regulatory framework, especially when the research may be conducted in a laboratory located in one state (e.g., New York) but will draw patients who are residents of neighboring states (e.g., the Tri-State Area) and beyond.

¶ 40 Although IRBs, scientific journals, and funding agencies may attempt to limit the conduct, publication, and funding of neuroimaging studies involving patients with DOC, other religious and political organizations, including organizations that oppose abortion and stem-cell research, support research into DOC.[150] The Vatican reportedly extended an invitation to Belgian neurologist Steven Laureys, one of the authors of fMRI Studies 2 and 3, because the Vatican liked his PET research findings showing brain activations in patients in VS who received electric shocks.[151] Not Dead Yet, a disability advocacy group that opposes the withholding and withdrawal of life-sustaining treatment from patients in VS and MCS, also supports research into DOC, especially when the study results show more clearly that these patients are not dead yet.[152] Indeed, a research analyst at Not Dead Yet hopes that continued consciousness research will show that patients in VS and MCS "clearly have significant cognitive activity going on" even though society may be "writ[ing] them off."

¶ 41 To further confuse matters, scientists have spoken publicly about their research findings and their desire to conduct additional research, and these statements have led to

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[143] Steinberg, *supra* note 12, at 1009.
[144] *Id.*
[145] *Id.*
[146] *Id.*
[147] *Id.*
[148] *See infra* Part III(D).
[149] *See infra* Part III(E).
[150] Steinberg, *supra* note 12, at 1009.
[151] *Id.* (referring to Steven Laureys et al., *Cortical Processing of Noxious Somatosensory Stimuli in the Persistent Vegetative State*, 17 NEUROIMAGE 732, 732 (2002) (measuring changes in regional cerebral blood flow during high-intensity electrical stimulation of the median nerve compared with rest in fifteen nonsedated patients and in fifteen healthy controls).
[152] Steinberg, *supra* note 12, at 1009.

misunderstandings by some of the nonscientists who read and hear the statements.[153] The scientists' statements to the media are excited and hopeful and, well, scientific.[154] After all, these individuals spend their lives studying and testing questions at the cutting edges of their fields. But someone must translate the scientists' complex research findings into copy that will be read by the general public.[155] Some journalists do not have clinical or scientific backgrounds and are not necessarily equipped to summarize complex research studies for laypersons.[156] Journalism, which is designed to sell, and the reporting of scientific findings in peer-reviewed journals, which is supposed to be objective and dispassionate, also may not be the best of partners. This problem, sometimes called the problem of "science in public," can result in journalistic distortion.[157] The problem becomes confounded when lawyers and ethicists, who may become aware of scientific developments first through the media, make relatively conservative legal and ethical pronouncements based on statements made in media reports or questions posed by reporters. In response, scientists attempt to re-explain their research findings back to the lawyers, ethicists, and media, all the while trying not to engage in therapeutic nihilism,[158] on one hand, or "engender[] expectations for the permanently unconscious," on the other.[159]

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[153] *See, e.g.*, JANE GREGORY & STEVEN MILLER, SCIENCE IN PUBLIC: COMMUNICATION, CULTURE, AND CREDIBILITY 1 (1998) ("In the last decade or so, scientists have been delivered a new commandment from on high: *thou shalt communicate*.").

[154] *See, e.g.*, note 11, *supra*.

[155] *See* GREGORY & MILLER, *supra* note 153, at 110.

[156] *Id.* at 108, 116.

[157] Fins, *supra* note 3, at 22-24. For example, a published research study titled "fMRI Reveals Large Scale Activation in Minimally Conscious Patients" (Schiff et al., *supra* note 8), which concludes just what its title suggests, was featured in the *New York Times* under the headline "Signs of Awareness Seen in Brain-Injured Patients." Carey, *supra* note 12. The fact that a magnetic resonance imaging scanner identified significant localized changes in blood oxygenation in patients in MCS who were presented with certain auditory stimuli, which is a very important scientific finding, does not necessarily mean that these patients were "aware" in the lay sense of the word. These individuals were not watching TV or using their cell phones. But we can understand, perhaps, how this distortion occurred. For a science story to be meaningful and relevant to the public, the story must fall within the scope of what the public normally thinks about. GREGORY & MILLER, *supra* note 153, at 110. Although the general public might not think about localized changes in blood oxygenation that occur in the brain as a result of passive auditory stimulation (*id.* at 110-11 (noting that "[s]cience . . . often deals with areas in which people do not engage as a matter of course . . . ")), the public does understand what it means to be awake and aware, at least in the lay sense. Benedict Carey, who wrote the article for the *Times*, probably selected the word *awareness* for his headline to make the article coverage more meaningful and relevant to the average person. Academics have been studying these and other problems of "science in public" for quite some time. *Id.* at ix-x.

[158] *See* Tovino & Winslade, *supra* note 41, at 30 n.172 (defining *therapeutic nihilism* as the failure to recognize the possible benefits of treatment).

[159] Fins, *supra* note 3, at 24. It goes without saying that the language barriers among scientists, reporters, lawyers, ethicists, and the general public are not insignificant. Each of us is trained in different research methodologies and in the use of different professional languages that can be misleading to persons unfamiliar with our professional cultures. *See* GREGORY & MILLER, *supra* note 153, at 115-16 (contrasting the objective and dispassionate scientific language used in formal scientific publications with news language, which is "immediate, positive, and active"; noting that "news reports often emphasize the potential applications and outcomes of scientific results, rather than the process by which they were developed. Emphasizing applications again makes the information seem more certain . . . .").

¶ 42 To begin to evaluate the seemingly opposing viewpoints of the scientists who conduct neuroimaging research and the lawyers, ethicists, and others who may be critical of the research, I provide in Part II an abbreviated history of research involving individuals with decisional impairments. Part II lays the foundation for Part III, in which I examine the ethical and legal appropriateness of additional neuroimaging research into disorders of consciousness.

III. AN ABBREVIATED HISTORY OF RESEARCH INVOLVING INDIVIDUALS WITH DECISIONAL IMPAIRMENTS

¶ 43 The ancient and modern history of human subjects research, its ethical implications, and its regulation in the United States and abroad have been thoroughly researched and documented elsewhere.[160] In this part, I provide an abbreviated history of medical experimentation involving individuals with psychiatric conditions and developmental disabilities as well as the development of relevant American[161] legal and ethical human-subjects protections. I review research studies involving individuals with psychiatric conditions and developmental disabilities for three interrelated reasons. First, a long and well-documented history of experimentation involving individuals with DOC does not exist. Second, analogies among the three populations (individuals with psychiatric conditions, developmental disabilities, and DOC) have, although not without controversy, been made because individuals in all three groups may have reduced, limited, or no capacity to make decisions to participate in research.[162] Third, the development of ethical and legal principles governing research participation by individuals with decisional impairments was attempted after it was discovered that scientists recruited individuals with psychiatric conditions and developmental disabilities into risky experiments, many of which were unrelated to their conditions.

A. Ancient and Modern Research Trends

¶ 44 If "experimentation in man for scientific purposes is as old as recorded

[160] For reviews of the modern history of human-subjects research and the development of human-subjects protections, see, for example, MARGARET L. EATON & DONALD KENNEDY, INNOVATION IN MEDICAL TECHNOLOGY: ETHICAL ISSUES AND CHALLENGES 37-46 (2007); LAINIE FRIEDMAN ROSS, CHILDREN IN MEDICAL RESEARCH: ACCESS VERSUS PROTECTION 12-43 (2006); JONATHAN MORENO, IS THERE AN ETHICIST IN THE HOUSE? 109-52 (2005); CARL H. COLEMAN ET AL., THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS 3-244 (2005); CYNTHIA MCGUIRE DUNN & GARY L. CHADWICK, PROTECTING VOLUNTEERS IN RESEARCH: A MANUAL FOR INVESTIGATIVE SITES 13-43 (3rd ed. 2004) (same); HAROLD Y. VANDERPOOL, THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY 1-144 (1996); GEORGE J. ANNAS & MICHAEL A. GRODIN, THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 1-275 (2002); RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT 151-232 (1986).

[161] *See supra* note 26.

[162] In Part III, I examine the differences between early twentieth-century experimentation involving individuals with psychiatric conditions and developmental disabilities and recent neuroimaging investigations into DOC. I argue that the ethical concerns arising from the former studies are not present to a significant degree in the latter. *Cf.* Joseph J. Fins, *Constructing an Ethical Stereotaxy for Severe Brain Injury: Balancing Risks, Benefits and Access*, 4 NATURE REV. NEUROSCIENCE 323, 325 (2003) (noting the salient differences between older psychosurgery experiments and current neuromodulation investigations).

history,"[163] then experimentation in captive and vulnerable men, including criminals and individuals with mental disorders, is almost as old. Criminals were considered fair game for medical experiments by ancient Persian Kings, the Ptolemies in Egypt, and Fallopius in Pisa during the Renaissance, in part because of their captivity, which eased the administrative burden associated with their recruitment.[164] Individuals with mental disorders also were used in ancient experiments, perhaps because they were considered expendable. A Persian prince at the time of Avicenna told new physicians, "[I]f you wish to gain experience and a reputation you must experiment freely, but you had better not choose people of high rank or political importance for your subjects."[165] Perhaps this philosophy opened the door for twentieth-century scientists to enroll individuals with psychiatric conditions and developmental disabilities in medical experiments.[166]

¶ 45 An early twentieth-century example is British researcher William Fletcher's beriberi experiment. In the early 1900s, beriberi (a nervous disorder caused by thiamine deficiency) was particularly problematic, and scientists were actively studying methods of prevention.[167] To that end, in 1905, Fletcher identified a captive population of research subjects among the patients of a lunatic asylum in Kuala Lumpur, Malaysia, and assigned each patient a number.[168] The odd-numbered patients were given the regular hospital diet.[169] The even-numbered patients were given rice cured with Vitamin B.[170] Forty-three of the 120 patients assigned to the regular hospital diet developed beriberi, eighteen of whom later died.[171] Only two of the patients assigned to the cured rice developed beriberi, neither of whom died.[172] Little attention was given to Fletcher's decision to use a confined population of individuals with psychiatric conditions to conduct his experiment.

¶ 46 The practice of enrolling vulnerable individuals in medical experiments continued throughout the early twentieth century. In about 1915, Austrian researchers injected tuberculosis bacilli and alcohol into individuals with mental disorders.[173] In 1917, Austrian physician Julius Wagner-Jauregg inoculated patients, diagnosed as insane by virtue of neurosyphilis, with malaria parasites—an experiment that proved successful and earned him the Nobel Prize in Medicine or Physiology in 1927.[174] The use of patients with mental disorders as research subjects apparently was not uncommon in the early 1900s.[175]

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[163] HENRY K. BEECHER, RESEARCH AND THE INDIVIDUAL: HUMAN STUDIES x (1970).
[164] Henry K. Beecher, *Experimentation in Man*, 169 J. M. ED. ASS'N 461 (1959); BEECHER, *supra* note 163, at 5.
[165] BEECHER, *supra* note 163, at 5.
[166] *Id.*
[167] *Id.* at 10.
[168] *Id.*
[169] *Id.*
[170] *Id.*
[171] *Id.*
[172] *Id.*
[173] MORENO, *supra* note 160, at 155.
[174] *Id.* at 156.
[175] *Id.*

¶ 47 Experimentation involving patients with mental disorders continued throughout the 1930s, 1940s, 1950s and 1960s. During the Second World War, the federal Committee on Medical Research of the White House's Office of Scientific Research and Development approved the use of Mississippi insane-asylum patients in research protocols designed to investigate influenza.[176] In 1949, Portuguese psychiatrist and neurosurgeon Egas Moniz won the Nobel Prize for his leucotomy experiments, during which he removed the frontal lobe of very anxious and aggressive patients with mental disorders to test whether surgery would lessen their anxiety and frustration.[177] Although Moniz used vulnerable research subjects in his experiments, his aim was to ease the symptoms that made them vulnerable in the first place.[178] In some cases, he succeeded.[179]

¶ 48 Not all twentieth-century research projects involving vulnerable populations were designed to improve the subjects' psychiatric or developmental conditions. Although the modern history of human subjects research contains dozens of examples of medical experiments that harmed vulnerable patients, I will review two particular experiments that I believe illustrate, to varying extents, some of the concerns raised by IRBs, scientific journals, and funding agencies with respect to neuroimaging research of DOC. These experiments include the U.S. Army's chemical warfare research, conducted in the early 1950s[180] and the hepatitis experiments conducted at Willowbrook Hospital from the late 1950s to the early 1970s.[181] The relevant legal and ethical concerns include, but certainly are not limited to, the (un)reasonableness of the research risks in relation to the expected benefits, scientists' use of captive, vulnerable populations for medical experimentation, and the lack of first-person informed consent (or continued consent) to research participation.

B. Harold Blauer and the Army's Chemical Warfare Research

¶ 49 In the mid-1900s, the U.S. Army became interested in the use of hallucinogenic compounds as potential chemical warfare agents, and in 1951, the Army Chemical Center proposed to study the effect of psychochemical agents on various confined populations, including patients at the New York State Psychiatric Institute ("Psychiatric Institute").[182] According to the Army Chemical Center's research proposal, "new technical data will be derived . . . which will provide a firmer basis for the utilization of psychochemical agents both for offensive use as sabotage weapons and for protection against them."[183] That same year, the Army Chemical Corps ("Army") and the Psychiatric Institute entered into two contracts for the psychological and psychiatric investigation of potential chemical

[176] DAVID J. ROTHMAN, STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING 87 (1991).
[177] MORENO, *supra* note 160, at 157.
[178] *Id.*
[179] *Id.*
[180] *See infra* Part II.B.
[181] *See infra* Part II.C.
[182] Barrett v. United States, 660 F. Supp. 1291, 1295 (S.D.N.Y. 1987).
[183] *Id.* (ellipsis in original).

warfare agents.[184] Pursuant to the contracts, the Army would give chemical derivates of mescaline, a hallucinogenic alkaloid of the phenethylamine class, to the Psychiatric Institute. The Psychiatric Institute would, in turn, inject the derivatives into a group of patients and report the findings back to the Army every three months.[185]

¶ 50 Around the same time, forty-two-year-old Harold Blauer, a tennis professional and former ranked tennis player,[186] voluntarily admitted himself to the Psychiatric Institute for treatment for his severe depression, which was later diagnosed as pseudo-neurotic schizophrenia.[187] Under the care of Dr. George Schnack, one of the therapists at the Psychiatric Institute, Blauer's condition steadily improved.[188] A few weeks before Blauer was set to be released, the Psychiatric Institute scheduled him to receive a series of mescaline injections pursuant to its research contract with the Army.[189] The mescaline injections for which Blauer was scheduled were completely unrelated to his psychiatric condition.[190] The injections were not intended to serve a diagnostic or therapeutic purpose; instead, their sole purpose was to help the Army gather data about the use of mescaline derivatives as potential chemical warfare agents.[191] According to a judicial opinion published almost thirty-five years following the experiment, Blauer reportedly was aware that the drugs he would be given were experimental in the sense that they did not come from a pharmacy; however, he was unaware that their purpose was not to help him but, instead, to help develop chemical warfare agents.[192] Blauer reportedly was not asked to give written informed consent to his own research participation, although he gave oral consent, at least initially.[193]

¶ 51 Blauer received one injection per week for five weeks in December 1952 and January 1953.[194] According to study records made immediately prior to his first injection, Blauer was "very apprehensive" about taking part in the study, and "considerable persuasion [was] required" to make him accept the first injection.[195] The chemical reportedly caused a feeling of pressure in Blauer's head and a slight tremor in his right leg.[196] The study records made prior to the second injection indicate that Blauer again was "apprehensive," although this time there was little or no physical reaction to the chemical.[197] Prior to his third injection, the nurses observed that Blauer was more disturbed about his continued participation in the research.[198] Blauer reportedly asked one of the nurses if she would call the physicians in charge of the study and tell them that

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[184] *Id.*
[185] *Id.*
[186] *Id.* at 1317.
[187] *Id.* at 1298.
[188] *Id.*
[189] *Id.*
[190] *Id.* at 1298-99.
[191] *Id.* at 1299.
[192] *Id.*
[193] *Id.*
[194] *Id.*
[195] *Id.*
[196] *Id.*
[197] *Id.*
[198] *Id.*

he had a cold, because the doctors would not believe Blauer if he told them.[199] Notwithstanding this request, Blauer received his third injection, which caused him to shake all over.[200] Prior to his fourth injection, Blauer stated that he did not want to receive any more injections.[201] In response, Blauer was told that if he did not continue his research participation, he would have to leave the Psychiatric Institute and return to Bellevue or Roosevelt Hospital, where he had been admitted and unhappy prior to his admission to the Psychiatric Institute.[202] Blauer reportedly did not pursue his complaints any further.[203] The fourth injection caused Blauer to suffer a violent reaction, including body tremors and repeated sitting up and flopping back down.[204]

¶ 52 For his fifth injection, Blauer was to receive 450 milligrams, or sixteen times the amount, of the derivative he had received in his first injection.[205] Before this injection, Blauer again complained to his therapist and the nurses about the injections.[206] Notwithstanding, Blauer received the injection sometime between 9:53 and 9:57 a.m. on January 8, 1953, after which he became restless and started sweating profusely and flailing his arms.[207] Then, his body stiffened, his teeth clenched, and he began frothing at the mouth.[208] Finally, he fell into a deep coma.[209] Harold Blauer was pronounced dead at 12:15 p.m.[210] Shortly thereafter, the Psychiatric Institute informed the New York City Medical Examiner of Blauer's death, stating in its written report that Blauer's injections were for diagnostic purposes, not research:

> The patient received an intravenous injection of a mescaline derivative at 9:53 a.m. on January 8, 1953 for diagnostic purposes. He had received this drug previously with no untoward reaction. A few minutes after the injection the patient became unconscious, showed a tonic rigidity of neck and arms and legs, became cyanotic, pulse became thready and blood pressure dropped to 110/40. He was given intravenous glucose and coramine and nasal oxygen and he showed a marked improvement. He started to speak and appeared to be on the way to recovery. Then he suddenly became pulseless, blood pressure dropped, respiration ceased and he expired. He was pronounced dead at 12:15 p.m.[211]

¶ 53 Although the experiment was conducted in late 1952 and early 1953, it was not until 1975 that it was publicly disclosed that the Army had supplied the chemicals Blauer received and that the injections were part of an experiment to develop chemical warfare

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[199] *Id.*
[200] *Id.*
[201] *Id.*
[202] *Id.* at 1299-1300.
[203] *Id.* at 1300.
[204] *Id.*
[205] *Id.*
[206] *Id.*
[207] *Id.* at 1321.
[208] *Id.*
[209] *Id.*
[210] *Id.* at 1300.
[211] *Id.*

agents.[212] In the meantime, Blauer's survivors, on behalf of his estate, brought several actions against the State of New York and the Psychiatric Institute, resulting in several judicial opinions that contain significant detail about the experiment, including copies of study records documenting Blauer's reactions to all five injections.[213] As explained by federal District Court Judge Constance Baker Motley in a judicial opinion authored in 1987, the Army and the Psychiatric Institute treated Blauer like a guinea pig:

> The case arises from the death of Harold Blauer, a mental patient who died in 1953 as a guinea pig in an experiment to test potential chemical warfare agents for the United States Army. Rather than admit its role in Blauer's death, the Government covered up its involvement in the affair, thus this opinion is issued today rather than in the early 1950's when the death occurred.[214]

The judge's reference to guinea pigs was, perhaps, an allusion to Englishman M. H. Pappworth's book *Human Guinea Pigs*, which exposed numerous experiments in which vulnerable human subjects, including individuals with mental disabilities who could not consent to their own research participation, were enrolled in nontherapeutic research.[215]

¶ 54 I selected the Blauer case for review because it illustrates several legal and ethical concerns relating to the reasonableness of research risks in relation to expected benefits, the use of captive, vulnerable populations for medical experimentation, and the lack of informed consent (or continued consent) to research participation. First, the Blauer case contains obvious issues relating to the reasonableness of the risks posed to Blauer and the other subjects by the mescaline injections in relationship to the anticipated benefits. According to the Army's own research proposal, the anticipated benefits included "new technical data . . . [that] will provide a firmer basis for the utilization of psychochemical agents both for offensive use as sabotage weapons and for protection against them."[216] The anticipated benefits did not include therapeutic benefits to Blauer or to the other research subjects.[217] The question thus becomes whether the risks posed by the chemicals were reasonable in relationship to the importance of the expected chemical warfare data. In hindsight, the question certainly would be answered in the negative. The death of a subject certainly outweighs any potential benefit to be derived from new chemical warfare knowledge. The question is supposed to be answered prospectively, however. Although the scientists probably did not know, at least definitely, that Blauer or another subject would die, they were aware, as a result of prior toxicity testing involving mice, that death (at least to mice) was a possibility.[218] They also knew (or at least one court found that they knew) that the scientists had not yet conducted additional toxicity testing sufficient to determine the chemical's safety in

[212] *Id.* at 1294.
[213] *Id.*
[214] *Id.*
[215] FADEN & BEAUCHAMP, *supra* note 160, at 159.
[216] Barrett, 660 F. Supp. at 1295.
[217] *Id.* at 1299 ("[N]o diagnostic or therapeutic purpose for Blauer, himself, was ever intended from the injections.").
[218] *Id.* at 1315.

humans.[219] Many believe that the risks posed to Blauer and to the other research subjects, even viewed prospectively, were not reasonable in relationship to the knowledge that was expected to result.

¶ 55 With respect to concerns relating to captivity and vulnerability, it is important to note that Blauer was an inpatient at a psychiatric hospital. Although he was a voluntary patient, which means he technically could have left the Psychiatric Institute against medical advice at any time, he appears to have wanted to stay and receive treatment until his condition resolved to the point where he could resume normal daily activities at work and home. This is supported by evidence that Blauer was unhappy and had left two previous psychiatric facilities, Bellevue and Roosevelt Hospital, and that Blauer was staying and making substantial progress at the Psychiatric Institute and had agreed, together with his therapist, to a release date a few weeks later, in early 1953.[220]

¶ 56 Note, however, that when Blauer stated prior to his fourth injection that he no longer wanted to receive the injections, he was told that if he did not continue the injections, he would be forced to leave the Psychiatric Institute and return to Bellevue or Roosevelt Hospital.[221] This statement supports Blauer's constructive captivity. Stated another way, although Blauer technically could have left the Psychiatric Institute at any time, it used Blauer's desire to receive further treatment to coerce him into participating in its research project. We also might say that Blauer's attempt to withdraw from research participation involved a penalty, which would be the loss of access to continued treatment at the Psychiatric Institute. As will be reviewed in Part II(D), federal law now requires scientists to allow research subjects to withdraw their research participation at any time without any penalties or the loss of any benefits to which they may be otherwise entitled.[222]

¶ 57 In addition to concerns relating to captive, vulnerable populations, the Blauer case raises potential competency issues and serious informed consent issues. Some patients with severe mental illness, such as untreated schizophrenia, may not be competent to consent to their own research participation because they may not be able to understand and appreciate the nature and consequences of a decision to participate in research.[223] Clinicians must make an individualized determination regarding whether a particular patient does or does not have decision-making capacity.[224] In Blauer's case, he did have an initial diagnosis of severe depression and/or pseudo-neurotic schizophrenia;

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[219] *Id.*
[220] *Id.* at 1298.
[221] *Id.* at 1299-1300.
[222] 45 C.F.R. § 46.116(a)(8) (2007) (Federal Common Rule provision requiring potential research subjects to be informed that "[their] participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.").
[223] *See, e.g.*, Paul S. Appelbaum, *Decisional Capacity of Patients with Schizophrenia to Consent to Research: Taking Stock*, 32 SCHIZOPHRENIA BULLETIN 22, 22 (2006) (explaining that patients with schizophrenia tend to have lower scores on measures of decisional capacity compared to individuals without schizophrenia, but noting that performance is highly variable and must be analyzed on an individual basis).
[224] *Id.*

however, he was scheduled to be released within a few weeks "without any disability," and it was expected that he would return to teaching tennis and parenting his children.[225] Even by today's standards, Blauer probably would be considered competent to give consent to his own research participation because he had the ability to understand and appreciate the nature and consequences of his own research participation and to reach an informed decision regarding the matter.[226] Blauer was not, however, informed of the true nature of the experiment to which he was asked to consent.[227] Remember, Blauer was unaware that his injections were being administered to help the Army's chemical warfare efforts and that the injections were not for his own benefit.[228] Blauer thus was competent to give his consent, but any consent that he did give was not informed and would not be considered valid by today's standards.[229]

C. Hepatitis Experimentation at Willowbrook Hospital

¶ 58 The Army's chemical warfare research project certainly was not the last experiment that involved patients with mental disorders. In 1967, British physician H. M. Pappworth wrote about a number of questionable research studies, including one experiment that investigated blood flow in the brains of over one hundred elderly patients with dementia.[230] During this experiment, scientists inserted long needles into each patient's jugular veins and femoral artery while the patient inhaled radioactive gas.[231] The publication of these and other study results in prestigious science journals such as *British Medical Journal* and *Journal of Clinical Investigation* suggests both the commonality and the acceptance of experiments involving patients with mental disorders in the mid-1900s.[232]

¶ 59 Even these experiments, however, are said to pale in comparison with the questionable research activities that occurred at the Willowbrook State School (Willowbrook) on Staten Island in New York in the mid-1960s.[233] During this study, Dr. Saul Krugman and a group of infectious-disease physicians from New York University decided to use students at Willowbrook to study the natural history of hepatitis and

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[225] Barrett, 660 F. Supp. at 1317 ("If he had not died, he would have been released soon from the Psychiatric Institute, without any disability that would have prevented him from working.").
[226] *Id.* at 1299 ("Blauer was competent to give consent to the experiment."). *Competence*, sometimes referred to as *decision-making capacity*, may be defined as the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment or research participation and the ability to reach an informed decision in the matter. *See, e.g.*, TEX. HEALTH & SAFETY CODE ANN.§ 313.002(3) (2007) (defining competence in the treatment context).
[227] Barrett, 660 F. Supp. at 1299.
[228] *Id.* at 1299.
[229] *See, e.g.*, 45 C.F.R. § 46.116(a)(3) (2007) (requiring informed consent documentation to describe to the potential subject "any benefits to the subject or to others which may reasonably be expected from the research."). For Blauer's consent to be informed, Blauer would have had to be told that he personally would not benefit from the research, that any benefits would go directly to the Army Chemical Corps, and that the corps' goal was to gain knowledge regarding the effects of mescaline derivatives in support of their chemical warfare efforts.
[230] MORENO, *supra* note 160, at 136-37.
[231] *Id.* at 137.
[232] *Id.*
[233] *Id.* at 139.

develop possible treatments.[234] The students at Willowbrook had severe mental retardation,[235] a condition we would now call severe intellectual or developmental disability,[236] and reportedly, many of the students acquired hepatitis following admission due to repeated exposure to each others' body fluids.[237]

¶ 60 During his study, Krugman intentionally infected Willowbrook students with the live hepatitis B virus.[238] Krugman justified his experiment by what he referred to as the inevitableness of hepatitis in the student body (according to Krugman, most of the Willowbrook students acquired hepatitis within the first six to twelve months of their admission[239]), the reported mildness of the disease symptoms in this particular school-aged population, and his belief that the students' research participation actually benefited them because mild hepatitis infection provides protection against future, and more severe, hepatitis infections.[240] Krugman reportedly obtained approval to proceed with his study from two New York State agencies: the Armed Forces Epidemiological Board and the human-experimentation committees of the New York University School of Medicine and the Willowbrook School.[241]

¶ 61 The Willowbrook students were incompetent to consent to their own research participation because many were less than eighteen years old and had severe intellectual and developmental disabilities, the latter of which made it impossible for even the older students to understand and appreciate the nature and consequences of a decision to participate in research.[242] Krugman thus obtained consent to the students' research participation from their parents.[243] In many cases, the consent was coerced.[244] For example, some of the children had yet to be admitted to Willowbrook.[245] Krugman encouraged the parents of these children to consent to their children's research participation by arranging for more rapid admission to the school.[246] Other parents, whose children already were admitted, were told that Willowbrook was closing due to

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[234] *Id.*; RONALD MUNSON, INTERVENTION AND REFLECTION: BASIC ISSUES IN MEDICAL ETHICS 240 (1979).
[235] *See* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 240.
[236] *See, e.g.*, Anna Prabhala, Mental Retardation *Is No More—New Name Is* Intellectual and Developmental Disabilities, AAIDD NEWS, Feb. 20, 2007, *available at* http://www.aamr.org/About_AAIDD/MR_name_change.htm (last visited July 26, 2007) (discussing society's struggle to find a socially acceptable way of addressing and referring to individuals with intellectual disabilities).
[237] *See* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 241.
[238] *See* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 241.
[239] *See* MUNSON, *supra* note 234, at 240.
[240] Saul Krugman, Letter to the Editor of Lancet, *republished in* INTERVENTION AND REFLECTION: BASIC ISSUES IN MEDICAL ETHICS 281, 281-82 (Ronald Munson ed., 1979) ("As early as 1960 we demonstrated the protective effect of this vaccine during the course of an epidemic. . . . It is well known that viral hepatitis in children is milder and more benign than the same disease in adults. . . . The statement by Dr. Goldby accusing us of conducting experiments exclusively for the acquisition of knowledge with no benefit for the children cannot be supported by the true facts."). *See also* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 241.
[241] MUNSON, *supra* note 234, at 241-42.
[242] *See, e.g.*, Appelbaum, *supra* note 223, at 22.
[243] *See* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 241.
[244] *See* MORENO, *supra* note 160, at 139; MUNSON, *supra* note 234, at 241.
[245] *See* MORENO, *supra* note 160, at 139.
[246] *Id.*

overcrowding; however, a week or two later, the same parents were told that there would be room (and vaccines) in the "hepatitis unit" for children whose parents consented to the experiment.[247]

¶ 62 Like the Army's chemical warfare research, the Willowbrook study raises concerns relating to the reasonableness of the research risks in relation to the expected benefits; the use of a captive, vulnerable population for medical experimentation; and coerced, third-party consent to research participation.[248] With respect to the reasonableness of the risks in relationship to the expected benefits, Krugman argued that the mild hepatitis infections benefited the students by protecting them against future, more severe strains of hepatitis.[249] Others believe that the intentional infection of students with hepatitis can in no way be classified as directly therapeutic, or a benefit, to the students and that it must be classified as a research harm because hepatitis B causes lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death.[250] The question thus becomes whether the harms associated with intentional hepatitis infection were reasonable in relationship to the knowledge that was expected to result. Most (other than Krugman) believe that the Willowbrook experiment was unreasonable because it offered no direct benefit to the students and directly caused the students' hepatitis infection, even though knowledge regarding the natural course of hepatitis and its treatment was expected to, and did in fact, result.[251]

¶ 63 With respect to concerns relating to captivity and vulnerability, the subjects were institutionalized at a school for individuals with intellectual and developmental disabilities. Although the students probably could have left the school with their parents' permission and agreement to care for them, some of the parents were told that their children would lose their current admissions if they did not volunteer their children for the study.[252] Other parents were told that their children could be admitted to the school if they volunteered their children for the study.[253] These facts support the children's constructive captivity. Stated another way, although the children technically could have left Willowbrook with their parents' permission, Krugman used the parents' desire to obtain or maintain institutional placement for their children to coerce (some say blackmail) the parents into volunteering their children for research.[254]

¶ 64 In addition to concerns relating to captive, vulnerable populations, the Willowbrook case raises very real competency and informed consent issues. Again,

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[247] M. H. Pappworth, Letter to the Editor of Lancet, *republished in* INTERVENTION AND REFLECTION: BASIC ISSUES IN MEDICAL ETHICS 282, 282 (Ronald Munson ed., 1979).
[248] MUNSON, *supra* note 234 at 242.
[249] Krugman, *supra* note 240; MORENO, *supra* note 160 at 139; MUNSON, *supra* note 234 at 241.
[250] *See, e.g.*, Stephen Goldby, Letter to the Editor of Lancet, *republished in* INTERVENTION AND REFLECTION: BASIC ISSUES IN MEDICAL ETHICS, 280, 280 (Ronald Munson ed., 1979).
[251] *Id.* at 280 ("If Krugman and Giles are keen to continue their experiments I suggest that they invite the parents of the children involved to participate. I wonder what the response would be."). Others believe that Krugman's research significantly furthered knowledge of the natural course of viral hepatitis and its methods of treatment. MUNSON, *supra* note 234, at 242.
[252] Pappworth, *supra* note 247, at 282.
[253] MORENO, *supra* note 160, at 139.
[254] *See* MUNSON, *supra* note 234, at 242.

some patients with mild developmental disabilities, such as attention deficit disorder, certainly are competent to consent to their own research participation. The minor students at Willowbrook, however, had severe intellectual disabilities that prohibited them from understanding and appreciating the nature and consequences of their own research participation. As a result, the scientists obtained consent from their parents. I already have discussed whether this consent was coerced. A second question, equally important, is whether the consent was informed. For example, were the parents told that intentional infection with hepatitis causes lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death?[255] If not, the parents' consent would not be considered valid by today's standards.[256]

D. The Development of Federal Protections

¶ 65 The Army's chemical warfare research and the Willowbrook study certainly were not the only questionable experiments involving patients with psychiatric conditions and developmental disabilities that led to the development of human-subjects protections. Dozens of other studies, including LSD research conducted on psychiatric patients in the 1960s[257] (and, more recently, drug-free, or "washout," studies in which scientists take patients who have schizophrenia off their medications to establish their baseline behavior prior to administering new medications, resulting in suicide in some cases),[258] called (and continue to call) attention to the need for, and the enforcement of, ethical and legal principles governing human subjects research.

¶ 66 The development of ethical and legal protections for human subjects has been thoroughly researched and documented elsewhere.[259] In this section, I provide a much abbreviated history of the development of relevant American ethical and legal human-subjects protections with a focus on the attempted development of protections for research subjects with decisional impairments. As you read this section, pay attention to the guidance provided by each ethical and legal authority regarding balancing research risks and benefits, especially in emerging disciplines, as well as who, if anyone, can consent to research participation on behalf of an individual with a decisional impairment.[260]

¶ 67 The first modern code mandating protection of human subjects was, ironically, adopted in Germany prior to the Third Reich.[261] The "Reich Circular of 1931," which built on a 1900 directive from the Prussian minister for religious, educational, and

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[255] Goldby, *supra* note 250, at 280.
[256] *See, e.g.*, 45 C.F.R. § 46.116(a)(2) (2007) (requiring informed consent documentation to describe to the potential subject "any reasonably foreseeable risks or discomforts").
[257] MORENO, *supra* note 160, at 154-55.
[258] *See, e.g.*, Paul S. Appelbaum, *Drug-Free Research in Schizophrenia: An Overview of the Controversy*, 18 IRB: ETHICS AND HUMAN RESEARCH 1-5 (1996) (examining the sudden interest in the ethics of psychiatric research); MORENO, *supra* note 160, at 137 (referencing drug-free schizophrenia research).
[259] *See supra* note 160.
[260] *See* LORD CHANCELLOR'S DEPARTMENT, WHO DECIDES? MAKING DECISIONS ON BEHALF OF MENTALLY INCAPACITATED ADULTS 1 (London: Lord Chancellor's Department, 1997).
[261] EATON & KENNEDY, *supra* note 160, at 37; FADEN & BEAUCHAMP, *supra* note 160, at 153-54.

medical affairs, established fourteen provisions, including provisions that required scientists conducting human-subjects research to establish a careful research design, to give to potential subjects appropriate information about the research project, to obtain consent prior to research, and to provide special protections for vulnerable subjects.[262] The Reich Circular required consent, whether first-party or proxy, to be given "in a clear and undebatable manner."[263] Given its requirement for special protections and its reference to proxy consent, the Reich Circular thus expressly considered that some research projects might involve vulnerable or incompetent subjects.

¶ 68 The story of *United States v. Brandt* (the "Nazi Doctors' Trial")[264] and the resulting Nuremberg Code[265] is, by now, well known. The Nazi Doctors' Trial was the first of twelve trials for war crimes that U.S. authorities held in their occupation zone in Nuremberg, Germany, following World War II.[266] Twenty of the twenty-three defendants (physicians who were accused of murder, torture, and other atrocities) had been involved in human experiments designed to contribute to knowledge regarding the survival of German pilots and soldiers.[267] The physicians had recruited human subjects from the Dachau prison camp and exposed them to low air pressures, lack of oxygen, ice-cold tubs of water, subfreezing temperatures, gunshot wounds, burns, amputations, and chemical and biological agents.[268] By the end of the Nazi Doctors' Trial in 1947, seven of the twenty-three defendants were acquitted, seven received death sentences, and the remainder received prison sentences ranging from ten years to life imprisonment.[269]

¶ 69 The chief medical advisor to the Nuremberg judges, Dr. Leo Alexander, wrote a memorandum to the trial judges, one part of which included standards for the ethical conduct of human subjects research.[270] (In his memorandum, Dr. Alexander had identified individuals with mental illness as a population that should receive special protection; however, the judges declined to incorporate these special protections in their final opinion.[271]) The standards that the judges included in their opinion became known as the Nuremberg Code.[272] Although the code contains several ethical requirements relating to yielding fruitful results, basing human experimentation on prior animal experimentation, avoiding all unnecessary physical and mental suffering and injury, and having no expectation of death or disabling injury,[273] the code perhaps is most well known for its first line: "The voluntary consent of the human subject is absolutely essential."[274] This requirement, which by its terms refers to *the* human subject,

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[262] EATON & KENNEDY, *supra* note 160, at 37-38.
[263] FADEN & BEAUCHAMP, *supra* note 160, at 154.
[264] *See* ANNAS & GRODIN, *supra* note 160 (devoting themselves to the Nazi Doctors Trial, the Nuremberg Code, and the application of Nuremberg Code principles to current research projects).
[265] The Nuremberg Code, *reprinted in* VANDERPOOL, *supra* note 160, at 431-32.
[266] DUNN & CHADWICK, *supra* note 160, at 14-16.
[267] *Id.* at 15-16.
[268] *Id.* at 15.
[269] *Id.* at 16.
[270] MORENO, *supra* note 160, at 163.
[271] *Id.*
[272] *Id.*
[273] The Nuremberg Code, *reprinted in* VANDERPOOL, *supra* note 160, at 431-32.
[274] *Id.*

immediately questions the propriety of research involving individuals who cannot consent to their own research participation.[275] The first line of the code is followed by some explanatory language:

> This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion, and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the methods and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.[276]

¶ 70 The meaning of this explanatory language continues to be debated. Some commentators believe that the "legal capacity" requirement prohibits individuals with decisional impairments and children from taking part in research; others believe that the requirement forbids only individuals with decisional impairments and children from signing the consent form.[277] Some commentators believe that the "so situated" clause refers to captive individuals, such as individuals in prisons and mental institutions, who may be coerced into consenting to research by reason of their captivity.[278] Moreover, some commentators believe that the "knowledge and comprehension" and "enlightened decision" references prohibit individuals with decisional impairments from participating in research.[279] Finally, although the Nuremberg Code does not so state, many believe that the entire first paragraph, which establishes the basic principle of informed consent, comes into play only following a positive assessment of research benefits and risks.[280]

¶ 71 With respect to balancing research risks and benefits, the Nuremberg Code contains two relevant statements: "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not

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[275] COLEMAN, *supra* note 160, at 585 ("A literal application of this provision would preclude any research with individuals who lack the mental capacity to provide informed consent—for example comatose patients. . . .").
[276] The Nuremberg Code, *reprinted in* VANDERPOOL, *supra* note 160, at 431.
[277] ADIL E. SHAMOO & FELIX A. KHIN-MAUNG-GYI, ETHICS OF THE USE OF HUMAN SUBJECTS IN RESEARCH 76 (2002). *See generally* CARL H. COLEMAN ET AL., THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS 585 (2005) (explaining that the "legal capacity" requirement could be interpreted to preclude any research with individuals who lack decision-making capacity but that such a policy would make it difficult to develop treatments for individuals affected with these conditions; further noting that the amount of research involving adults who lack decision-making capacity is growing exponentially, thus suggesting that the scientists who conduct this research do not interpret the "legal capacity" requirement to preclude such research).
[278] SHAMOO & KHIN-MAUNG-GYI, *supra* note 277, at 76.
[279] *Id.*
[280] FADEN & BEAUCHAMP, *supra* note 160, at 154.

random and unnecessary in nature,"[281] and "[t]he degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."[282] Taken together, these statements suggest that nontherapeutic research (i.e., research that does not directly or potentially benefit individual subjects) is permissible so long as it contributes to nonrandom generalizable knowledge and is not risky. (In contrast, the new Atomic Energy Commission in a meeting held the same year unsuccessfully attempted to impose a requirement of potential benefit for the subject.)[283]

¶ 72 The distinction between therapeutic and nontherapeutic research became even more important in the 1960s, although the distinction was relevant only to the requirement of consent, not the permissibility of the conduct of the research. In 1964, during its Eighteenth Assembly in Helsinki, Finland, the World Medical Association adopted a code (the Declaration of Helsinki) that distinguished therapeutic research, defined as research combined with patient care, from nontherapeutic research, defined as "purely scientific research that has no therapeutic value or purpose for the specific subjects studied."[284] The declaration did not require informed consent for therapeutic research if consent was not "consistent with patient psychology."[285] The declaration did require consent for nontherapeutic research except when mental incapacity made it impossible to obtain informed consent (in which case permission from the responsible relative would replace the subject's consent if allowed under applicable national law).[286]

¶ 73 With the Nuremberg Code and the Declaration of Helsinki firmly in place, the U.S. government increased its protective efforts in the 1970s.[287] In 1971, the federal Department of Health, Education, and Welfare (HEW) established guidelines for the protection of federally funded human research subjects, including a requirement for prior IRB approval of research protocols.[288] Among other things, IRBs now had the responsibility of balancing the risks posed to subjects by particular research protocols against the combination of the benefits to the subjects and the importance of the

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[281] The Nuremberg Code, *reprinted in* VANDERPOOL, *supra* note 160, at 431.
[282] *Id*.
[283] *See* MORENO, *supra* note 160, at 116. The question of whether direct or potential research subject benefit is required, as well as the meaning of such benefit, will become important when I discuss in Part III(A) the knowledge and benefits that may result from neuroimaging research into disorders of consciousness.
[284] World Medical Assembly, Declaration of Helsinki, *in* VANDERPOOL, *supra* note 160, at 433-35 ("In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research."). *See also* FADEN & BEAUCHAMP, *supra* note 160, at 156.
[285] World Medical Assembly, Declaration of Helsinki, *in* VANDERPOOL, *supra* note 160, at 435. *See also* FADEN & BEAUCHAMP, *supra* note 160, at 156.
[286] World Medical Assembly, Declaration of Helsinki, *in* VANDERPOOL, *supra* note 160, at 435. *See also* FADEN & BEAUCHAMP, *supra* note 160, at 156. The provision allowing permission from a responsible relative would not apply in countries, such as the United Kingdom, where the law, with some exceptions, does not recognize proxy consent. MEDICAL RESEARCH COUNCIL, THE ETHICAL CONDUCT OF RESEARCH ON THE MENTALLY INCAPACITATED 9 (London: Medical Research Council 1993).
[287] EATON & KENNEDY, *supra* note 160, at 42.
[288] *Id*.

knowledge to be gained.[289] Only if the benefits outweighed the risks could the IRB approve the study and allow subjects to be offered research participation.[290]

¶ 74 In 1974, Congress passed the National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the "Commission").[291] The Commission was charged with recommending the basic ethical principles that should underlie the conduct of human-subjects research and developing guidelines to assure that human-subjects research complied with these principles.[292] In February 1978, near the end of its tenure, the Commission issued a special report (the "Commission Special Report") making recommendations for human-subjects research involving individuals "institutionalized as mentally infirm," which included "individuals with mental illness, mental retardation, emotional disturbances, psychoses, senility, and other impairments of a similar nature who reside in an institution."[293] The Commission recommended that research participation not interfere with the care of such individuals and that research projects be relevant to the condition of any subjects who cannot consent to their own research participation.[294] Although HEW proposed regulations based on the recommendations set forth in the Commission Special Report in November 1978,[295] the agency did not adopt them in final form then or thereafter in 1981 or 1983, when the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research further recommended their adoption.[296]

¶ 75 At the very end of its tenure (in late 1978), the Commission completed its by-now-famous Belmont Report, which established three basic ethical principles (respect for persons, beneficence, and justice) and examined their application to requirements relating to informed consent, the assessment of research risks and benefits, and the selection of

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[289] *Id.*
[290] *Id.*
[291] *Id.* National Research Act Service Award Act of 1974, Pub. L. No. 93-348, §§ 201-202, *codified at* 42 U.S.C. § 289l-1 (1974).
[292] National Research Act, §§ 201-202. *See* EATON & KENNEDY, *supra* note 160, at 42 (discussing the National Research Act).
[293] NAT'L COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, RESEARCH INVOLVING THOSE INSTITUTIONALIZED AS MENTALLY INFIRM xvii (defining "institutionalized mentally infirm") and cover letter from Kenneth J. Ryan to Walter F. Mondale, Feb. 2, 1978 (identifying the Commission's recommendations), DHEW Pub. No. (OS) 78-0006 (1978), *published at* 43 Fed. Reg. 11328 (Mar. 17, 1978) [hereinafter, Commission Special Report]. Although individuals with DOC are not specifically listed in the definition of "individuals institutionalized mentally infirm," an analogy may be made to the psychiatric and developmental disability conditions listed, especially to the extent individuals with these conditions reside in nursing homes and similar institutions. *See id.* at xviii (listing "nursing homes for the mentally disabled, and similar institutions" as qualifying institutions).
[294] Commission Special Report, *supra* note 293 (cover letter from Kenneth J. Ryan to Walter F. Mondale, Feb. 2, 1978). More specific recommendations relating to minimal-risk and more-than-minimal-risk research are set forth in the body of the Commission Special Report. *Id.* at 1-22. *See generally* MORENO, *supra* note 160, at 164 (discussing the history of the Commission Special Report).
[295] Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled, 43 Fed. Reg. 53,950 (Nov. 17, 1978).
[296] *See, e.g.*, Robert J. Levine, *Proposed Regulations for Research Involving Those Institutionalized as Mentally Infirm: A Consideration of Their Relevance in 1996*, 18 IRB: ETHICS AND HUMAN RESEARCH 1, 1 (1996).

research subjects.[297] HEW formally published the Belmont Report in the *Federal Register* on April 18, 1979.[298] With respect to the involvement of individuals with decisional impairments in human-subjects research, the Belmont Report recognized that (1) special provisions may need to be made for these individuals, (2) the principle of respect for persons requires consent to research participation to come from a third party who is most likely to understand the individual's situation and to act in the individual's best interest, and (3) the third party should have the opportunity to observe the research as it proceeds and withdraw the individual from the research if withdrawal is in the individual's best interest.[299]

¶ 76 In 1981, the federal Department of Health and Human Services (HHS), which was the successor to HEW, and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report.[300] Ten years later, more than a dozen federal agencies adopted the core of the HHS regulations, which are now referred to as the Common Rule.[301] Today, the Common Rule is shared by seventeen federal departments and agencies[302] and regulates U.S. federally funded research, research conducted at an institution that has obligated itself through a multiple project assurance to comply with the Common Rule with respect to all of its research, and research conducted in contemplation of a submission to the FDA.[303]

¶ 77 As amended over the years, the Common Rule contains special subparts for several vulnerable populations, including fetuses, pregnant women, and human in vitro fertilization,[304] as well as prisoners[305] and children.[306] The Common Rule also requires IRBs to ensure vulnerable research groups, including "mentally disabled persons," receive additional safeguards designed to protect their health and welfare.[307] Finally, the

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[297] NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 1-20, DHEW Pub. No. (OS) 78-0012 (1978) (hereinafter, BELMONT REPORT]. *See generally* EATON & KENNEDY, *supra* note 160, at 42 (discussing the history of the Belmont Report).

[298] The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,192,(Apr. 18, 1979).

[299] BELMONT REPORT, *supra* note 297, at 13.

[300] 45 C.F.R. Part 46 (1981) (HHS regulations); 21 C.F.R. Part 50 (1981) (FDA regulations).

[301] Division of Research and Graduate Studies, University of Nevada at Las Vegas, History of Research Ethics, http://research.unlv.edu/OPRS/history-ethics.htm (last visited August 1, 2007).

[302] *See* OFFICE FOR PROTECTION FROM RESEARCH RISKS, OFFICE OF EXTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK 2-1, NIH Pub. No. 93-3470 (1993) (listing sixteen of the agencies that have adopted the Common Rule in whole or in part); MORENO, *supra* note 160, at 165 (discussing the adoption of the Common Rule by seventeen different federal agencies); EATON & KENNEDY, *supra* note 160, at 42 (same).

[303] *See* EATON & KENNEDY, *supra* note 160, at 42-43.

[304] 45 C.F.R. Part 46, Subpart B.

[305] 45 C.F.R. Part 46, Subpart C.

[306] 45 C.F.R. Part 46, Subpart D.

[307] 45 C.F.R. § 46.111(b) (2007) ("When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects."). The safeguards could involve consultation with specialists concerning the risks and benefits of a procedure for these populations or special monitoring of

Common Rule requires IRBs to consider the inclusion of one or more individuals who are knowledgeable about and experienced in working with individuals who are members of these vulnerable populations if the IRB regularly reviews research involving such populations.[308]

¶ 78 The Common Rule does not, however, contain a special subpart governing human-subjects research involving adults who have decisional impairments due to a severe psychiatric condition, intellectual or developmental disability, disorder of consciousness, or other mental or neurological disorder.[309] Why a special subpart was not included continues to be debated. HEW, through its secretary, suggested that the rules it proposed in 1978 "had produced a 'lack of consensus'" and that the core of the Common Rule "adequately . . . protect[ed]" individuals with decisional impairments.[310] Former Commission member Al Jonsen reported concern by others that the Commission's recommendations would stifle research into mental conditions accompanied by decisional impairments.[311] Harvard Professor Neil Chayet shared these concerns and stated that "the legal and medical perspectives on the subject are fundamentally incompatible—particularly in the area of the mentally disabled, where appreciation of the concept of informed consent is well on its way to paralyzing research and treatment."[312]

¶ 79 Without a special subpart to guide their efforts, scientists who design (and IRBs that review) research projects involving adults with decisional impairments must ensure that each project complies with the generic criteria set forth in the core of the Common Rule.[313] Among other things, these core criteria require the following: (1) the risks to subjects to be minimized; (2) the risks to subjects to be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result"; (3) informed consent to be "sought from each prospective subject or the subject's legally authorized representative"; and (4) "when some or all of the subjects are likely to be vulnerable to coercion or undue influence," including individuals with mental disorders, additional safeguards to be included to protect the rights and welfare of these subjects.[314]

¶ 80 The multi-agency adoption of the Common Rule in 1991 did not end the federal government's struggle with how best to protect human research subjects. The Clinton Administration in 1995 formed the National Bioethics Advisory Commission (NBAC) and charged it with studying important issues in bioethics, including human-subjects

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consent processes to ensure voluntariness. It is not known how frequently IRBs implement these and other safeguards. *See generally* MORENO, *supra* note 160, at 165.

[308] 45 C.F.R. § 46.107 (2007).

[309] *See* MORENO, *supra* note 160, at 165.

[310] Levine, *supra* note 296, at 1.

[311] *See generally* MORENO, *supra* note 160, at 164.

[312] Neil L. Chayet, *Informed Consent of the Mentally Disabled: A Failing Fiction*, 6 PSYCHIATRIC ANNALS 82, 82 (1976); MORENO, *supra* note 160, at 165 (quoting Chayet).

[313] 45 C.F.R. § 46.111 (2007).

[314] *Id.*

research.[315] Over the next two years, the NBAC held hearings on several issues, including research participation by individuals with decisional impairments.[316] In December 1998, NBAC issued a special report (the "NBAC Report") addressing research involving individuals whose mental disorders may affect their decision-making capacity.[317] NBAC acknowledged the tension between the rapid advances in science and technology, especially in the area of the diagnosis and treatment of individuals with mental disorders, and the rather staid core provisions of the Common Rule:

> During the nearly two decades in which the current federal regulations for the protection of human subjects have been in place, important scientific research on the cause and treatment of mental disorders has continued and expanded. . . . NBAC shares what it believes to be a broad base of support for continuing efforts to more fully understand and treat mental disorders. NBAC recommends additional new protections with the deepest respect for the many people involved in research on these disorders: those with a disorder that may affect decisionmaking capacity.[318]

¶ 81 With this lead in, it was not surprising that the NBAC found that "a cogent case could be made" for the establishment of a new subpart in the Common Rule that would govern human-subjects research involving adults with decisional impairments.[319] The NBAC also recommended that IRBs be permitted to approve a research study that presents only minimal risk (as are many fMRI investigations into DOC) so long as the subject consents or, if the subject cannot consent due to lack of decision-making capacity, the subject's legally authorized representative (LAR) consents.[320] The NBAC also recognized that years, if not decades, could pass before a federal agency would adopt final regulations implementing their recommendations and therefore suggested that scientists, academic medical centers, and IRBs voluntarily adopt and comply with the

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[315] Clinton Executive Order 12975, Protection of Human Research Subjects and Creation of National Bioethics Advisory Commission, 60 Fed. Reg. 52,036 (Oct. 5, 1995) (mandating the review of current human subjects regulations). *See generally* EATON & KENNEDY, *supra* note 160, at 44.

[316] *See generally* SHAMOO & KHIN-MAUNG-GYI, *supra* note 277, at 79 (discussing the work of the NBAC).

[317] NATIONAL BIOETHICS ADVISORY COMMISSION, RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY (1998), http://bioethics.georgetown.edu/nbac/capacity/TOC.htm (last visited August 2, 2007) [hereinafter, NBAC REPORT].

[318] *Id.* at Executive Summary, *available at* http://bioethics.georgetown.edu/nbac/capacity/Executive.htm (last visited Aug. 2, 2007).

[319] *Id.* ("NBAC believes that a cogent case can be made for requiring additional special protections in research involving as subjects persons with impaired decision making capacity, but has chosen to focus this report on persons with mental disorders, in part because of this population's difficult history of involvement in medical research."); *id.* at Summary and Recommendations, *available at* http://bioethics.georgetown.edu/nbac/capacity/Moving.htm#NewRegs (last visited Aug. 2, 2007) ("Many of the regulatory proposals made by NBAC could, however, also be accomplished by the creation of a new subpart in 45 CFR 46. Adoption of a subpart has the advantage of permitting affected federal agencies to act as expeditiously as they choose to change the regulatory requirements for their own intramural and extramural research."). *See generally* SHAMOO & KHIN-MAUNG-GYI, *supra* note 277, at 79 (examining the NBAC Report).

[320] NBAC REPORT, *supra* note 317, at Recommendations 10 and 14, *available at* http://bioethics.georgetown.edu/nbac/capacity/Moving.htm#NewRegs (last visited Aug. 2, 2007).

substance of the NBAC Report.[321]

¶ 82 As of today, neither HHS nor any other signatory to the Common Rule has adopted in federal regulations the NBAC's recommendations.[322] The absence of federal law governing research involving adults with decisional impairments does not mean, however, that scientists are not conducting research projects involving these populations; in fact, the number of projects has recently increased.[323] Without any specific federal guidance,[324] scientists, IRBs, federal agencies, lawyers, ethicists, and advocacy groups are left to draw their own opinions regarding the following: the appropriateness of enrolling individuals with decisional impairments, including DOC, into research studies; the class of risk to which various types of neuroimaging should be assigned; how to balance research risks and benefits; and who constitutes a LAR permitted to consent to the individual's research participation.[325]

E. The Development of State Protections

¶ 83 Perhaps due to the lack of express federal guidance, some state legislatures, state courts, and state agencies have attempted to more specifically address—via legislation, regulation, judicial opinions, and attorney general guidance—the rights of human subjects with decisional impairments.[326] New York, for example, adopted a "Protection of Human Subjects" statute designed to "protect its people against the unnecessary and improper risk of pain, suffering or injury resulting from human research conducted without their knowledge or consent."[327] The New York statute requires a human-research review committee to determine that the risks to human subjects are outweighed by the potential benefits or by the importance of the knowledge to be gained.[328] In the case of human subjects who do not have decision-making capacity, the statute expressly permits another person who is legally empowered to act on the subject's behalf to consent

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[321] *See* SHAMOO & KHIN-MAUNG-GYI, *supra* note 277, at 79.
[322] *Id.*
[323] COLEMAN, *supra* note 160, at 585.
[324] *Id.*
[325] *See, e.g.*, Rebecca Dresser, *Mentally Disabled Research Subjects: The Enduring Policy Issues*, 276 JAMA 67, 72 (1996) ("In the meantime, it will be up to investigators and IRBs to maintain the precarious balance between the interests of mentally disabled subjects and the public's desire for medical progress."); J. de Champlain & J. Patenaude, *Review of a Mock Research Protocol in Functional Neuroimaging by Canadian Research Ethics Boards*, 32 J. MED. ETHICS 530, 533 (2006) ("The risk-benefit component is the most difficult for [research ethics boards] to assess, more so when the study relates to an emerging discipline. REBs have little guidance to turn to in risk-benefit assessment. That they are thus effectively left to find their own way may partly account for the variability of decisions in our study.").
[326] *See, e.g.*, Diane E. Hoffmann & Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired in Medical Research—Maryland's Policy Initiative*, 1 J. HEALTH CARE L. & POL'Y 123, 125 (1998) ("Because federal law leaves unanswered the question of who is a 'legally authorized representative' for consent to research, researchers who seek to rely on this provision of federal law must turn to relevant state law for guidance. Unfortunately, little, if any, state law directly addresses this issue.").
[327] N.Y. PUB. HEALTH L. § 2440 (2007).
[328] *Id.* § 2444(2).

to the subject's research participation.[329]

¶ 84 New York is not the only state to have considered research involving individuals with decisional impairments. The Maryland Legislature found that "[r]esearch involving decisionally incapacitated individuals may be essential under some circumstances if science is to understand and ultimately combat diseases of the brain, including . . . severe trauma" and that "[r]esearchers should seek to enroll decisionally incapacitated individuals as research subjects only if the research is likely to yield generalizable knowledge important to the understanding or amelioration of the subjects' disorder or condition, and the knowledge cannot be obtained without their participation."[330] California also has a relevant statute that allows for consent to research participation by a conservator but only "for medical experiments related to maintaining or improving the health of the human subject or related to obtaining information about a pathological condition of the human subject."[331] A number of other states have statutes that require court approval before a guardian or conservator may consent to the research participation of an individual with decisional impairment if the court can determine that the experimental treatment will be in the individual's best interests.[332] In states that do not address consent to research participation, some scientists rely on consent-to-treatment statutes or durable power of attorney for healthcare statutes to find a proxy.[333]

¶ 85 In addition to state statutes and regulations, state courts and attorneys general weigh in on ethical and legal questions relating to human-subjects research. In *T.D. v. New York State*, for example, the Supreme Court of New York, Appellate Division, reviewed a challenge to state regulations governing more-than-minimal-risk nontherapeutic and possibly therapeutic experiments.[334] The court found that the regulations did not adequately safeguard the health and welfare of human research subjects and violated both the federal and the New York due process clauses.[335] Likewise, the Maryland Attorney General issued a report on Alzheimer's disease care and part of the report addressed the applicability of Maryland's surrogate consent to treatment statute to the research setting. The attorney general concluded that healthcare agents and surrogates may consent to an individual's research participation if, and only if, the research "presents a reasonable prospect of direct medical benefit," reasoning that the statute was designed to regulate only healthcare, not experimental studies designed only

[329] *Id.* § 2442 ("If the human subject be otherwise legally unable to render consent, such consent shall be subscribed to in writing by such other person as may be legally empowered to act on behalf of the human subject.").
[330] Draft, An Act Concerning Research—Protection of Decisionally Incapacitated Individuals, Appendix A, May 5, 1997, Part I, § 20-501(c)-(d) (on file with author).
[331] CAL. HEALTH & SAFETY CODE § 24175(e) (2007).
[332] *See, e.g.*, CONN. GEN. STATE ANN. 45a-677(e) (West Supp. 2007) (requiring proof that the experiment is intended to preserve the life or prevent serious impairment of the physical health of the ward or it is intended to assist the ward to regain his abilities and has been approved for that person by the court); 405 ILL. COMP. STAT. ANN. 5/2-110 (West 2007) (requiring proof that the experiment is in the individual's "best interests").
[333] Hoffmann & Schwartz, *supra* note 326, at 131-32 (discussing the application of state consent to treatment and durable power of attorney for health care statutes to consent to research participation).
[334] T.D. v. New York State Office of Mental Health, 650 N.Y.S.2d 173, 175 (N.Y. App. Div. 1996).
[335] *Id.* at 194.

to acquire knowledge.[336] Research, according to the attorney general, should not be conflated with healthcare.[337]

IV. MORAL IMPERATIVE OR LEGAL AND ETHICS FAILURE?

¶ 86 Keeping these federal and state developments in mind, I now examine the ethical and legal implications of neuroimaging research into DOC. To start, I identify the anticipated benefits of these studies, if any, and the importance of the knowledge that may reasonably be expected to result. Then, I balance these benefits against the relevant risks.

A. Neuroimaging Benefits

¶ 87 A benefit may be defined as "a valued or desired outcome; an advantage."[338] Research benefits may be divided into direct benefits, indirect benefits, and aspirational benefits.[339] Direct benefits, which are those benefits that arise from the subject's receipt of the intervention under study, include positive physiological responses, diagnostic benefits, and preventive benefits.[340] The analysis of direct benefits in the context of neuroimaging research into DOC is tricky because neuroimaging research is not expected to produce an immediate positive physiological response. For example, the authors of fMRI Studies 1, 2, and 3 were not studying the ability of a neural implant to reduce the length of a subject's impaired consciousness or to assist a subject in progressing from one DOC, such as VS, to MCS or consciousness.[341] So we might state that the research

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[336] OFFICE OF THE MARYLAND ATTORNEY GENERAL, POLICY STUDY ON ALZHEIMER'S DISEASE CARE Chapter 2 at 22 (2004), *available at* http://www.oag.state.md.us/Healthpol/Alzheimers.htm (last visited August 1, 2007).

[337] *Id*.

[338] OFFICE FOR PROTECTION FROM RESEARCH RISKS, OFFICE OF EXTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK 3-1, NIH Pub. 93-3470 (1993).

[339] Walter Glannon, *Phase I Oncology Trials: Why the Therapeutic Misconception Will Not Go Away*, 32 J. MED. ETHICS 252, 252 (2006). *See also* OFFICE FOR PROTECTION FROM RESEARCH RISKS, OFFICE OF EXTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK 3-8, NIH Pub. No. 93-3470 (1993) [hereinafter, IRB GUIDEBOOK] ("The benefits of research fall into two major categories: benefits to subjects and benefits to society.").

[340] *See* King, *supra* note 18, at 333; University of Miami, Human Subjects Research Office, Special Considerations for International Research (June 5, 2007), *available at* https://eprost.med.miami.edu/eprost/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity%5BOID%5B6901EE84C6E8274EA34B8AEA8FE55518%5D%5D (last visited Aug. 5, 2007) (defining non-therapeutic research as research conducted without the intent to produce a diagnostic, preventive, or therapeutic benefit to the current subjects).

[341] *See supra* Parts I(B), (C), and (D). Although the authors of fMRI Studies 1, 2, and 3 were not studying the efficacy of neural implants or other interventions for the treatment of disorders of consciousness, other clinicians and scientists have. Famous Floridian Terri Schiavo, for example, was transported to California for the implantation of a neural stimulator, although it ultimately had no effect on her VS. Other patients who have received implants reportedly have demonstrated a positive physiological response. *See* Tom Avril, *Brain Implant Revives Injured Man*, PHILLY.COM, Aug. 1, 2007, *available at* http://www.philly.com/philly/news/breaking/20070801_Brain_implant_revives_injured_man.html (last visited Aug. 4, 2007).

subjects in fMRI Studies 1, 2, and 3 (as well as participants in other similar neuroimaging studies) were not receiving an immediate, positive physiological benefit as a result of research participation (although I will discuss possible secondary rehabilitation-planning benefits in a moment).

¶ 88 Neuroimaging research into DOC has, however, resulted in several diagnostic benefits. Recall fMRI Study 3, in which the study authors used fMRI to scan and compare the brain activations of seven patients in VS and four patients in MCS.[342] Among other things, the study authors found that two of the patients in VS and all four of the patients in MCS showed activation not only in the primary auditory cortex but also in hierarchically higher-order associative temporal areas.[343] The scientists also conducted additional behavioral testing at one, two, and three months poststudy to examine the prognostic value of the study[344] and found that the two patients in VS who showed the most widespread activation actually had improved to MCS.[345] Thus, we might say that the research subjects in fMRI Study 3 (especially the two patients in VS who showed the most widespread activation and eventually emerged to MCS) received a more accurate differential diagnosis and prognostic assessment.[346] fMRI Study 3 is not the only neuroimaging study that has yielded these diagnostic and prognostic benefits.[347] A review article speaks more generally about the potential diagnostic and prognostic benefits of other fMRI studies, as well as benefits relating to rehabilitation planning:

> The results of these studies, although preliminary, suggest a number of potential clinical applications. Although bedside clinical examination remains the criterion standard for establishing diagnosis, fMRI activation profiles may serve an adjunctive diagnostic role when behavioral findings are limited or ambiguous. Patients who demonstrate activation of language network loci in response to linguistic stimulation may be more likely to retain receptive and expressive language functions than those who fail to selectively activate these structures. In such cases, clinicians should be particularly cautious before rendering a diagnosis of vegetative state. fMRI activation profiles may also inform prognosis in patients who show no behavioral evidence of language or visual processing. In such patients, robust activation of cortical networks that mediate language or visuoperception may presage subsequent recovery of these functions. Interestingly, [certain] patients [have] regained expressive speech as well

[342] Di et al., *supra* note 10, at 896.
[343] *Id.* at 897 and 898.
[344] *Id.* at 896.
[345] *Id.* at 897.
[346] *See, e.g.*, Giacino et al., *supra* note 7, at S67 ("Novel applications of functional neuroimaging in patients with disorders of consciousness may aid in differential diagnosis, prognostic assessment and identification of pathophysiologic mechanisms.").
[347] To simplify my benefit analysis, I have focused only on fMRI Study 3, but fMRI Studies 1 and 2 also yielded diagnostic benefits. In fMRI Study 1, the study authors found neural activity in the two patients in MCS in response to the forward playing of the audio narratives. Schiff et al., *supra* note 8, at 514. In fMRI Study 2, the authors found that their subject, a twenty-three-year-old woman in VS, exhibited neural responses that were indistinguishable from the responses of healthy subjects. Owen et al., *supra* note 9, at 1402.

> as the ability to consistently follow basic commands. [Another] patient, who initially showed no evidence of object recognition, regained the ability to identify and use common objects in a functional manner before hospital discharge. . . .
>
> The fMRI findings may also provide guidance in rehabilitation planning. In patients with disorders of consciousness, it is often difficult to determine if the absence of command-following is due to impaired arousal, aphasia, akinesia, or motor impairment. The approach to treatment may differ considerably depending on which of these disorders accounts for the failure to follow commands. If one were to find significant activation of left temporal structures involved in language processing, but minimal activation of mesial frontal structures linked to behavioral initiation, it would be reasonable to assume that akinesia was the principal factor in the command-following deficit. Consequently, rehabilitative interventions would likely include aggressive behavioral prompting strategies and neurostimulants rather than aphasia therapy.[348]

¶ 89 Some believe that neuroimaging research into DOC yields not only diagnostic, prognostic, and rehabilitation-planning benefits but also benefits that I will call, for want of a better term, "preventive benefits." Specifically, some families and ethicists are comfortable withholding and withdrawing life-sustaining treatment from patients in VS but not patients in MCS.[349] Arguably, one preventive benefit of a study involving a patient previously diagnosed as VS who, via fMRI, demonstrates minimally conscious–like processing, would be that the patient's life support will remain intact and the patient will not be allowed to die. Others would disagree about the characterization of such a finding as a benefit, emphasizing that the findings of neuroimaging studies should not alter end-of-life decision making: "None of this changes the fact however that most people wouldn't want to be kept alive artificially in a MCS either and going from a [persistent] VS to an MCS is no real improvement in the big scheme of things."[350]

¶ 90 In summary, neuroimaging studies into DOC, at least currently, do not and are not expected to yield an immediate positive physiological benefit to research subjects. However, a review of the relevant literature shows that some neuroimaging research yields (1) immediate diagnostic and prognostic benefits (especially for patients believed

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[348] Giacino et al., *supra* note 7, at S73.

[349] *See*, e.g., Laureys et al., *Brain Function*, *supra* note 11, at 544 ("Foremost is the concern that diagnostic and prognostic accuracy is certain, as treatment decisions typically include the possibility of life-support."); GLANNON, *supra* note 33, at 170, 171-72 ("Mechanical ventilation and artificial hydration and nutrition can permissibly be withdrawn from patients who have lost all higher brain function. These would include patients diagnosed as permanently vegetative. Withdrawing these forms of life support is permissible because they lack the capacity for interests and therefore cannot be harmed. . . . Would we make the same claims about patients who fall into and remain in a minimally conscious state? . . . [H]e or she could have an interest in continuing to live. Although some might consider this to be a weak sense of interest, it could be enough to prohibit any action that might cause him or her to permanently lose the capacity for consciousness, however minimal this capacity might be. By defeating such a person's interest in continuing to live, such an action could harm that person.").

[350] *See*, *e.g.*, Rosielle, *supra* note 129.

to be in VS but in whom fMRI reveals minimally conscious-like processing), (2) the benefit of assistance with rehabilitation planning, and (3) an arguable preventive benefit, which would be the nonapplication of measures to withhold or withdraw life-sustaining treatment.

¶ 91 The second type of research benefit includes indirect benefits, also called collateral benefits.[351] Indirect benefits arise from being a subject even if the subject does not receive the intervention under study.[352] Indirect benefits can be physiological, such as a free physical examination, or psychological, such as the psychological reward of inclusion.[353] The participants in fMRI Studies 1, 2, and 3 received some collateral benefits. All of the participants in fMRI Study 3, for example, received extensive and repeated clinical examinations, including examinations using five different validated behavioral scales, to arrive at an initial diagnosis of VS or MCS prior to the participants' brain scans.[354]

¶ 92 The third type of research benefit includes aspirational benefits, which include benefits to society and future patients as a result of the study.[355] The production of generalizable knowledge has been described as the *raison d'être* of research.[356] A research project must offer a reasonable prospect of producing generalizable knowledge; otherwise, the risks of the project will not be justified, even if the subjects will directly benefit.[357] Aspirational benefits are, perhaps, the easiest of the three benefits to identify in neuroimaging research involving individuals with DOC. Relevant aspirational benefits include knowledge regarding the underlying functional neuroanatomy of the different DOCs, data that might be used by future clinicians to make more accurate differential diagnoses, data that might be used by future clinicians to herald further recovery, and data that might be used by future clinicians to plan rehabilitation strategies.[358] Some scientists believe that neuroimaging studies also may, someday, lead to the development of methods of communication with some individuals with DOC[359] and, further down the road, support interventions such as neuromodulation that may help restore function to some individuals with DOC.[360]

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[351] King, *supra* note 18, at 333.
[352] *Id.*
[353] *Id.* at 334.
[354] Di et al., *supra* note 10, at 896.
[355] King, *supra* note 18, at 333-34.
[356] *Id.*
[357] *Id. See also* 45 C.F.R. § 46.102(d) (2007) (defining *research* as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge").
[358] *See, e.g.*, Giacino et al., *supra* note 7, at S74 ("potential benefits [include] . . . a better understanding of mechanisms of recovery, improved neuroimaging, electrophysiologic, and behavioral assessment techniques and the development of effective neurorehabilitative interventions.") (internal citations omitted).
[359] *See, e.g.*, Owen et al., *supra* note 9, at 1402 ("However, in the case described here, the presence of reproducible and robust task-dependent responses to command without the need for any practice or training suggests a method by which some noncommunicative patients, including those diagnosed as vegetative, minimally conscious, or locked in, may be able to use their residual cognitive capabilities to communicate their thoughts to those around them by modulating their own neural activity.").
[360] *See, e.g.*, Giacino et al., *supra* note 7, at S67 (2006) ("Improvements in patient characterization may, in turn, provide new opportunities for restoration of function through interventional neuromodulation.").

¶ 93 Before I balance these direct, indirect, and aspirational benefits against the risks of neuroimaging research, a historical comparison may help place these benefits in their proper context. Recall Harold Blauer, the tennis professional who was enrolled in the Army's chemical warfare research project in late 1952 and early 1953, a few weeks before he was scheduled to be released from the New York State Psychiatric Institute.[361] Blauer received no direct benefits as a result of his research participation. The mescaline injections Blauer received were completely unrelated to his psychiatric condition[362] and were not intended to serve any diagnostic or therapeutic purpose.[363] Blauer also received few, if any, indirect benefits. Although some subjects experience a psychological benefit due to their inclusion in a research project, Blauer most likely did not; indeed, he was "apprehensive" about his participation in the study, which required "considerable persuasion," and he verbally expressed both his dislike of the injections and his desire to withdraw from the study on more than one occasion.[364] Perhaps one could attempt to characterize the free postinjection nursing examinations[365] as an indirect benefit; however, since these examinations served only to document Blauer's suffering, they likely would not qualify. The study did, however, involve aspirational benefits. According to the Army's research proposal, "new technical data will be derived . . . which will provide a firmer basis for the utilization of psychochemical agents both for offensive use as sabotage weapons and for protection against them."[366] These wartime aspirations were, however, completely unrelated to the subjects' psychiatric conditions. Stated another way, the Army was using a population of individuals with mental illness to conduct an experiment that would in no way contribute to knowledge regarding the diagnosis or treatment of mental illness.

¶ 94 Like the Army's chemical warfare research, the Willowbrook study also yielded no direct benefits (unless one wants to classify intentional infection with hepatitis as a preventive benefit) and few, if any, indirect benefits, although fair aspirational benefits (many of which ultimately were achieved) relating to the treatment and prevention of hepatitis B.[367] Again, though, the scientists were using a population of individuals with developmental disabilities to conduct an experiment that would in no way contribute to knowledge regarding the diagnosis or habilitation of such developmental disabilities.

¶ 95 The slim benefits of the Army chemical warfare research and the Willowbrook study certainly do not stand as a minimum threshold above which all other study benefits will tend to favorably balance against research risks. Other studies yielding direct and indirect benefits of a greater likelihood and magnitude also may not balance favorably against research risks. The Army chemical warfare study and the Willowbrook study are, however, classic examples of the types of experiments the Common Rule and other ethical and legal guidelines were designed to protect against; that is, experiments

[361] *See supra* Part II(B).
[362] Barrett, 660 F. Supp. at 1298-99.
[363] *Id.* at 1299.
[364] *Id.*
[365] *Id.* at 1321 (providing detailed nursing notes that document Blauer's post-injection suffering, including especially detailed nursing notes following the fifth injection from which he died).
[366] *Id.* at 1295 (ellipsis in original).
[367] *See supra* Part II(C).

involving vulnerable populations that are expected to yield no direct benefits, few if any indirect benefits, and some aspirational benefits that are completely unrelated to the subjects' vulnerable conditions. In contrast, fMRI Studies 1, 2, and 3, as well as other neuroimaging studies into DOC, involve fair diagnostic, prognostic, and rehabilitation-planning benefits; an arguable preventive benefit; some indirect benefits; and several aspirational goals that directly relate to the management and treatment of DOC.

B. Neuroimaging Risks

¶ 96 Although the Common Rule defines only minimal risk, not risk, [368] a research risk may be defined as the probability of harm or injury (physical, psychological, social, or economic) that occurs as a result of research participation.[369] IRBs must consider not only the nature of research risks but also their likelihood and magnitude.[370] Research involving MRI, including fMRI, requires its subjects to lie inside a relatively narrow horizontal cylinder located within a larger machine that houses a permanent magnetic field of high intensity, usually 1.5 Tesla or more.[371] Body images, including neuroimages, are acquired via technologies that cause "the fast commutation of smaller additional magnetic fields ([called] gradients) and the sending of quick but intense radio-frequency pulses."[372] For purposes of this article, I will simply assume that neuroimaging research does raise some social and economic risks, including the possible loss of confidentiality and privacy.[373] The question I will address here is whether MRI poses physical, or possibly psychological, risks to human subjects with DOC.

¶ 97 The FDA regulates two of the parameters that can be used during MRI: the deposition of heat and the threshold for commuting the magnetic field.[374] To the extent scientists involved in neuroimaging research use MRI machines that are approved for clinical use by the FDA and contain software that both compute the correct parameters and ensure they are not exceeded, any possible risks relating to the rise of the subject's tissue temperature or the stimulation of the subject's peripheral nerves should be

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[368] 45 C.F.R. § 46.102(i) (2007) (failing to define *risk*; defining *minimal risk* as when "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."). *See generally* IRB GUIDEBOOK, *supra* note 339, at 3-1 (discussing the meaning of *risk*).
[369] *Id.*
[370] *Id.*
[371] *See, e.g.*, Unité de Neuroimagerie Cognitive, *Practical and Ethical Aspects of Neuroimaging Research In Infants*, *available at* http://www.unicog.org/main/pages.php?page=InfantEthics (last visited Aug. 5, 2007) (describing an MRI procedure).
[372] *Id.* (describing MRI technology).
[373] The social and economic risks posed by fMRI are important and warrant discussion, although they are beyond the scope of this article. They have been addressed elsewhere. *See, e.g.*, Stacey A. Tovino, *Functional Neuroimaging: A Case for Neuro Exceptionalism?* 34 FLA. ST. UNIV. L. REV. (forthcoming 2007) (examining the confidentiality, privacy, identity, employment, and disability implications of advances in fMRI); *Brain Imaging and the Law Symposium*, 33(2-3) AM. J. L. & MED. (forthcoming 2007) (a collection of articles examining many of the social and economic implications of advances in fMRI under criminal law, constitutional law, evidence law, and research ethics).
[374] Unité de Neuroimagerie Cognitive, *supra* note 371.

minimized.[375] Most would agree that "there are no known significant risks with [MRI] at this time since the radiofrequency magnetic fields and magnetic fields, at the strengths used, are felt to be without harm," at least in nonpregnant persons.[376]

¶ 98 As a result, many believe that the only possibly risky aspects of MRI relate to its magnetic field, which is strong enough to displace ferromagnetic objects, and its noise.[377] MRI's permanent magnetic field can easily move coins, pens, watches, hair clips, belts, the underwire in some bras, chairs, clipboards, and any other object that contains metal that might happen to be located in the imaging suite or on or within the subject.[378] In the clinical setting, including hospitals and imaging centers, the FDA has found lapses in human-controlled screening and safety measures that have resulted in patient injury and death, including one case in which a patient died when her aneurysm clip moved during a clinical MRI scan and lacerated her middle cerebral artery.[379] This result occurred notwithstanding the policy of most hospitals and imaging centers to assign to scanning procedures only certified radiology technicians who have completed one to four years of relevant coursework, including coursework in MRI safety, and to hold them responsible for complying with detailed and redundant screening policies and procedures that ensure that no metal objects are left in the imaging suite or on the patient and that patients in whom metal is identified are not scanned.[380] Some, although not all, suggest that safety procedures may be less standardized (and the risks of adverse events may be greater) in the research setting, where individuals who conduct screening examinations (including

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[375] *Id. See also* Brown University MRI Research Facility Informed Consent Addendum, *available at* http://research.brown.edu/pdf/HRPO.MRI.consent.w-FDA11-22-06.pdf (last visited Aug. 6, 2007) [hereinafter, Brown Policy] ("There is a risk of heating from radiofrequency imaging coils, the cables of radiofrequency imaging coils, and/or the cables from monitoring devices such as those that record physiologic processes by way of an electrocardiogram, pulse oximeter, and/or plethysmograph. Please report any heating/burning sensation immediately. You are encouraged to signal to have the scan stopped at any time if this occurs.").

[376] Brown Policy, *supra* note 375. *See also* NATIONAL INST. MENTAL HEALTH, MRI RESEARCH SAFETY AND ETHICS: POINTS TO CONSIDER (2005), *available at* http://www.nimh.nih.gov/council/mri-research-safety-ethics.pdf (last visited July 7, 2007) [hereinafter, NIMH Report] ("At present, there is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risk under normal operating procedures. Nonetheless, the possibility that risks may be discovered in the future cannot be ruled out. Therefore, exposure of fetuses to MR scanning without any prospect of direct benefit may not be ethically justifiable. Indeed, the general policy in many clinical Radiology Departments is not to scan anyone who may be pregnant, absent compelling clinical need. Thus, it is appropriate to screen for pregnancy and to exclude pregnant participants for the sake of caution.").

[377] Unité de Neuroimagerie Cognitive, *supra* note 371.

[378] *Id.*

[379] *See, e.g.*, U.S. FOOD & DRUG. ADMIN., FDA SAFETY ALERT: MRI RELATED DEATH OF PATIENT WITH ANEURYSM CLIP (Nov. 25, 1992), *available at* http://www.fda.gov/cdrh/safety/112592-mriclip.pdf (last visited Aug. 6, 2007) ("FDA has learned of a fatal injury sustained by a patient with a cerebral aneurysm clip while she was being prepared for an MRI procedure. It was reported that upon exposure to the magnetic field in the room, the clip moved and lacerated the patient's middle cerebral artery. The explanted device was subsequently shown to be magnetically active. This particular style or clip, which was implanted in 1978, was listed in several articles and recent medical texts as non-deflecting in a magnetic field.").

[380] *See, e.g.*, U.S. DEP'T LABOR, BUREAU OF LABOR STATISTICS, RADIOLOGY TECHNOLOGISTS AND TECHNICIANS, *available at* http://www.bls.gov/oco/ocos105.htm#training (last visited Aug. 6, 2007) (discussing the training and qualifications of radiology technicians).

scientists, their graduate students, and other members of their research team) are less trained in MRI safety than their clinical counterparts.[381]

¶ 99 To minimize the risks associated with flying or emerging metal objects, scientists and other study team members who are involved in the actual scanning portion of an fMRI study must be specifically trained regarding the ferromagnetic dangers of MRI and required to perform sufficiently detailed and redundant screening procedures.[382] Although metal objects located in the imaging suite or on the subject's person are not too difficult to identify, less obvious are metal objects that lie within the subject's body, including pacemakers, aneurysm clips, surgical clips, other metal implants and prostheses, metallic shavings from war shrapnel or employment that involved grinding metal including metal filings remaining in the eye, dental and orthodontic apparatuses, and even metallic substances remaining around the eye due to the application of cosmetic eye shadow.[383] Although conscious potential subjects can inform study coordinators whether they have been exposed to metal in one or more of these ways, subjects with DOC cannot. The potential subject's exposure to metal would have to be revealed by a family member or other person familiar with the subject's medical and employment history, a handheld metal detector, another method of body scanning, or preferably, a combination of all three.[384]

¶ 100 The other possible MRI risk relates to the noise of the MRI machine. The sound of the magnet working within the MRI machine can be quite loud.[385] Analyzing the likelihood of the risk of hearing damage or discomfort associated with loud noises to individuals with DOC is tricky because one pressing scientific question is whether individuals with DOC demonstrate neural activity (and, if so, what kind and what it means) when they are exposed to passive auditory tasks.[386] Stated (and very much conflated) in layperson's terms, can individuals with DOC hear?[387] Assuming only for

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[381] *See, e.g.*, Jennifer Kulynych, *The Regulation of MR Neuroimaging Research: Disentangling the Gordian Knot*, 33 AM. J. L. & MED. 295, 311-12 (2007) (discussing MRI safety); Stacey A. Tovino, *Imaging Body Structure and Mapping Brain Function*, 33 AM. J. L. & MED. 193, 225 and text accompanying nn. 299 and 300 (2007) (quoting Kulynych).

[382] *Id*. In particular, the authors and the members of their study team should be familiar with the MRI safety information and recommended scanning procedures set forth by the NIMH Report, *supra* note 376 at B-1 ("Given that the MRI environment presents many potential dangers to untrained or improperly screened individuals, the Workgroup recognized the need for appropriate levels of training for all individuals who operate the scanner and/or have routine access to the MRI suite and for a clearly specified scheme for training and certifying individuals for each level of authorization. A range of options was mentioned for certification, including didactic training, mastery of written materials, and terms of apprenticeship, as well as written and/or practical tests.").

[383] *See, e.g.*, Brown Policy, *supra* note 375 (identifying all of the metal objects for which Brown University scientists screen in MRI studies); *see also* NIMH Report, *supra* note 376, throughout (mentioning several different types of metal objects that can pose risk to subjects).

[384] *See* NIMH Report, *supra* note 376, at A-6 (discussing the supplementary, not replacement, value of a hand-held metal detector).

[385] *Id.* at D-3.

[386] *See supra* Introduction, at second sentence; Laureys, *Neural Correlate*, *supra* note 1, at 557 (asking, "Do patients in a vegetative state feel or hear anything?"); Hirsch et al., *fMRI Reveals Intact Cognitive Systems*, *supra* note 3.

[387] *Id.*

the sake of argument that individuals with DOC can process auditory stimuli, the magnitude of any hearing damage or noise discomfort and the ability of scientists to minimize these risks must be assessed.

¶ 101 Studies involving infants show that an MRI's magnet noise can be minimized to 12 decibels (dB) higher than quiet conversation, which is 18 dB lower than a lawn mower and 38 dB lower than a car horn.[388] In neuroimaging studies involving infants, scientists minimize magnet noise by covering the magnet tunnel with a special noise-protection foam and placing over each infant's head a noise-protection helmet that includes headphones that are, in turn, covered by an additional foam mold.[389] The combination of the foam applications and the headphones reduces noise and vibrations inside the tunnel.[390] Even after implementing these noise protections, the scientists still may deliver any auditory stimuli required by the research protocol to the subject through piezoelectric loudspeakers located in the headphones.[391] In neuroimaging studies involving infants, "[t]he level of sound presentation is adjusted to a comfortable level, easily understandable above the residual scanning noise by a normal adult. . . . The success of [these] noise protection measures is indicated by the fact that many babies fall asleep during the imaging procedure, or stay asleep throughout."[392]

¶ 102 Before I balance these possible risks and discomforts against the benefits of neuroimaging research and the knowledge that may reasonably be expected to result, a historical comparison may help place these risks in their proper context. In the case of Harold Blauer and the Army's chemical warfare research,[393] the scientists were aware, as a result of prior toxicity testing involving mice, that death (at least to mice) was a fair possibility.[394] They also knew (or at least one court found that they knew) that the scientists had not yet conducted additional toxicity testing sufficient to determine the chemical's safety in humans.[395] Likewise, the authors of the Willowbrook study knew that the Willowbrook students would be intentionally infected with the hepatitis B virus and that such infection can cause lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death.[396] The significant risks of the Army chemical warfare research and the Willowbrook study certainly do not stand as a threshold below which all other study risks will tend to favorably balance against research benefits. Other studies yielding risks of a lower likelihood and magnitude also may not balance favorably against research benefits. The Army chemical warfare study and the Willowbrook study are, however, classic examples of the types of experiments the Common Rule and other ethical and legal guidelines were designed to protect against—that is, experiments that involve risks of great magnitude, including death and lifelong infection, which could not (then) be prevented. In contrast, most would agree that current neuroimaging studies into

[388] Unité de Neuroimagerie Cognitive, *supra* note 371.
[389] *Id.*
[390] *Id.*
[391] *Id.*
[392] *Id.*
[393] *See supra* Part II(B).
[394] Barrett, 660 F. Supp. at 1315.
[395] *Id.*
[396] *See, e.g.*, Goldby, *supra* note 250, at 280.

DOC involve two possible risks—ferromagnetic injuries and deaths and noise injury or discomfort—although each risk carries a very low probability that can be minimized, if not eliminated, with human-controlled safety precautions.

C. Balancing Risks and Benefits

¶ 103 Neuroimaging research into DOC thus raises a decades-old question: How do we balance the rights and interests of research subjects with scientific progress and benefits to future patients?[397] Current federal law establishes a reasonableness test: Are the risks of neuroimaging reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result?[398] This assessment is considered the major ethical and legal judgment made in the context of human-subjects research.[399] The analysis is difficult in part because federal and state law provide so little guidance regarding the required balancing and because the studies under question involve functional neuroimaging, which many still consider an emerging discipline.[400]

¶ 104 The former Office for Protection from Research Risks (OPRR) (now, the Office for Human Research Protections) has provided some questions to help guide risk-benefit assessments, including whether the research involves "the use of interventions that have the intent and reasonable probability of providing benefit for the individual subjects or only involves procedures performed for research purposes."[401] "In research involving an intervention expected to provide direct benefit to the subjects, a certain amount of risk is justifiable."[402] On the other hand, "in any trial of a new or not yet validated treatment, the ratio of benefits to risks should be similar to those presented by any available alternative therapy."[403] As discussed in detail in Part III(A), neuroimaging research into DOC may offer its subjects some diagnostic, prognostic, and rehabilitation-planning benefits, as well as a debated preventive benefit and several aspirational benefits relating to the management and possible treatment of future patients with DOC. Neuroimaging research does not, however, provide an immediate, positive physiological benefit to subjects. Neuroimaging research is, thus, "in between" with respect to benefits. Again, it is not directly and immediately therapeutic; however, it can yield diagnostic and prognostic benefits that may, in turn, yield secondary rehabilitation and clinical management benefits. It also may, according to several scientists, help support future patients with DOC with respect to methods of communication and, eventually, therapy. Importantly, scientists cannot study DOC or contribute to their understanding by studying healthy subjects. Only by enrolling individuals with DOC can the relevant direct and aspirational benefits be achieved. Stated another way, only through better understanding of DOC can care for individuals with DOC be improved.

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[397] MORENO, *supra* note 160, at 126.
[398] 45 C.F.R. § 46.111(a)(2) (2007).
[399] IRB GUIDEBOOK, *supra* note 339, at 3-8.
[400] *See* Champlain & Patenaude, *supra* note 325, at 533.
[401] IRB GUIDEBOOK, *supra* note 339, at 3-8–3-9.
[402] *Id.* at 3-9.
[403] *Id.*

¶ 105 According to the former OPRR, in research where no direct benefits to the subject are anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable.[404] There should be a limit to the risks that society (through the government and research institutions) asks individuals to accept for the benefit of others, but IRBs should not be overly protective.[405] As discussed above, neuroimaging conducted without proper screening procedures may pose a ferromagnetic risk of injury or death and may cause noise discomfort. However, with sufficiently detailed and redundant screening procedures as well as foam installation and headphones, these risks can be minimized if not completely eliminated. The question here is whether these risks, as minimized, are reasonable in relation to the benefits of neuroimaging research. I think they are.

¶ 106 My opinion is based, in part, on my balancing of human-subjects protections and access to therapies. Taking a purely protectionist stance, we could refuse to allow individuals with DOC to participate in neuroimaging research even though the remote risks of the research could be minimized if not eliminated by human controls.[406] The theory behind this position is that it is preferable to protect potential subjects from harm, including potential, unlikely harm, even if the result is less progress with respect to generalizable knowledge and less progress with respect to the creation of and access to new therapies designed to manage, improve, or treat the very conditions from which the potential subjects suffer.[407] Taking a pure "access" stance, on the other hand, we could view any barriers to enrolling individuals with DOC in neuroimaging research as suspect because these barriers would prevent the subjects from realizing any diagnostic, prognostic, and rehabilitation-planning benefits, as well as prevent future patients from realizing the benefits of new therapies.[408] From this position, it may be considered unethical to exclude an individual with a tentative DOC diagnosis whose research participation may lead to a more accurate diagnosis or prognosis. Neither of these approaches is optimal. Under the first approach, we are protecting human subjects but not furthering understanding and possible treatment of the very conditions from which they suffer. Under the second approach, we are contributing to knowledge and potentially supporting the development of new methods of communication and new therapies although the subjects may not be receiving some or all of the protections they deserve.

¶ 107 I worry that the tragic history of human-subjects research involving individuals with psychiatric conditions and developmental disabilities[409] is causing IRBs, scientific journals, and funding agencies to underappreciate the potential benefits of minimally risky fMRI research and to overstate its risks, with the end result being the wholesale adoption of a protectionist model with regard to neuroimaging research into DOC.[410] I think that a careful, detailed, and thoughtful review of the history of exploitation of

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[404] *Id.*
[405] *Id.*
[406] COLEMAN, *supra* note 160, at 589.
[407] *Id.*
[408] *Id.*
[409] *See supra* Part II(A)-(C).
[410] Fins, *supra* note 162, at 326.

vulnerable human research subjects (and the relevant ethical and legal principles) is necessary each and every time we commence research in an emerging discipline, including functional neuroimaging. This rich history can guide us in our assessment of risks, benefits, and their proper balance, as well as the identification of relevant ethical and legal principles. I do not think, however, that neuroimaging research into DOC conducted with proper screening procedures and adherence to other protections warrants a purely protectionist stance. Accordingly, I recommend that IRBs, scientific journals, and funding agencies no longer stall the conduct, publication, and funding of neuroimaging research into DOC if, and only if, all the following criteria are satisfied.

D. Criteria and Recommendations

¶ 108 To minimize risks and ensure that they are reasonable in relation to anticipated benefits, scientists conducting neuroimaging research involving individuals with DOC should adhere to the following eleven criteria.[411] First, scientists must not be able to conduct their proposed research projects with less vulnerable populations. In the case of neuroimaging research involving individuals with DOC, this means that the aim of the research cannot effectively be accomplished with healthy subjects or subjects with less severely impaired consciousness.

¶ 109 Second, the neuroimaging research must have the aim of contributing to the scientific understanding of DOC. Individuals with DOC should not be included in research unrelated to their conditions.

¶ 110 Third, participation in neuroimaging research must not adversely affect the individual's underlying DOC. If a potential research subject requires medical or other support that must be discontinued during the scan, the individual shall be excluded from research participation.

¶ 111 Fourth, scientists conducting neuroimaging studies into DOC must familiarize themselves with all aspects of MRI safety, including the proceedings and safety recommendations of the National Institutes of Mental Health Council Workgroup on MRI Research Practices, established in 2005.[412] Any study team member who is involved in the actual scanning process must be thoroughly educated regarding the ferromagnetic and noise risks associated with MRI and shall perform or support sufficiently detailed and redundant screening of the imaging suite and the body of the potential subject. I highly recommend that the study team contract with an independent certified radiology technician or another individual who has comparable education in MRI safety. Although this recommendation will cause the research team to incur additional costs, these costs are worth the assurance that the imaging suite and all subjects have been properly screened and that the screening process is not rushed.

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[411] These criteria are designed to comply with the Common Rule provision requiring adoption of additional safeguards to protect the rights and welfare of subjects and potential subjects with mental disabilities. 45 C.F.R. § 46.111(b) (2007).
[412] NIMH REPORT, *supra* note 376.

¶ 112 Fifth, if there are any doubts regarding a potential subject's exposure to metal due to the mixed or ambivalent results of another method of body scanning, such as a handheld metal scanner, or the family's unfamiliarity with the individual's medical or employment history, the individual shall be excluded from research participation.[413]

¶ 113 Sixth, scientists conducting neuroimaging research shall identify and implement the best noise-reduction strategies currently available, which may include foam helmets, foam headphones, and foam wrapping of the MRI tunnel.[414] Scientists shall consult the noise-reduction measures adopted in other neuroimaging studies involving vulnerable populations, including infants. Research designs shall incorporate neuroimaging techniques that are "maximally comfortable, fast, and efficient" and should include consideration of rapid-acquisition protocols.[415]

¶ 114 Seventh, any LAR[416] who is approached regarding the research participation of an individual with DOC must be informed through both conversation and documentation (1) that the neuroimaging study constitutes research, not treatment and that the scientists expect the research to yield no direct, immediate physiological benefits to the individual;[417] (2) of any reasonably foreseeable risks or discomforts to the subject,[418] including applicable ferromagnetic risks and any possible noise injuries or discomfort; and (3) of any benefits to the subjects or to others that may reasonably be expected to result[419] including, as applicable, more accurate diagnoses and prognoses, as well as any secondary rehabilitation planning or clinical management benefits.

¶ 115 Eighth, the scientists must allow the LAR to withdraw her consent to the individual's research participation at any time for any reason, including during a scanning procedure already begun.[420] The scientists or other study team members involved in the scanning process shall monitor any verbal or nonverbal signs or signals from the individual that may be interpreted as symptoms of distress resulting from the scanning procedure. I anticipate assessment of these signs and signals to be difficult, especially with individuals in higher levels of MCS who may display both reflexive movements and inconsistent responses to environmental stimuli. If any member of the study or scanning team believes that a particular sign, signal, movement, or response suggests distress, the

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[413] *See, e.g.*, Unité de Neuroimagerie Cognitive, *supra* note 371 ("If we have any doubt about the presence of metallic material (e.g. surgical material), we do not proceed with the examination. Because we are dealing with normal volunteers, there is simply no reason to take any risk.").

[414] *Id.* (noting that a "noise protection helmet, providing noise attenuation between 30 and 35 dB for frequencies between 250 and 8000 Hz, is placed on the infants' ears, then covered by a foam mold that provides supplementary noise protection and ensures that the helmet stays in place during the study"); NIMH REPORT, *supra* note 376.

[415] *See, e.g.*, Judy Illes et al., *Prospects for Prediction: Ethics Analysis of Neuroimaging in Alzheimer's Disease*, 1097 ANNALS. N.Y. ACAD. SCI. 278, 285 (2007) (making this suggestion in the context of neuroimaging research involving individuals with Alzheimer's disease).

[416] *See* 45 C.F.R. § 46.111(a)(4) (2007) ("Informed consent will be sought from each prospective subject or the subject's legally authorized representative . . . .").

[417] *See id.* § 46.116(a)(1).

[418] *See id.* § 46.116(a)(2).

[419] *See id.* § 46.116(a)(3).

[420] *See id.* § 46.116(a)(8) ("[Research] participation is voluntary . . . and the subject may discontinue participation at any time . . . .").

scanning procedure shall be immediately discontinued. This criterion is meant to incorporate the research ethics concept of "continuous consent," also called "behavioral consent."[421]

¶ 116 Ninth, both scientists and clinicians must be especially careful to assure LARs that the care of an individual with DOC will not be affected if the LAR chooses not to enroll the individual in research. Like patients, LARs "may be susceptible to real or imaginary pressure" to consent to research.[422] If a scientist also happens to be the individual's physician, the LAR may feel obligated to consent to the individual's research participation "out of a desire to please, gratitude, or fear that failure to do so will result in hostility or abandonment."[423] LARs who act on behalf of individuals who reside in facilities such as rehabilitation hospitals or long-term-care hospitals may be particularly worried that the individual will receive poor treatment if the LAR refuses to consent.[424] Patients who are not enrolled in research must continue to receive the same attention, care, and compassion as patients who are enrolled. This criterion is designed to prevent the exploitation of captive populations such as the patients at the New York State Psychiatric Institute and the student body at Willowbrook.

¶ 117 Tenth, scientists conducting neuroimaging research into DOC shall adhere to the other requirements set forth in the Common Rule including, but not limited to, provisions relating to IRB approval of research,[425] the informed consent process,[426] and documentation of informed consent,[427] as well as relevant state law.

¶ 118 Finally, the risk-benefit assessment set forth in this article shall be reviewed periodically as neuroimaging research progresses. Current prospects for neuroimaging (including the potential diagnostic, prognostic, clinical management, and rehabilitation-planning benefits) are optimistic. Should, however, additional neuroimaging research fail to yield these benefits, or should the potential support provided by neuroimaging to future methods of communication or therapies evaporate, the anticipated benefits of neuroimaging research may no longer outweigh the risks. In this case, neuroimaging research into DOC shall be discontinued until such time as new potential benefits, identified through new research hypotheses, again outweigh neuroimaging risks.

¶ 119 In addition to these eleven criteria, I have one broad recommendation regarding consent to research participation by surrogates,[428] or proxies,[429] which I will simply refer

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[421] *See, e.g.*, P. Allmark & S. Mason, *Improving the Quality of Consent to Randomised Controlled Trials by Using Continuous Consent and Clinician Training in the Consent Process*, 32 J. MED. ETHICS 439 (2006).
[422] IRB Guidebook, *supra* note 339, at 3-24.
[423] *Id.*
[424] *Id.*
[425] 45 C.F.R. § 46.111 (2007).
[426] *Id.* § 46.116.
[427] *Id.* § 46.117.
[428] A surrogate is a person or persons who are legally authorized to make decisions regarding care or research participation in the name of a patient or potential subject. *E.g.*, DOREEN M. TOWSLEY-COOK & TERESE A. YOUNG, ETHICAL AND LEGAL ISSUES FOR IMAGING PROFESSIONALS 58 (1999) ("A surrogate may be a parent, an individual named by the patient while competent, or a person or persons appointed by the courts.").

to as LARs because that is the language of the Common Rule.[430] In the seventh and eighth criteria, I referred to the subject's LAR; however, I intentionally left my discussion of LARs until last to prevent conflation of an LAR's consent to an individual's research participation with a favorable risk-benefit assessment. The minimization of risks and a favorable risk-benefit assessment must occur prior to offering research participation—either to the potential subject or to her LAR.[431] Stated another way, research in which risks are not minimized or that does not yield a favorable risk-benefit assessment may not be offered to a potential subject or her LAR. I hope the organization of this article makes clear the primacy of the minimization of risks and a favorable risk-benefit assessment.

¶ 120 To guide the offering of research participation once the research design minimizes risk and a favorable risk-benefit assessment has been made, I recommend a federal regulation (or, barring a federal regulation, uniform state laws) that address LAR consent to human-subjects research involving individuals with decisional impairments if the research relates to the individual's impairment or the same class of impairments. I impose the "relates to" requirement in an attempt to prevent exploitation of individuals with decisional impairments in research that is not designed to benefit them or future patients with the same type of condition.

¶ 121 The core of the Common Rule currently allows LARs to consent,[432] but the definition of LAR refers to "applicable law"[433] (i.e., state law in this case), which varies.[434] Some states allow "any person legally empowered to act" to consent to research participation on behalf of an individual with a decisional impairment,[435] while some states designate only certain individuals, such as court-appointed guardians or conservators to consent.[436] Other states fail to address consent to research participation at all. State-law variation is especially troublesome in the context of biomedical and behavioral research, which may be conducted at a laboratory located in one state (e.g., New York) but may draw subjects from surrounding states (e.g., the Tri-State Area).[437]

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[429] *See, e.g.*, Marian W. Fischman, *Informed Consent*, *in* ETHICS IN RESEARCH WITH HUMAN PARTICIPANTS 44 (Bruce D. Sales & Susan Folkman eds., 2000) ("Therefore, for those potential participants who lack the legal capacity to consent, a proxy consent can be obtained from a parent, guardian, or legally authorized representative."); Benjamin Freedman, *A Moral Theory of Consent*, *in* INTERVENTION AND REFLECTION: BASIC ISSUES IN MEDICAL ETHICS 266, 273 (Ronald Munson ed., 1979) ("Proxy consent is consent given on behalf of an individual who is himself incapable of granting consent.").

[430] 45 C.F.R. § 46.102(c) (2007) (defining *LAR* as an "individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's" research participation); *id.* § 46.111(a)(4) ("Informed consent will be sought from each prospective subject or the subject's legally authorized representative. . . . ").

[431] *Id.* § 46.111(a) (requiring research projects to satisfy each of seven core criteria, including risks to subjects being reasonable in relation to anticipated benefits).

[432] *Id.* § 46.111(a)(4).

[433] Moreno, *supra* note 18 at 14.

[434] *See supra* Part II(E) (discussing the variation of state law in this area).

[435] *See, e.g.*, N.Y. PUBLIC HEALTH LAW § 2442 (McKinney 2007) ("If the human subject be otherwise legally unable to render consent, such consent shall be subscribed to in writing by such other person as may be legally empowered to act on behalf of the human subject.").

[436] *See, e.g.*, CAL. HEALTH & SAFETY CODE § 24175(b)(1) (2007).

[437] *See* Steinberg, *supra* note 12, at 1011.

IRBs, scientific journals, and funding agencies, the latter two of which may be located in still other states, are not trained in conflict-of-law principles and currently make ad hoc decisions regarding whether LAR consent is ethical or legal regardless of whether applicable state law permits such consent.[438] I therefore recommend one federal law[439] (preferably) or uniform state laws identifying both the persons empowered to consent to research participation on behalf of an individual with a decisional impairment and the process for such consent.

¶ 122 The ethical and legal issues raised by research involving individuals with decisional impairments are not going away. Mental disorders, including psychiatric conditions, developmental disabilities, and DOCs, are particularly recalcitrant, and scientists face tremendous public and peer pressure to discover new therapies.[440] Compliance with the criteria and recommendations set forth above should ensure the minimization of risks, a favorable balance of risks and benefits, and uniformity in decision making with regard to surrogate consent in the context of neuroimaging research involving DOCs.

[438] *Id.* at 1010.
[439] The federal law may be established as a new subpart within the Common Rule at 45 C.F.R. Part 46, Subpart E.
[440] *See* MORENO, *supra* note 160, at 157.