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Gray Matters: Neuroethics in the Twenty-First Century

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FROM THE EDITOR
Neurology in the Postmodern Era

The human brain, as philosophers will attest, has a metaphysical claim to fame: it is the only object in the universe that ponders itself. Such cosmic uniqueness should come as no surprise, given the brain's unrivaled complexity. Containing some 100 billion neurons and 100 trillion synapses, it is saddled with the Sisyphean job of running the body—releasing hormones on cue, moving limbs on request, breathing ad infinitum—like the stage manager of an endless neurochemical Cirque du Soleil show. As if that weren't enough, the brain also faces the inscrutable mission of generating the mind, which requires merging the input from our senses with the din of our thoughts and the fog of our memories to produce the wispy, quasidivine realm known as consciousness. And so this gifted, self-aware brain of ours, as Emily Dickinson wrote, is not just wider than the sky. It is also deeper than the sea.

The human brain is also the only machine in the universe capable of fixing itself, thanks to the science of neurology. By this, of course, I mean that a neurologist can use his or her brain to help itself or those of other people. Neurologists have been treating patients with measurable success since the early nineteenth century, when French physician Jean-Martin Charcot established a neurology clinic at the renowned Salpetriere hospital in Paris. Charcot was the first to describe multiple sclerosis and to explore the pathophysiology of conditions like epilepsy, neurosyphilis, and stroke, and many medical historians consider him to be the founder of modern neurology.

If Charcot's neurology was modern, then the field in which neurology residents find themselves today is decidedly postmodern. New genetic discoveries and neuroimaging modalities are fueling exponential growth in the knowledge physicians are expected to retain. New drugs are bringing hope to patients with previously untreatable diseases such as Alzheimer.

With the advancing frontier come new ethical challenges for neurologists. Many of these challenges come to light in this month's issue of *Virtual Mentor*, titled "Gray Matters: Neuroethics in the Twenty-First Century."

What should a physician do, for example, when a patient requests a neuroenhancement pharmaceutical—a "smart pill"—for a non-medical reason? In this month's second clinical case, Dan Larriviere, MD, JD, a neurologist at the University of Virginia, explains the circumstances under which such a prescription can be justified; in the medicine and society column, neuroethicist Peter Reiner, MD, PhD, considers the impact of neuroenhancers on the physician's practice as new drugs enter the market and consumers (literally) get wise.

Conversely, some people who do have—or whose children have—bona fide neurological diseases view their conditions merely as normal variations in human function. So when parents of a boy with autism tell a doctor they do not want medical care for his condition, is that tantamount to child abuse? Johns Hopkins University neurologist Margaret Moon, MD, advises the pediatrician who disagrees with well-meaning parents in the first clinical case.

The challenges of communicating and collaborating with parents are even more pronounced when treatment of a very young child may be futile. In this month's journal discussion, Jay Desai, MD, a resident in child neurology at Childrens Hospital Los Angeles, critiques a recent paper on end-of-life decision making and intensive care for newborns with severe neurological insult.

Neurologists also bear the burden of deciding exactly when the adult brain—and thus the patient—is dead. The current criteria vary considerably from one institution to the next. Henry Ford Hospital neurologists James Bartscher, MD, and Panayiotis Varelas, MD, PhD, detail the history of brain death determination and urge the establishment of a certification process for physicians charged with making the determination and the adoption of a national standard for the procedure.

Also in the legal arena, brain imaging is being advocated as a way to test the reliability of witness testimony in court. University of Pennsylvania Law School student Benjamin Bumann considers the promises and challenges of inferring subjects' mental states from their brain activity and whether such inferences are admissible in judicial proceedings.

On the flip side of the question of truthfulness, is it acceptable to deceive a patient's mind in an effort to treat his or her brain? In the issue's third clinical case, Dartmouth University neurologist and bioethicist James Bernat, MD, casts a critical eye on the use of a dramatic—and utterly bogus—diagnostic procedure designed to induce a psychiatric patient to have a nonepileptic seizure.

In the case of many other neurological problems, effective detection eschews technology in favor of plain old observation. With the publication of the much-anticipated fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* expected in 2013, a major revision is anticipated in the way autism spectrum disorders (ASD) are classified. Child psychologist Carla Mazefsky, PhD, and child neurologist Nancy Minshew, MD, both of the University of Pittsburgh, outline the latest information on the etiology and pathophysiology of autism and elucidate its proper diagnosis.

In the images of healing and learning section, we examine the neuroscience of the most intangible brain-based process of them all: creativity. What are neuroimaging studies telling us about the biological underpinnings of human epiphanies and flights of fancy? Is a person's intelligence quotient a factor? University of Florida neurologist Glen Finney, MD, tackles these questions and others.

Our op-ed contributor, Donna T. Chen, MD, MPH, of the University of Virginia School of Medicine, also draws from neuroimaging findings in her discussion of the implications of perspective-taking studies on advance care planning. Since different parts of the brain activate when people consider their own perspectives and those of others, Chen wonders whether asking patients to consider what they would like their surrogates to decide would result in greater clarity in their advance directives.

Yet for all the richness of this issue of *Virtual Mentor*, countless other topics remain for you to discuss with your real-life mentors and colleagues. For example, what does the budding field of artificial neuroimplants portend for neurology? What role could neurofeedback play in the rehabilitation of convicted criminals? And, turning the table on the ethics of neurology, what will neuroscience soon discover about the biological basis of ethics?

You and your colleagues will provide the answers to these questions while shaping postmodern neurology. I wish you success, happiness, and wisdom.

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CLINICAL CASE

Can Parents of a Child with Autism Refuse Treatment for Him?

Margaret Moon, MD, MPH

Dr. Pittman was nearing the end of her shift at a busy community clinic on a Friday afternoon. Her last appointment was with a new patient, Dayton, a 6-year-old boy who, according to his parents, had an earache. Dr. Pittman quickly diagnosed otitis media and talked with Dayton's parents about treatment.

Dayton's behavior troubled Dr. Pittman far more than his inflamed eardrum. He did not make eye contact or respond to her questions. He flinched whenever she approached him, cried out in fear when she peered in his ear with an otoscope, and hopped up and down, shaking his hands compulsively, several times during the visit. When Dr. Pittman questioned Dayton's parents about his behavior, they told her he had been diagnosed with autism at age 4. His development, they said, was delayed.

She asked what treatment Dayton's parents had sought for him, and the answer shocked her. They were members of the autism self-advocacy movement and believed that Dayton's condition was simply an example of neurodiversity and was not pathologic. They clearly adored their son, doting on him during the clinic visit and telling Dr. Pittman how they home-schooled him after the public school system failed to meet his social and educational needs. They accepted Dayton as he was and were determined to provide him with lifetime care.

Dr. Pittman viewed Dayton's situation differently. She knew that with proper therapy and medication his condition could improve considerably—but only if treatment were begun as soon as possible. She worked at a nearby autism clinic, where Dayton could probably qualify for long-term treatment. When she mentioned this to Dayton's parents, they wanted nothing to do with it. They were adamant in their belief that Dayton's condition required no medical intervention.

Dr. Pittman had encountered many adult patients with culture-based opinions about their health problems that she found hard to understand, but this was the first time she'd disagreed so fundamentally with parents about a situation that she believed would harm their child by limiting his future opportunities. She fought the urge to reprimand them for what she considered their neglect of his debilitating developmental problem. Did their treatment constitute child endangerment, she wondered? Would she be justified in contacting a child protection agency?

Commentary

Medical practice involves moral obligations, and, inevitably, conflicts arise between those obligations. Ethics is a way of examining different or competing moral claims in a given situation, a framework for identifying the "should." In this case, the first step in understanding what should be done lies in identifying the competing moral obligations that create tension. Using the familiar principles of biomedical ethics, duties—to respect autonomy, to promote well-being, to avoid harm, and to act justly—have to be considered.

Respect for Autonomy

When the patient is a child, the duty to respect autonomy has to encompass his or her developing autonomy as well as that of the parents. Young children are generally presumed to have autonomy that is incomplete—due to age and cognitive development—but not inconsequential; the ultimate goal of pediatric medicine is to help children develop into autonomous, healthy adults. In this case, maximizing Dayton's future autonomy seems an important manifestation of the duty.

When a child's autonomy is limited, we usually rely on parents as decision makers. That reliance derives from our beliefs about the parent-child relationship and our social and political notions about the family and its rights to privacy. We presume that parents are the best decision makers for children because they have a privileged understanding of the child's best interests and are likely to have them—or at least the child's good-enough interests—at heart.

Still, our duty to respect parental choices is not absolute; respect for autonomy does not trump other moral obligations of medicine. Additionally, the duty to respect autonomy does not transfer perfectly from the child to the parent. We recognize a duty to respect bad choices made by competent individuals for themselves, but we don't recognize the same duty when parents are making choices for children. We stand prepared to set limits on parental decisions, particularly when the parental choice puts a child in imminent danger, when we suspect that the relationship is abusive, or when parents seem to lack decision-making capacity. In the case at hand, there is no reason to suspect an abusive relationship between parents and child; in fact, Dayton's parents appear loving and generous. Similarly, there is no evidence that the parents lack decision-making capacity. Their belief that autism is a nonpathologic example of neurodiversity is uncommon, but it is not delusional.

The question about imminent danger is harder and requires interpretation of the literature on treatments for autism and outcomes. If treatments are effective and failure to treat will likely cause severe and irreparable damage to current health or future autonomy, the duties to promote well-being (beneficence) and to avoid harm (nonmaleficence) are likely to outweigh the duty to respect parental autonomy.

The duties of beneficence and nonmaleficence oblige us to consider the meaning of well-being and harm. We ought to be clear that the medical definition of good health is only one facet of wellness. In every case, the relevant definitions of well-being and

harm have to reflect the patient's broad experience and individual perspective. In this case, as Dayton is unlikely to be able to articulate his own notions, we rely on his family. In doing so, we do not hold parents to the highest standard and ask that they consider only the interests of the child. We accept that the family may reasonably balance benefits and harms for the child with those of the family. We set a limit when it seems that the child's interests are inadequately represented.

Balancing Conflicting Duties

This case includes apparent conflicts in two areas. The physician's duty to respect parental autonomy and decision-making authority is challenged by her duty to promote Dayton's well-being and optimize his future autonomy; conversely, her duty to promote Dayton's well-being is in tension with her duty to avoid harm to the family's interests in raising him according to their belief about what constitutes his well-being. Within these conflicts lies the specific question for the physician: what might justify overriding the parents' decision to reject medical interventions for autism.

Doug Diekema sets out eight conditions for state interference with parental decision making, which can serve as a useful template for the situation Dr. Pittman must navigate [1]:

1. By refusing to consent, parents place the child at significant risk of serious harm;
2. Harm is imminent and requires immediate action to prevent it;
3. The intervention that has been refused is necessary to prevent serious harm;
4. The intervention that has been refused is of proven efficacy and therefore likely to prevent the harm;
5. The intervention that has been refused does not place the child at significant risk of serious harm, and its projected benefits outweigh burdens more favorably than the option chosen by the parents;
6. There is no other option to prevent serious harm that is less intrusive to parental autonomy and more acceptable to the parents;
7. The state intervention can be generalized to other similar situations;
8. Most parents would agree that the state intervention was reasonable.

This list makes clear that, in this case as in so many others, good ethics requires good facts. A richer understanding of the parents' intentions and goals for Dayton is important. We understand that they do not wish to label the boy as abnormal, but they want him to thrive and be happy. It isn't clear that their rejection of medical intervention for autism means they have rejected all therapy. Parents of physically and mentally healthy children accept therapies to enhance behavior, improve school performance, or treat chronic health problems; Dayton's parents might, too.

Assessing Harm

Data on the outcomes of therapies for autism are needed to assess the effectiveness of available treatments and the likelihood of imminent or irreversible harm due to refusal of intervention. Numerous articles report on a wide array of psychopharmacologic, behavioral, educational, and complementary/alternative

treatments for autism, with a broad range of results. Justification for overriding parental refusal of therapy is strongest when the therapy is known to be highly effective and low-risk and other options are inadequate. A recent review article by Susan Levy notes that the weight of the available evidence suggests that early intervention improves outcomes, but that data for long-term prognosis are scarce, and concludes that more knowledge about neurobiology and effective treatments is needed [2].

Even if there were no questions about the short- and long-term efficacy of autism treatments, the justification for contravening parental decisions requires that harms be "significant" and "imminent" and that the treatment not carry significant risk. Interpretation of these terms is seldom black and white, particularly in the case of a condition like this, for which outcomes vary widely.

The Therapeutic Alliance: Meeting on Common Ground

Beyond questions of justification, there are excellent practical reasons to avoid overriding parental refusal in this case. Most of the early-intervention therapies for autism are highly dependent on intensive parental involvement. Forced participation is unlikely to be successful. There is evidence that family stress is an independent predictor of failure of autism therapies [3]. Antagonizing the parents by imposing treatment may result in their avoiding Dr. Pittman or medical care altogether. Another approach, one that seeks to optimize the therapeutic alliance with this family seems much more likely to realize the desired outcome: promoting the child's short-*and* long-term well being.

A therapeutic alliance is a dynamic and interactive partnership between parents and physician that focuses on negotiating mutual goals and collaborating to meet them. A powerful therapeutic alliance with parents is critical to success in pediatric medicine. At this point in the case, we know only that these loving parents and the well-meaning physician both want what is best for Dayton and that they disagree on just what that is. Behind the conflict is the mutual goal of promoting the well-being of a vulnerable child. Dr. Pittman must use this mutual goal to establish an alliance that will open the door to collaboration and negotiation.

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CLINICAL CASE
"Doc, I Need a Smart Pill"—Requests for Neurologic Enhancement
Commentary by Dan Larriviere, MD, JD

Dr. Warren, the only neurologist in a hardscrabble town of 7,000 residents, looked at his new patient and chewed his lip. They were sitting in a small examining room at Dr. Warren's clinic. The patient, Mr. Conway, was a soft-spoken 28-year-old unemployed sales clerk who had just explained the reason for his visit: recently laid off, and with no other job prospects in sight, he wanted to attend graduate school. This would require him to take the Graduate Record Examination (GRE), but Mr. Conway said he would have "extreme difficulty" remaining focused for the full 4-hour length of the exam. He wanted Dr. Warren to prescribe something to help him stay focused and think better.

"Just temporarily, Dr. Warren," the polite Mr. Conway said. "Just so I can do my best on the exam."

Dr. Warren had listened to his patient's story with great sympathy. Mr. Conway needed a scholarship to attend graduate school, and a low score on the test would spoil his chances. Based on a growing literature, modafinil might help Mr. Conway focus during the long test. Dr. Warren had explained to Mr. Conway that, because he did not have symptoms of attention deficit disorder (ADD) or other neurological problems, prescribing a cognitive-enhancement drug would be hard to justify.

Dr. Warren asked himself whether helping people without medical impairment perform better academically was an accepted goal of medicine. How strong was the evidence that the medication would improve Mr. Conway's performance? Supposing it would, could *not* prescribing the drug be considered "harming" Mr. Conway, that is, making him worse off than he was now?

Alternatively, rebuffed by Dr. Warren, Mr. Conway might seek the desired drugs from a local family doctor or other nonneurologist who lacked experience with such medications and would provide him with a lower standard of care. But granting Mr. Conway's wish could entail serious complications. First, Mr. Conway would receive a powerful psychotropic drug for a nonmedical reason. Mr. Conway predicted having trouble concentrating for the entire test, but that didn't constitute real cognitive impairment in Dr. Warren's opinion, given the protracted nature of the exam. Second, if Mr. Conway aced the test and received a scholarship, he might brag about the achievement to his family and friends, earning Dr. Warren a reputation for dispensing "smart drugs" and flooding him with other patients seeking prescriptions for even less legitimate reasons.

Finally, there was matter of Mr. Conway's long-term goals. Delighted by his performance on the GRE, he might find himself "needing" more cognitive-enhancement drugs to stay sharp during long hours of graduate study. Writing papers, taking exams—it wouldn't end with the GRE. He wouldn't want the drug " just temporarily." He'd be back.

Commentary

This case raises the issue of neuroenhancement (NE)—the use of prescription medications such as methylphenidate or modafanil to enhance memory or cognitive abilities, rather than to treat a diagnosed medical or mental condition. Although the actual prevalence is unknown, some data suggest that NE is widespread. Surveys of college students have found that between 4 percent and 34 percent of the respondents had used NE illegally, over half of them for the first time while in college. The vast majority of respondents used NE to "stay awake to study" or to "concentrate on my work."

NE is not limited to college students. In 2008, the journal *Nature* surveyed its readers and found that one in five of the 1,400 respondents from 60 countries had used NE to stimulate their focus, concentration, or memory, and 80 percent of them were of the opinion that healthy adults should be permitted to take such drugs if they wished to do so. With the sales of the two best-selling drugs used for NE approaching $1 billion a year and consumer demand continuing to grow, the issue is unlikely to disappear anytime soon. Physicians should therefore expect requests for NE to reach them with increasing frequency during their careers.

Is Someone Who Requests NE a Patient?

While an argument can be made that a physically and mentally healthy person who requests NE is not a patient because he or she does not require treatment of symptoms, disease, injury or disorder, it is important to remember that the existence of a patient-physician relationship does not depend on the patient's state of health. Rather, the establishment of the relationship is voluntary, and the formation requires the intent of both parties (except in emergency situations). Physicians may generally decide which patients they will accept and may refuse to see someone as long as the reasons for refusal do not violate legal principles against discrimination.

In the present case, a patient-physician relationship was formed when Dr Warren agreed to see Mr. Conway, and Mr. Conway arrived at the scheduled time. The presence of the patient-physician relationship creates professional and ethical obligations that Dr. Warren must fulfill until the relationship is ended in an appropriate manner. Mr. Conway's request for NE does not negate that relationship.

How Should Dr. Warren Respond?

Dr. Warren is ethically obligated to take his patient's request for NE seriously. However, Dr. Warren also has an obligation to minimize harm (nonmaleficence) and maximize good (beneficence) for his patients. Rather than dismissing Mr. Conway's request out of hand, Dr. Warren may wish to interpret the request as one that stems

from a decline in cognitive functioning. Thus viewed, the request becomes a chief concern and Dr. Warren has a duty to perform an appropriate history and physical exam to determine the patient's current level of function and whether it represents a significant change from Mr. Conway's baseline. After the history and physical exam, Dr. Warren will need to decide whether any further tests are necessary to complete an adequate evaluation. If Mr. Conway does not have sufficient signs, symptoms, or abnormal test results to satisfy criteria for a medical or mental health condition, then he would be considered "normal," and a prescription would be an enhancement rather than a treatment.

Is It Ethical to Prescribe NE?

While much has been written about the ethics of NE, there is no consensus concerning the ethics of the practice. Recently, the Ethics, Law and Humanities Committee of the American Academy of Neurology (AAN) published a guidance statement for neurologists fielding adult patients' requests for NE [1]. To frame the question of NE's appropriateness, the committee considered physicians' professional activities as they relate to the traditional goals of medicine: prevent and diagnose disease or injury; cure or treat disease or injury; reduce suffering; educate patients about disease and injury; help patients die with peace and dignity; reassure the "worried well." They then divided those activities into three domains.

In the first of the AAN's domains of physician activity are those practices that are consistent with the traditional goals of medicine outlined above; they are considered ethically obligatory. In the second domain are those practices that do not serve the traditional goals of medicine, but are accepted by society because they require medical knowledge, serve other socially useful purposes, and do not compromise the profession's ability to fulfill its social mission. Examples of these practices are aesthetic forms of surgery and the provision of expert witness testimony in malpractice cases. Activities in this domain are considered ethically permissible without being ethically obligatory. The third domain consists of those practices that undermine the profession's core values and consequently are considered ethically prohibited. Examples of such practices include participation in executions and the torture and interrogation of detained prisoners.

The committee concluded that prescribing neuroenhancers was most analogous to aesthetic surgery and would fall into the second domain of ethically permissible activity, which makes its use subject to the individual physician's judgment. Physicians who believe their role should be limited to the traditional goals of medical practice will be less likely to prescribe NE than physicians who view their role as assisting more broadly with patient-defined goals of well-being.

Ethical and Social Considerations

As mentioned above, physicians are under a general ethical obligation to maximize benefits and minimize harm to patients under their care. In traditional medical practice, this obligation involves weighing harms due to illness or injury against the risks and benefits of a proposed treatment. In the case of neuroenhancement, the

risks must be weighed against what a patient hopes to gain from the medication—in this case performing well on a standardized test. Such a benefit may be difficult to quantify, since test performance is determined not only by ability to concentrate during the test but by adequate preparation, among other factors. Dr. Warren is also correct to expect that a high test score will act as positive reinforcement, perhaps persuading Mr. Conway that he should continue to use the medication during graduate school—an area where the benefits of taking the drug may be even harder to define.

In addition to the difficulty of identifying and defining the goals of therapy, Dr. Warren must keep in mind that the data for the efficacy of NE in a normal population are not robust. Published studies suggest that effects vary with patient characteristics (e.g., IQ), age, and task type (novel or repetitive) and, in some cases, actually worsen cognitive function. The idea that simply taking a NE drug "makes someone smarter" ignores the complexity of cognitive function. Too, the long-term effects of NE medications in a normal population have not been adequately studied. Dr. Warren may ethically refuse to prescribe NE for these clinical reasons.

Students of ethics will point out that Dr. Warren is under an ethical obligation to respect the autonomy of his patient. This principle does not always supersede other ethical principles, however, and physicians do not honor autonomy by giving patients prescriptions just because they request them. Physicians should decline to honor the request for NE if, in their clinical judgment, the patient's welfare will be compromised. If Dr. Warren declines to prescribe NE, respect for autonomy requires that he explain his reasoning to Mr. Conway in terms that the latter can understand, without being demeaning or disrespectful. Dr. Warren should also help Mr. Conway identify ways in which he may strive to achieve his goals without the use of NE, such as making sure that he has proper sleep hygiene, is getting adequate exercise, and so on.

One other implication of respect for autonomy bears mention. If he chooses to prescribe NE to Mr. Conway, Dr. Warren must adequately inform him about the risks associated with the use of the medication so that Mr. Conway's decision can be truly autonomous. The information disclosed must include that paucity of data concerning NE efficacy and its short- and long-term effects on patients who do not need it for medical reasons.

Finally, Dr. Warren should consider the fact that NE medications are not likely to be covered by third-party payors. Consequently, patients have to pay for them out-of-pocket. Can Mr. Conway afford them? This will have the effect of limiting use of these medications to people who can afford them—probably a small segment of the population. Our society tolerates inequality of distribution related to inability to pay (for example, in cosmetic surgery or concierge medical practice), but Dr. Warren may not hold that belief.

Conclusion

Decisions about prescribing NE take place within the patient-physician relationship, one in which physicians have professional and ethical obligations, even if the patient's sole purpose is to acquire neuroenhancement drugs. Physicians are not ethically obligated to prescribe NE to patients who request it and may ethically refuse to do so. On the other hand, according to the recent American Academy of Neurology guidelines, prescribing NE is ethically permissible, provided that the physician adheres to bioethical principles of respect for autonomy, beneficence, nonmaleficence, and distributive justice and that practice standards derive from those principles.

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CLINICAL CASE

The Ethics of Diagnosing Nonepileptic Seizures with Placebo Infusion

Commentary by James L. Bernat, MD

Ms. Lamonica was admitted for a neurological evaluation after experiencing 2 severe seizures. At 38, Ms. Lamonica was overweight, but otherwise in good health. All studies including electroencephalograms (EEG) were normal. Because her description of her seizures seemed to exclude epilepsy—she remained fully conscious during the events, for example, and experienced no confusion afterward—her team of neurologists led by Dr. Patel began to suspect that her episodes were nonepileptic seizures (NES). The physicians contemplated using a provocative test to confirm the diagnosis.

The test was controversial because it entailed deceiving the patient. Ms. Lamonica would have EEG electrodes attached to her scalp and an intravenous catheter inserted. Dr. Patel would then tell her he was administering a solution designed to provoke a seizure. In reality, the solution would be simple saline. If Ms. Lamonica had a seizure, Dr. Patel would stop the infusion, tell her the drug was leaving her system, and watch for a concomitant end to the seizure. If no abnormal electrical activity was seen during a seizure, the diagnosis of NES would be confirmed.

An estimated 10 to 20 percent of patients who are hospitalized for seizures or treated at epilepsy clinics are suspected to have NES; some have epilepsy and NES. Nonepileptic seizures are treated with psychiatric rather than neurological interventions. While epilepsy can often be managed with medications, pharmacologic treatment for NES tends to be ineffective. Anticonvulsants are inappropriate. Psychotherapy is useful for some patients, but many remain unimproved long after diagnosis.

The key to distinguishing NES from epilepsy is whether EEG evidence of a true seizure is recorded by EEG during a typical spell. To avoid keeping the patient attached to the EEG machine for hours or days in hopes of witnessing an episode, some physicians choose to employ the so-called provocative saline infusion—the sham test described above—to expedite the diagnosis. Provocative saline infusion is thus a nocebo, a drug the patient perceives as harmful, which in Ms. Lamonica's case would mean seizure-inducing.

Dr. Patel decided to administer the provocative saline infusion to Ms. Lamonica, and she promptly had a seizure. During the seizure, her EEG remained normal. She was therefore diagnosed with NES.

Afterward, Dr. Patel wrestled with the question of whether to tell Ms. Lamonica that the provocative test had been a ruse. Though the physical risks associated with a saline infusion are minimal and the definitive diagnosis would help her by obviating the need for daily anticonvulsant drug treatment, he regretted the necessity of deceiving the patient, and felt he should reveal the truth.

Commentary

In this case, Dr. Patel chose to perform a deceptive provocative test of intravenous saline infusion because he believed it was necessary to prove that Ms. Lamonica's episodes were caused by NES. The test was safe insofar as the pharmacological effect of the infused placebo was concerned, but it produced potential harm because its use required deception. It is the deception implicit in the use of diagnostic placebos that raises ethical problems and produces their resulting harms.

As shown in this case, placebos can be used for diagnostic purposes in addition to their more familiar use in therapy and for clinical trial research controls. A placebo is a pharmacologically inactive substance that is prescribed by a physician for a patient who is expecting to receive an active agent. The placebo effect, a benefit resulting from suggestion and expectation, is the desired response. Deception is implicit in their use for diagnostic and therapeutic purposes but, because a placebo is a known condition of the control arm of a clinical trial, its use in clinical research is not considered deceptive.

Scholars have written detailed ethical analyses of physician placebo prescribing for therapeutic purposes, including the formulation of criteria for their ethical use [1]. Three published ethical analyses that addressed the use of the provocative saline infusion test to prove NES all concluded it should not be performed because of the harms resulting from the required deception [2-4]. I review the salient points here; specifically, is a test that requires deception necessary or desirable to diagnose NES? What are its risks and benefits? Does the overall harm from deception justify its benefits? What are the alternatives? Should patients later be told of the deception? Should we formulate a medical practice standard permitting deception in such cases?

Use of Deception

The placebo saline intravenous infusion test to deceptively provoke and prove NES has been described since at least 1982 [5]. Additional reports of its efficacy by advocates have continued into the 21st century [6]. Its advocates claim it is safe, reliable, and effective, and that it is justified because it benefits patients by preventing them from being wrongly diagnosed with and treated for epilepsy [7].

That deception is essential in this test is obvious. Dr. Patel lied to Ms. Lamonica when he told her that the drug he was infusing was an activating agent that would provoke a seizure when he knew it was simply saline. I am unsympathetic to the putative justification that he did not lie to her because the infusion did, in fact, provoke an episode of her "seizure." His intent was unarguably deceptive.

Purposefully lying to patients violates the mutual trust that both parties have in the truthfulness of the other and the respect that is the foundation of the patient-physician relationship. Physicians have a fiduciary duty to tell the truth based on their responsibility to respect the dignity and autonomy of the patient.

A practical risk of lying or deception on the part of patient or physician is that the other party no longer believes what she is told, a situation that damages the therapeutic value of the patient-physician relationship. The patient's discovery that she has been deceived could lead her to lose confidence in the trustworthiness of other physicians. Her loss of trust in the integrity of the medical profession would exert a negative effect on her ability to establish and maintain faith in physicians in the future and would thereby harm her future medical care.

Some patients with NES have a special vulnerability to the harms of deception. A disproportionate percentage of young women with NES have been victims of childhood sexual and physical abuse, often perpetrated by a trusted family member or friend [8]. Thereafter they have difficulty in establishing long-term trusting relationships and may be particularly harmed by physician deception [9].

Medical professionalism is a further casualty of using a deceptive test. Lying to patients coarsens and degrades a physician's integrity and self-image as an ethical professional. When physicians perform the provocative saline test in academic medical centers where trainees participate in the testing, the trainees become unwitting partners in the deception. In the medical training hierarchy, they are disempowered to protest that a procedure is unethical when ordered to participate by an attending physician who is their superior, and, thus, are forced to compromise their integrity and professionalism [3].

Paternalism

Dr. Patel undoubtedly believed that his deception was justified by the good that the positive test did for the patient. Physicians who purposely lie to or deceive a patient for "the patient's own good" are practicing paternalism. Paternalism has a long and hallowed tradition in medical practice, evolving from the fiduciary duty of a physician to identify and act in the best interest of the patient. But paternalism becomes unethical when it disenfranchises patients who wish to be fully aware of their condition and to participate in their own medical decision making.

Most paternalistic practices in medicine cannot be rigorously justified. The ethical justification of paternalism requires satisfying the following criteria: (1) the harms to the patient that the physician's act will avoid are very great, such as death or disability; (2) the harms imposed by the physician's act are, by comparison, relatively small; (3) the patient's behavior that the act will address is seriously irrational; and (4) rational persons would routinely publicly advocate deception in this circumstance [10].

Is the Provocative Test Necessary?

What are the benefits of the paternalistic act of deceptive saline NES provocation? Its primary benefit is to confirm that a clinical episode that might be an epileptic seizure is, in fact, a nonepileptic seizure. The provocative saline test is only partially accurate at this task because it has been shown to induce true epileptic seizures in some patients with epilepsy [7].

Furthermore, the mere demonstration that NES is present does not prove that the patient does not also have epilepsy. Some patients with NES also have true epilepsy, although the precise frequency of this concurrence is debatable [11]. Therefore, demonstrating that a particular observed seizure is NES, while useful, does not necessarily exclude concomitant epilepsy.

Is deception required to prove that a patient has NES? In the commonly used diagnostic protocol for suspected NES, the patient is admitted to a video-monitored epilepsy unit for several days of continuous EEG and video-monitoring. If routine EEGs are normal or have nonspecific abnormalities and if the index of suspicion for NES is high, the patient's anticonvulsant drugs usually are discontinued. Nondeceptive provocative measures, such as falling asleep and awakening, suggestion, photic stimulation, and hyperventilation are routinely employed [12].

Benbadis and colleagues studied the rate of positive identification of NES in an inpatient epilepsy unit, comparing accepted provocative procedures and the deceptive provocative intravenous saline infusion. They showed that the percentage of patients found to have NES after routine provocative procedures was identical to that found by using the provocative saline infusion. They concluded that a deceptive saline infusion provocative test was unnecessary to diagnose NES; simply using routine procedures without deception was a successful strategy that avoided ethical problems [13].

Consensus and Guidelines

Over the past two decades, a consensus has emerged that the paternalism behind use of the provocative saline infusion test for NES cannot be justified because the harms to the patient and physicians exceed the benefits [14]. Although a few scholars have argued that placebo prescription can remain good medical practice if it is conducted under ethical circumstances, these arguments were developed for prescribing therapeutic placebos and do not apply to conducting deceptive diagnostic testing [15]. If neurologists choose to conduct the provocative saline infusion, they should avoid deception by informing the patient of what substance is being infused and why.

There are now medical practice guidelines for physicians who choose to prescribe a placebo. The American Medical Association Council on Ethical and Judicial Affairs issued a recommendation for physicians who prescribe placebos for therapeutic or diagnostic purposes, cautioning that [16]:

> In the clinical setting, the use of a placebo without the patient's knowledge may undermine trust, compromise the patient-physician relationship, and result in medical harm to the patient. Physicians may use placebos for diagnosis or treatment only if the patient is informed of and agrees to its use.

In summary, testing for NES using the deceptive saline provocative test is not necessary to make the diagnosis, has troublesome false positive and negative results, and causes short-term and long-term harms to patients and physicians. It has been proscribed by American medical practice standards and abandoned by most epilepsy centers.

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THE CODE SAYS
The AMA *Code of Medical Ethics*' Opinions on Using Drugs and Surgery for Purposes Other than Treatment

Opinion 8.06 - Prescribing and Dispensing Drugs and Devices

(1) Physicians should prescribe drugs, devices, and other treatments based solely upon medical considerations and patient need and reasonable expectations of the effectiveness of the drug, device or other treatment for the particular patient.

(2) Physicians may not accept any kind of payment or compensation from a drug company or device manufacturer for prescribing its products. Furthermore, physicians should not be influenced in the prescribing of drugs, devices, or appliances by a direct or indirect financial interest in a firm or other supplier, regardless of whether the firm is a manufacturer, distributor, wholesaler, or repackager of the products involved.

(3) Physicians may own or operate a pharmacy, but generally may not refer their patients to the pharmacy. Exceptionally, a physician may refer patients to his or her pharmacy in accord with guidelines established in Opinion 8.032 "Conflicts of Interest: Health Facility Ownership by a Physician." Physicians may dispense drugs within their office practices provided such dispensing primarily benefits the patient.

(4) In all instances, physicians should respect the patient's freedom of choice in selecting who will fill their prescriptions as they are in the choice of a physician and, therefore, have the right to have a prescription filled wherever they wish. (See Opinions 9.06 "Free Choice," and 8.03 "Conflicts of Interest: Guidelines.") Physicians should not urge patients to fill prescriptions from an establishment which has entered into a business or other preferential arrangement with the physician with respect to the filling of the physician's prescriptions.

(5) A third party's offer to indemnify a physician for lawsuits arising from the physician's prescription or use of the third party's drug, device, or other product, introduces inappropriate incentives into medical decision making. Such offers, regardless of their limitations, therefore constitute unacceptable gifts. This does not address contractual assignments of liability between employers or in research arrangements, nor does it address government indemnification plans.

(6) Patients have an ethically and legally recognized right to prompt access to the information contained in their individual medical records. Since a prescription is part of the patient's medical record, the patient is entitled to a copy of the physician's prescription for drugs or devices, including eyeglasses and contact lenses. Therefore,

physicians should not discourage patients from requesting a written copy of a prescription.

This opinion is a consolidation of previous Opinions 6.04 "Fee Splitting: Drug or Device Prescription Rebates"; 8.06 "Drugs and Devices: Prescribing"; and 8.07 "Gifts to Physicians: Offers of Indemnity."

Opinion 5.015 - Direct-to-Consumer Advertisements of Prescription Drugs
The medical profession needs to take an active role in ensuring that proper advertising guidelines are enforced and that the care patients receive is not compromised as a result of direct-to-consumer advertising. Since the Food and Drug Administration (FDA) has a critical role in determining future directions of direct-to-consumer advertising of prescription drugs, physicians should work to ensure that the FDA remains committed to advertising standards that protect patients' health and safety. Moreover, physicians should encourage and engage in studies regarding the effect of direct-to-consumer advertising on patient health and medical care. Such studies should examine whether direct-to-consumer advertising improves the communication of health information; enhances the patient-physician relationship; and contains accurate and reasonable information on risks, precautions, adverse reactions, and costs.

Physicians must maintain professional standards of informed consent when prescribing. When a patient comes to a physician with a request for a drug he or she has seen advertised, the physician and the patient should engage in a dialogue that would assess and enhance the patient's understanding of the treatment. Although physicians should not be biased against drugs that are advertised, physicians should resist commercially induced pressure to prescribe drugs that may not be indicated. Physicians should deny requests for inappropriate prescriptions and educate patients as to why certain advertised drugs may not be suitable treatment options, providing, when available, information on the cost effectiveness of different options.

Physicians must remain vigilant to assure that direct-to-consumer advertising does not promote false expectations. Physicians should be concerned about advertisements that do not enhance consumer education; do not convey a clear, accurate, and responsible health education message; do not refer patients to their physicians for more information; do not identify the target population at risk; and fail to discourage consumer self-diagnosis and self-treatment. Physicians may choose to report these concerns directly to the pharmaceutical company that sponsored the advertisement.

To assist the FDA in enforcing existing law and tracking the effects of direct-to-consumer advertising, physicians should, whenever reasonably possible, report to them advertisements that (1) do not provide a fair and balanced discussion of the use of the drug product for the disease, disorder, or condition; (2) do not clearly explain warnings, precautions, and potential adverse reactions associated with the drug product; (3) do not present summary information in language that can be understood

by the consumer; (4) do not comply with applicable FDA rules, regulations, policies, and guidelines as provided by the FDA; or (5) do not provide collateral materials to educate both physicians and consumers.

Based on the report "Direct-to-Consumer Advertisements of Prescription Drugs," adopted December 1998.

Opinion 2.076 - Surgical "Placebo" Controls

The term surgical "placebo" controls refers to the control arm of a research study where subjects undergo surgical procedures that have the appearance of therapeutic interventions, but during which the essential therapeutic maneuver is omitted.

The appropriateness of a surgical "placebo" control should be evaluated on the basis of guidelines provided in Opinion 2.07 "Clinical Investigation," as well as the following requirements:

(1) Surgical "placebo" controls should be used only when no other trial design will yield the requisite data.

(2) Particular attention must be paid to the informed consent process when enrolling subjects in trials that use surgical "placebo" controls. Careful explanation of the risks of the operations must be disclosed, along with a description of the differences between the trial arms emphasizing the essential procedure that will or will not be performed. Additional safeguards around the informed consent process may be appropriate such as using a neutral third party to provide information and get consent, or using consent monitors to oversee the consent process.

(3) The use of surgical "placebo" controls may be justified when an existing, accepted surgical procedure is being tested for efficacy. It is not justified when testing the effectiveness of an innovative surgical technique that represents only a minor modification of an existing, accepted surgical procedure.

(4) When a new surgical procedure is developed with the prospect of treating a condition for which no known surgical therapy exists, using surgical "placebo" controls may be justified, but must be evaluated in light of whether the current standard of care includes a non-surgical treatment and the benefits, risks, and side effects of that treatment.

(a) If foregoing standard treatment would result in significant injury and the standard treatment is efficacious and acceptable to the patient (in terms of side effects, personal beliefs, etc), then it must be offered as part of the study design.

(b) When the standard treatment is not fully efficacious, or not acceptable to the patient, surgical "placebo" controls may be used and the standard treatment foregone, but additional safeguards must be put in place around the informed consent process.

Based on the report "Surgical Placebo Controls," adopted June 2000; updated June 2003.

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JOURNAL DISCUSSION
Guidelines for Prognostication and End-of-Life Decision Making for Newborns with Severe Neurologic Damage
Jay Desai, MD

Racine E, Shevell MI. Ethics in neonatal neurology: when is enough, enough? *Pediatr Neurol*. 2009; 40(3):147-155.

There have been tremendous advances in newborn care in the United States since the opening of the nation's first neonatal intensive care unit in 1960. These have led to improved survival of extremely premature newborns, many with complex medical and surgical needs [1]. Perception of what is acceptable in terms of neurologic handicap and its effect on quality of life has changed significantly since 1984, when the Baby Doe Amendment was signed into law [2]. In the post-Schiavo era, the roles of physicians, family, law, society, and government in end-of-life decision making have come under intense scrutiny and continue to evolve [3]. In "Ethics in Neonatal Neurology: When is Enough, Enough?" Eric Racine and Michael Shevell examine the ethical questions raised by the increasingly complex processes of prognostication and end-of-life decision making for newborns with severe neurologic insult [4].

The article focuses on newborns with severe injuries for whom an adverse neurologic outcome is highly probable. The authors start by defining the concept of futility, a label which is applied automatically in only two specific circumstances: anencephaly and brain death. Though in other situations, treatment is not considered *necessarily* futile, withdrawal of care may be considered when a severe adverse neurologic outcome is highly probable.

Racine and Shevell represent these clinical scenarios through two vignettes. The first one describes a 4-day-old boy with history of intrapartum asphyxia with apgars of 0, 0, 2, and 4 at minutes 1, 5, 10, and 20, respectively, and a cord pH of 6.88. He has seizures with multisystem involvement at 2 hours of age that are difficult to control. An EEG on the second day of life shows a burst suppression pattern. A head computed tomography scan shows diffuse edema, attenuation, and loss of grey-white matter differentiation with involvement of deep grey matter structures. Vignette two portrays a 21-day-old girl born second of twins at 27 weeks' gestation. She has bilateral grade IV hemorrhages noted on cranial ultrasound at 7 days of life. On day 21 of life, her fontanel is noted to be full and a head computed tomography scan shows ventriculomegaly and cystic periventricular lesions. Although a severe adverse outcome is highly likely in both these cases and withdrawal of care may be considered, the authors emphasize that an outcome with relatively mild neurologic

impairments cannot be completely ruled out. It is just not possible to prognosticate with accuracy.

After defining the circumstances in which withdrawal of care can be considered, the authors discuss ethical principles that come into play in these situations. Unique challenges are involved in end-of-life decision making for newborns, like inapplicability of respect for autonomy and the lack of advanced directives for proxy decision making. Parents are the obvious proxy decision-makers, but do not have unlimited authority, and their judgment may be questioned if medical personnel or others believe that parents are not acting in the best interests of the neonate's current comfort and future development.

Most often, a mutually acceptable joint decision is made between the health care professionals and parents. On rare occasion, however, parents do not agree with the physicians. Such conflicts can often be resolved with the help of mediators and hospital ethics committees, but may occasionally lead to judicial proceedings.

The authors identify challenges other than disagreements about medical care between parents and caregivers. As has been documented in the literature, the approach of the caregivers can often be influenced by professional position, gender, age, length of experience, religiousness, and ethical perceptions of the relationship between withdrawal of care and euthanasia, among other things. They then discuss ethical issues in palliative care, explaining the difference between withdrawal of care and physician-assisted suicide or euthanasia, and the need for more training for medical professionals involved in end-of-life decision making and palliative care.

This is a remarkably well-written article that comprehensively covers the ethical issues involved in making care decisions for severely neurologically damaged newborns. One area in which the authors should have elaborated further, however, is the published statistical data about long-term outcome in these cases. The authors' emphasis on the fact that accurate prognostication is impossible gives the reader an impression that this lack of certainty is the most critical information one can convey to the parents. The most crucial task for child neurologists and other physicians in these circumstances is to be aware of and counsel the parents as accurately as possible about future neurologic outcome based on published evidence.

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CLINICAL PEARL

The Spectrum of Autism—From Neuronal Connections to Behavioral Expression

Carla A. Mazefsky, PhD, and Nancy J. Minshew, MD

Autism spectrum disorders are defined behaviorally by the *Diagnostic and Statistical Manual (DSM) IV-TR* based on abnormal development in social interaction and communication and restricted, repetitive, and stereotyped patterns of behaviors and interests that are evident before the age of 3. After decades of debate, research has demonstrated that the distinctions among autism, Asperger disorder, and pervasive developmental disorder not otherwise specified are neither clinically reliable nor based on valid neurobiological or genetic differences. The fifth edition of the *DSM* therefore proposes to collapse all of the clinical syndromes under the single diagnosis of autism spectrum disorder (ASD).

Etiology

There will continue to be no separate category of ASD diagnoses for cases with a known etiology in *DSM-5*. These etiologies are typically discovered after the diagnosis is made, though autism spectrum disorder sometimes manifests after an early diagnosis of a primary disorder such as Down syndrome, neurofibromatosis, or inborn errors of metabolism. Currently, the most common identifiable causes of ASD are tuberous sclerosis and fragile X syndrome. Many other disorders are infrequently associated with ASD. ASD cases co-occurring with recognizable genetic syndromes are classified as syndromic autism spectrum disorder, and those without a recognizable syndrome are termed nonsyndromic or idiopathic [1].

The list of identifiable causes is growing as a result of the rapid pace of genetic discoveries about autism spectrum disorder [1]. At present, about 15 or 20 genes or chromosomal syndromes have been identified that each account for a small percentage of cases. The distribution of these genes over the genome explains why ASD has been "nonspecifically" associated with chromosomal abnormalities. The study of families with these rare genes has shown that they are associated with autism, ASD, and intellectual disability without ASD, all of which can occur within the same family. Genes code for protein formations, which, in this context, affect brain development; disorders with similar manifestations likely have overlapping brain differences. Likewise, a number of the genes associated with autism spectrum disorder have also been associated with attention deficit disorder/hyperactivity (ADHD), depressive disorders, schizophrenia, and obsessive compulsive disorder (OCD).

Pathophysiology

Major strides have also been made in understanding the pathophysiology of ASD. Alterations in cortical connectivity are now widely accepted as a central pathophysiologic mechanism [2, 3]. The alteration is typically characterized as (functional) underconnectivity of cortical systems (cortico-cortical intra-hemispheric connectivity) and (functional) overconnectivity of local cortical connections [4]. In many respects, ASD could be conceptualized as a failure or underdevelopment of the specialization of cortical systems and organization responsible for both voluntary and automatic functions [5].

The idea that ASD stems from genes that guide neuronal development is supported by "neuropathologic studies indicating malformations in the minicolumnar structure of the cortex, volumetric studies indicating early brain overgrowth and a subsequent abnormal trajectory of brain growth, and the functional imaging studies that indicate abnormalities in the functional connections between brain regions during cognitive processing" [6]. The importance of this pathophysiologic characterization is that it provides a framework for interpreting all of the clinical manifestations of ASD: selective underdevelopment of higher-order abilities with or without enhanced basic abilities in the same domain of function. This perspective makes it possible to understand why ASD not only affects the social, communication, and reasoning domains (those with the highest information processing demands) but also higher cortical sensory and motor abilities, balance, and memory. Altered connectivity also appears to explain the co-occurrence of anxiety disorder, affective disorder, and OCD with ASD.

Diagnosis

Despite autism spectrum disorder's neurobiological and genetic basis, diagnosis remains focused on behavior. The behavioral manifestations of ASD are variable in nature and degree, as would be expected from the underlying pathophysiology and genetics described above. Even among individuals of the same age and similar IQ with rigorously diagnosed autistic disorder, there are variations in everything from motor apraxia to developmental trajectory of head and brain growth. The most noticeable phenotypic heterogeneity is in IQs, which can range from severely impaired to superior, and in language, which can vary from nonverbal to overly verbose. Many comorbid medical conditions or associated psychiatric disorders and symptoms also contribute to ASD's heterogeneity [7].

Further, even the most common symptoms of ASD are not definitive in isolation or universal (e.g., while poor eye contact is frequently considered indicative of ASD, it is present in other disorders such as ADHD, and some individuals with ASD do make natural eye contact or learn to do so through intervention). Therefore, evaluation by a specialist in autism spectrum disorder (usually a psychologist, psychiatrist, neurologist, or related team) is typically needed to make a formal diagnosis. Nonetheless, all physicians should be aware of the common presentations and refer individuals for further assessment when ASD is suspected.

Lower-Functioning and Younger Children

A recent summary of research on the infant siblings of children with autism has provided new insights into the early development of ASD, with some surprising findings [8]. Few differences are apparent at 6 months in children who eventually receive ASD diagnoses despite the social nature of infants of this age. In fact, at 9 months old, most infants who go on to receive ASD diagnoses demonstrate some social engagement and many normal social behaviors, such as anticipation during peekaboo and orienting to their name and others' voices. Onset patterns are variable, but the infant research suggests that the earliest signs for many children with ASD are differences in motor development and unusual visual interest in objects.

Most differences in development become more apparent between 12 and 24 months, including general developmental delays (including dramatic decreases in IQ for some children), more prominent repetitive behaviors, atypical sensory responsivity (e.g. being either hyper- or hyposensitive to touch, sounds, and so on), and increasingly difficult temperaments. Social and communicative impairments certainly still play a major role, but they are only two of many domains impacted in ASD and tend to appear later. This is consistent with principles governing the presentation of neurologic disorders of brain development in childhood. Specifically, signs and symptoms manifest when development reaches the point at which the defective mechanism is called into operation to support brain development and function.

While symptoms in the three diagnostic domains (social, communication, and repetitive behaviors) are not necessarily the first signs, they do remain the principal considerations for the differential diagnosis of autism spectrum disorder. The best predictors of later ASD diagnosis are lack of response to one's name at 14 months and lack of self-initiated and spontaneous use of eye contact to direct someone's attention to an object or activity of interest ("joint attention") [8]. Several practice parameters have been developed to aid in the early diagnosis of ASD [9, 10] due to research supporting the benefit of early, intensive intervention [11, 12]. Both routine developmental surveillance and ASD-specific screening (particularly at 18 months or when risk factors are present) are supported by both the Child Neurology Society [10] and the American Academy of Pediatrics [9]. Each has a detailed algorithm for when and how to make referrals, as well as key warning signs that warrant an immediate referral for further assessment. For example, the Child Neurology Society notes that the following developmental patterns should be considered abnormal [10]:

- No babbling by 12 months;
- No gesturing by 12 months;
- No single words by 16 months;
- No 2-word spontaneous phrases by 24 months;
- Any loss of language or social skills at any age.

Higher-Functioning and Older Children, Adolescents, and Adults

ASD diagnoses for children in the average or greater range of intellectual ability and with on-time language development often go undetected or misdiagnosed until later

childhood, or even adulthood, in some cases. Many of these individuals are thought of as "weird" or eccentric and go without a diagnosis. Alternatively, emotional or behavioral concerns may be what draws clinical attention to higher-functioning individuals with ASD [13]. A red flag for a missed ASD diagnosis in older children, adolescents, or adults is a history of other psychiatric diagnoses. Common previous diagnoses include combinations of ADHD, oppositional defiant disorder, bipolar disorder, OCD, and schizophrenia-spectrum disorders. Often individuals have received treatment for these other concerns without much success or are on a medley of medications and still have poor functioning.

The presentation of individuals with high-functioning ASDs changes over the course of their development [14]. In 3- to 6-year-olds, poor peer relationships may emerge, though attention problems and difficulty regulating emotions and arousal may be the prominent features. They may have a limited range of play skills and exhibit unusual sensory sensitivity.

Over the next few years, peers further notice and highlight their differences. Some higher-functioning children with ASD may self-isolate, whereas others have great interest in making friends, but are awkward or pushy in their attempts. As high-functioning children with autism spectrum disorder go through elementary school, a perseverative interest, disruptive behaviors, and problems with social speech may emerge or worsen. Even among children with ASD who are thought to have normal language development, many higher-order language concerns become evident as they get older, including problems with conversational speech (especially a tendency to be "one-sided"), atypical prosody, overly literal comprehension, and formal or stilted speech [6].

Learning difficulties also often emerge, particularly as academic demands become more integrative. Individuals with ASD have a characteristic pattern of cognitive development that includes intact or enhanced skills in some areas (attention, sensory perception, elementary motor movement, simple memory, formal language, rule-learning, and visuospatial processing), and deficits in higher-order skills involved in complex information processing (e.g., concept formation, aspects of abstract reasoning, face recognition, skilled motor movements, higher cortical sensory perception, and complex memory) [15].

Increased social isolation is also likely to occur throughout adolescence and adulthood and may be accompanied by depression and disorganized thinking. Particularly as their peers mature, the level of social and emotional immaturity in the adolescent or adult with high-functioning autism spectrum disorder becomes more noticeable. This, combined with poor problem solving, lack of flexibility, and difficulty with perspective taking, often leads to many functional challenges in achieving independence.

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Further Reading

Autism Speaks (www.autismspeaks.org) and First Signs (www.firstsigns.org) offer a variety of resources, including an ASD Video Glossary with video clips to aid in understanding ASD presentation.

The Centers for Disease Control ASD Information for Healthcare Providers (http://www.cdc.gov/ncbddd/autism/hcp.html) includes a health care provider resource kit, guidelines and recommendations for screening, links to download recommended screening measures, and research summaries.

The Organization for Autism Research (http://www.researchautism.org/resources) offers a series of research-based guides, additional links to other resources, and a DVD series focused on higher-functioning individuals with ASD and adults with ASD in particular.

The National Institutes of Health (http://health.nih.gov/topic/Autism) offers links to each institute's relevant information on ASD, with information on both clinical and biological aspects of ASD and information on the latest and ongoing research.

The Woman Who Thinks Like a Cow, the HBO movie about Temple Grandin, a highly successful adult with high-functioning autism, also provides helpful insight into understanding the perspective and thinking of individuals with ASD.

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HEALTH LAW

The Future of Neuroimaging in Witness Testimony

Benjamin Bumann

Imagine a defense attorney who, faced with an eyewitness who claims to have seen the defendant at the scene of the crime, wants to demonstrate that the eyewitness's memory is false, the product of flawed recall. A company offers to put the witness into a brain scanner, ask her to recall the memory in question, and judge the likely fidelity of the memory based on the parts of the brain brought to the task. The eyewitness is scanned, and the company reports that the brain activity pattern of the witness looked very similar to the brain activity pattern associated with the false memory conditions in the neuroscience literature.

Should the scan be allowed as evidence in court, and, if not, what criteria must be met before it should be? To answer this question, we first shall explore functional magnetic resonance imaging (fMRI) as a specific form of general functional neuroimaging methods.

Functional neuroimaging describes a category of noninvasive methods by which brain activity may be recorded [1]. The term "imaging" is something of a misnomer, since the techniques by which these methods derive data entail mostly collecting and analyzing information on brain activity in the dimensions of space and time; the final step of translating this information into an image is not necessary, though it often helps in comprehension of the data. On the other hand, as we will see, presenting the data in the visual format is often misleading for those unversed in its genesis [2].

fMRI in the Experimental Setting

fMRI measures changes in the levels of oxygenated blood delivered to areas of the brain, with the assumption that more neural activity in an area of the brain creates the subsequent need for more oxygenated blood [3]. The change is referred to as the blood oxygen level dependent (or BOLD) signal in the brain. If an increase in the BOLD signal correlates with a certain cognitive process, researchers may hypothesize that the part of the brain where the BOLD signal increased is involved in that cognitive process.

Numerous mental states unrelated to the task of interest may occur in a subject during an experiment. Due to this, studies run the risk of measuring the neural correlate of a mental process unrelated to the one being investigated. Thus, before fMRI data are allowed in court, it must be established that the experiment was well controlled; the mental process the party is attempting to correlate with the recorded

BOLD response must be the mental process the subjects were undergoing while being scanned.

Assuming the experiment is well controlled, the researcher must decide what statistical power he or she needs to call the change in BOLD response significant [4]. A change in BOLD response is quite a weak signal, and thus researchers run many different subjects many times in the same experiment, seeking to see the signal reliably reproduced. The researcher may choose which of several possible statistical thresholds, methods, and computer programs to use to establish significance [4]. Data that is not significant under one combination of thresholds, methods, and programs might become so under a different combination [4].

Once activation data is analyzed for each subject in an experiment, averages of subjects' responses are composed, normally by warping each subject's slightly different brain structure to the coordinates of a standard anatomical brain model [5]. As soon as each subject's brain activation patterns have been fitted onto the standard model, the overlapping areas of activation are said to be the group-level activation patterns for that condition [5].

Variables unrelated to the experiment might affect the BOLD response. Every scanner is differentially sensitive to BOLD response changes in a way that is not clearly commensurable with other scanners [6]. Other factors, such as age, medical history, or possibly intrasubject variables such as stress level or time of day the scan is conducted, can affect the BOLD response [7]. Thus, average brain patterns gathered by one scanner, on one group of subjects, under one set of conditions are not necessarily comparable to those gathered by another running the same experiment.

In summary, then, most images produced through brain scanning are graphical representations of data that are the result of many choices made by the researcher during collection and analysis using possibly idiosyncratic equipment. This data is dependent on particular experimental choices and averaged over many subjects whose brain patterns could each be affected by variables unrelated to the experiment. Hence, there are many opportunities for an expert to manipulate the data to look the way an attorney wants, or, less cynically, to inadequately control for crucial variables.

Making a Reverse Inference from Group to Individual Activity Patterns

For the brain activity patterns (BOLD response) of the eyewitness in our scenario to be comparable to the group-level brain activity patterns found in the literature, there should be uniformity in the experimental design, characteristics of the subjects, statistical methods, and, optimally, the equipment used. Even if these criteria are met, the predictive value of any brain activation pattern for a particular mental event or capacity depends on the extent to which we can confidently infer the presence of a mental event from the activity patterns seen.

In our attorney's case, the ability to do this is hampered by the "reverse inference" problem, which has two parts. First, we usually cannot conclude that a cognitive process is not present just because the brain state correlated with it in prior group studies is absent [8]. It is entirely possible that other brain states besides the one found to be correlated at the group level in past studies may also produce or imply the mental state or capacity. Second, even if the individual's brain state does correlate with the brain state associated with a false memory in previous studies, we usually cannot be certain that this activation pattern is not also correlated with other mental processes or capacities [8]. Indeed, the same parts of the brain are used for many different mental processes.

Making inferences from group studies also faces intragroup problems. If there is variance in the group, an individual brain pattern that is quite different from the average may be subsumed in the averaging [9]. Indeed, no single subject may have an activation pattern that matches the averaged version, and thus group data does not tell how any individual's brain pattern correlated with a cognitive process or capacity, but only how the average activation pattern correlated with an average process or capacity. For this reason, the data needed to establish the correlation is often hidden behind the averages at the group level.

At this point, it should be made clear that there need not be perfect correlation in order for brain data to be probative regarding the presence of a mental state. Rather, we need to have a reasonable amount of confidence in the correlation being claimed, even if the brain state predicts the mental state only, say, 60 percent of the time. *Currently*, most scientists do not believe correlations between known brain activity patterns and mental states are reliable enough to make a reasonable reverse inference [8].

Criteria for Admissible Evidence

Although the legal analysis is more complicated than the following might suggest, this is a starting point for thinking about the issues. Suppose the defense attorney now wants the company's expert to testify for the jury about the findings, so that the jury might discount the eyewitness's report. The prosecution may challenge the evidence on various grounds [10]. First, according to Federal Rules of Evidence (FRE) 901(a), the evidence must be "authenticated," or, in other words, must be the product of methods that are reliable and scientifically valid, so that the court can be confident that the evidence demonstrates what the proponent claims that it does [11]. As we have seen, fMRI methods do not produce objective "pictures" of mental states, nor do the group level activation patterns normally allow a confident reverse inference at the individual level. As long as the court understands what the evidence actually illustrates, and the process used to create it, the prosecution's argument that the evidence is inadmissible should be overcome.

Secondly, if the evidence is presented along with expert testimony, it may be challenged under the *Daubert* standard (which has been codified as FRE 702) [12]. This standard requires that the evidence be scientifically valid and reliable for the

purpose for which it is being offered. Again, if the expert for the defense is trying to use the fMRI evidence to make statements about the witness's mental states or capacity with undue certainty, it should not be allowed to be presented to the jury. Some states employ the *Frye* standard in place of the *Daubert* standard. The *Frye* standard requires the science on which the testimony relies to be accepted by the relevant community, in our case the community of cognitive neuroscientists [12]. This standard is also likely to bar unjustified testimony of the kind we have been discussing.

Finally, the evidence may be challenged under FRE 401 and 403, which together require that the evidence's probative value outweigh any undue prejudice created by presenting it to the jury [13]. We have seen that the probative value of neuroimaging evidence is usually low when inferences from group data in a lab experiment are applied to an individual in a court case. The FRE 403 requires that the probative value of evidence outweigh its misleading effect. Many commentators and studies suggest that the seemingly objective nature of the "image" of the brain scan causes jurors to overestimate its probative value [14]. Thus, if the expert can convey to the jury the limited nature of the evidence, reverse inference problem included, the fMRI report may still be admitted as having some probative value.

When analyzing whether the evidence passes the FRE 403 standard, a court can consider whether other pieces of evidence address the same fact with less undue prejudicial effect [15]. If so, even if the fMRI evidence is more probative than prejudicial, the court may decide that less prejudicial evidence should be used. As Emily Murphy and Teneille Brown point out, in the case of fMRI, psychological tests and inferences from the subjects' actions are both alternatives that could speak just as well to mental state or capacity with less potential for prejudicial effect [15]. Whether Murphy and Brown are right is an empirical question that deserves further exploration.

There are ways to minimize the reverse inference problem. One method measures many more dimensions of brain activity than the typical study, leading to a very high threshold for specificity before brain patterns are said to be the same [16] and reducing the possibility that multiple mental states could be instantiated by that brain pattern. Researchers can also do scans under enough conditions with a representative population that the rate at which a brain state correlates with a mental state is better understood. However, given the large number of unique mental states that exist, and the variation in brain patterns in the population for the same general mental event, it seems a difficult task to establish correlations by this method [17].

An easier method for the individual experimenter is to scan a single subject enough times that a reverse inference can be made. This reduces the problem of high variation between subjects and the overall number of scans necessary to have the same level of confidence in the reverse inference. In our example, the company would be better off scanning the witness while she recalls a memory they know to be false (false memories can be planted in subjects with different methodologies), and

those they know to be real. This would establish the brain patterns more robustly associated with false and true memories for this unique subject.

One day, perhaps, our fundamental understanding of the brain will advance to the point where we could observe an individual's brain pattern and deduce the mental events instantiated. For now, however, our ability to read brain states is heavily dependent on an ability to make confident reverse inferences based on correlations. The use of neuroimaging research as evidence is currently a difficult enterprise that requires a court to carefully analyze the concerns outlined above. As cognitive neuroscience progresses as a field, efforts to satisfy the criteria necessary to responsibly use neuroimaging methods in court will surely expand and bear the fruit so many in the legal system desire.

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4. Brown, Murphy, 1144-1153.
5. Brown, Murphy, 1150-1153.
6. Brown, Murphy, 1144.
7. Brown, Murphy, 1150.
8. See generally, Poldrack RA. Can cognitive processes be inferred from neuroimaging data? *Trends Cogn Sci*. 2006;10(2):59-63.
9. Brown, Murphy, 1152.
10. Although the following are all federal rules, these rules have equivalents in most states, and thus the theories are largely transferable to state law. The exception is the Frye standard, found in a handful of states, which is not federal law. *See* Brown, Murphy, 1174-1178.
11. Brown, Murphy, 1164-1169.
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17. Such an effort will likely take the form of collaboration between many researchers contributing the correlations found in their studies to an international database. For an example of how this type of database might look, see http://brainmap.org/index.html.

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POLICY FORUM

Determining Brain Death—No Room for Error

James F. Bartscher, MD, and Panayiotis N. Varelas, MD, PhD

Brain death is a uniquely modern, largely hospital-based phenomenon. Without mechanical ventilation, the cessation of brain function leads quickly and inevitably to apnea and cardiac arrest, but with it, patients may be kept in the ICU with an intact heartbeat and circulation, thereby preserving other bodily functions for some time. First described by Mollaret and Goulon over 50 years ago [1], the concept of brain death (BD) has evolved to become a standard widely accepted by clinical, ethical, and legal authorities as an alternative to cardiorespiratory death. Despite its canonization across the United States, however, BD remains an amorphous and unfamiliar concept to most of the public and even to many within the health care profession.

In fact, recent data show that BD policies are still remarkably heterogeneous, even amongst some of the nation's most vaunted medical institutions [2]. If death (much like its obverse, birth) is to be viewed in the traditional manner as a singular, unambiguous event—one about which it is possible to make an objective evaluation, complete with time and date—should such variability in its declaration be acceptable? If not, should action be taken to improve matters? Doing nothing to address such inconsistencies tacitly endorses a system in which a given patient might be declared brain-dead by one hospital, but not dead by that of another facility across the street or across state lines.

We argue that urgent attention must be given to consistent application and regular review of our adopted medical and legal standards—a position which we believe will serve to strengthen research and facilitate ongoing ethical debate surrounding BD. The reasons for such standardization are many, but should include ensuring accuracy in such an irreversible declaration, securing equitable treatment under the law, and allaying public suspicion and misunderstanding about BD determination.

A Brief History of Brain Death

The development of BD as a medicolegal paradigm is a direct result of two important advances in twentieth-century medicine: the adoption of the mechanical ventilator in treatment of critical illness and the advent of successful organ transplantation.

The "iron lung," an artifact of the poliomyelitis epidemic, gave rise to a new category of illness—first described as *coma-depasse* in 23 patients who survived on the ventilator despite the lack of any respiratory effort [1]. An ad hoc committee of

Harvard Medical School proposed the first clinical definition of such an "irreversible coma" in 1968. This diagnostic framework, shown to be feasible in a 1977 prospective trial of 503 comatose patients [3], together with the dead-donor rule (vital organs should only be taken only from dead patients) [4] and growing demand for organ transplantation, propelled brain death into the legal arena. The need for standardization led to the 1981 Uniform Determination of Death Act (UDDA), which quickly became the legal precedent for the subsequent passage of state laws throughout the country. The UDDA states that

> an individual who has sustained
> 1. irreversible cessation of circulatory and respiratory functions, or
> 2. irreversible cessation of all functions of the entire brain, including the brain stem
>
> is dead. A determination of death must be made in accordance with *accepted medical standards* [5].

The first systematic attempt to establish such standard practice parameters was not made until the American Academy of Neurology's 1995 guidelines were issued [6]; an update was published in mid-2010 [7].

Variability in Policy and Procedures

The concise language of the UDDA is the key to the persistent variability in brain death policy. Firstly, it clearly defines whole brain death as legally equivalent to cardiorespiratory death. Yet, while the latter is an easily recognizable state intimately known to all health care workers as a defining moment of the human condition, the former is a much less frequently encountered state. It is palpably different from cardiorespiratory death at the bedside, often evoking discomfort and questions from even the most astute and well-meaning practitioner, questions which take on added urgency due to the finality of the diagnosis. What is the best procedure for proving cessation of all brain function? How does one confirm irreversible injury? Who should examine the patient, how many times, and over what interval?

Answers to these questions exist, but can vary with the source consulted. Do the "accepted medical standards" to which the UDDA refers truly exist? Should one first consult local hospital policy? What if that policy conflicts with national guidelines? What if no policy exists? Can apnea testing always be justified, given that it may put the patient at increased risk for hypotension and arrhythmia and allow serum carbon dioxide concentrations to increase, potentially raising intracranial pressure to lethal levels [8-10]? In cases of disagreement (e.g., about which confirmatory test to perform in any given patient who is a poor candidate for apnea testing), who adjudicates? The law is silent on these and a host of other questions, ultimately leaving it up to states, organizations, and individual physicians to decide what is meant by "accepted medical standards." Yet, studies have repeatedly shown lack of procedural consensus [2, 11] even after the publication of the AAN guidelines [6, 12].

The most recent such study evaluated BD policies of the neurology and neurosurgery programs named by *U.S. News and World Report* as the top 50 in the U.S.[2]. Out of 41 respondent hospitals, three did not even have a BD policy. Among the remaining 38, the authors reported tremendous variability in each step of the BD evaluation process recommended by the AAN. The qualifications of the examiner, how many exams and at what intervals, what clinical prerequisites should be met, how the apnea test should be conducted, and what ancillary tests could be ordered in what specific situations all varied extensively. As an example, 11 different minimum temperatures were quoted as the threshold above which the BD exam could be initiated. These findings may represent merely the tip of the iceberg, since we might suspect that even more variability exists in less prominent and nonacademic hospitals.

Individual physicians may vary still further in how they conduct and interpret evaluations [13, 14], an observation borne out in our personal experience. Common errors include failure to adequately establish the presence of a biologically plausible cause leading to irreversible whole brain death, inadequate screening for confounding substances, and performance of a confirmatory test prior to a proper clinical exam and apnea test. In one memorable case, a consulting physician had already "declared" BD and communicated this finding to the family when an astute colleague realized, upon re-examination, that the patient had not been off all sedation when initially examined. After propofol was stopped for a reasonable period, brain stem reflexes were once more detectable, which led to a change in diagnosis and confusion and distrust on the part of the agonized family. A primary goal of BD determination should be to drastically minimize (if not eliminate altogether) such false positives. As the above example illustrates, the absence of a more rigorous approach to such assessment may unacceptably compromise the accuracy of diagnosis in the irreversible determination of life and death.

Nonstandardization at the state level adds to the confusion. Although state laws are generally similar, having largely been modeled after the UDDA, significant differences persist. For example, regarding the number and qualifications of examiners, Virginia requires that 2 examiners be involved—one a specialist in neurology, neurosurgery or encephalography—while in Georgia, a single exam by any physician or registered nurse will do [15]. The statutes in New York and New Jersey require physicians to consider accommodating family wishes to continue mechanical ventilation for patients declared dead by neurological criteria, if the requests are made on religious grounds. Given the number of legal proceedings that may be affected by the timing and declaration of death (e.g., prosecution, insurance claims, organ donation), such variation undermines the idea of equal protection under the law.

Based on the reported variability in BD determination and the poor quality of empirical clinical evidence in support of current recommendations, some have voiced valid ethical concerns about the reliability, internal consistency, and even the necessity of the concept of BD [16]. A detailed review of such arguments is beyond

the scope of this paper, but it is worthwhile to note that the new evidence-based AAN guideline update published in June 2010 [7] attempts to address some of these common ethical and technical questions while promoting "uniformity in diagnosis." For example, after careful review of the literature, it found that *when AAN guidelines for determining brain death were properly followed*, no person meeting such criteria has ever been reported to recover neurological function.

This puts to rest one major concern about equating brain death and cardiorespiratory death and could help to combat the cynical belief that the idea of brain death was invented to provide transplantable organs for a worldwide donation-transplantation "industry." Such patient and family misconceptions [17] may be attenuated by a more uniform approach to the determination of BD, helping to reassure families of its credibility and rigor.

Towards Standardization

Nearly 30 years after the Uniform Determination of Death Act, and 15 years after the initial American Academy of Neurology guidelines, continued variability in the determination of BD from state to state, hospital to hospital, and, most likely, physician to physician undermines the validity of the concept in the minds of practitioners and the public alike [18]. We agree with other authors who have argued that the time has come for the adoption of a national standard [15, 19] regarding the minimum procedural requirements necessary for a determination of death by neurological criteria.

A national consensus panel representing expert opinion and knowledge of the published literature should meet regularly to review and revise national standards as necessary, given the ever-evolving state of medical science and technology. It is noteworthy, for instance, that 4 out of 5 recommendations in the recently published AAN guidelines update are level U (data inadequate or conflicting, given current knowledge) and only one is level C (possibly effective, ineffective, or harmful for the given condition in the specified population), underscoring the ongoing need for more research [7]. Accountability for the implementation of such a national standard would make the most sense at the hospital level, and an existing accrediting body such as the Joint Commission would be well-positioned to ensure compliance.

Standards and policies are only the first step, however. One way to maximize such implementation might be a certification process for those who want to be involved in the assessment of these patients at this crucial moment. A concerted educational effort, followed by simulation and a certification test, much like Advanced Cardiac or Trauma Life Support training (1- or 2-day courses that train health care professionals to successfully resuscitate patients in cardiac arrest or those who have undergone stroke or severe trauma), would create a cadre of health care practitioners proficient in BD evaluations, who could be a strong source of support for implementation of the guidelines. The development and implementation of bedside checklists could reinforce such learning while further reducing errors of omission.

We should expect and welcome ongoing debate regarding the definition of death and some have argued that, in a pluralistic society, multiple definitions should be allowed to coexist [20]. In fact, in the Japanese Transplantation Law and the New Jersey Death Declaration Law, a patient's right to accept or reject the concept of death by neurological criteria is legally preserved. We should eschew pluralism, however, when it comes to evaluating patients. A standardized, rigorous approach to BD determination is something that we owe our patients and their families—for in such a diagnosis, there is no room for correcting mistakes.

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MEDICINE AND SOCIETY

Distinguishing between Restoration and Enhancement in Neuropharmacology

Peter B. Reiner, MD

A patient comes to your office telling you that she finds herself having a bit of difficulty maintaining concentration. At 51 years old, she has a demanding job in the financial industry, is never far from either a computer or her PDA, and carries two cell phones, one for friends and family and the other for work. You give her a thorough examination (noting that she checks her PDA twice during the exam), which reveals that she is healthy and without any neurological or psychiatric dysfunction. She mentions that one of her coworkers, who is also continually bombarded by information and multitasks ferociously, went to his physician and received a drug which seemed to help him. He seems happier now and his life is less out of control. She tells you that she generally would prefer not to take drugs, but the combined demands of her job, her family, and modern life are such that she needs some kind of help, and she needs it now.

The hypothetical scenario described above is hardly uncommon. A steady stream of media reports [1] has substantially raised the public profile of the new phenomenon of cosmetic neuropharmacology—the use of drugs to modify brain function in people who have no underlying disease [2]. Even in the absence of direct-to-consumer marketing on the topic, patient requests for such drugs, particularly those that improve one or another domain of cognition, are increasingly becoming a fact of life. What does this mean for physicians?

One answer comes from the Ethics, Law and Humanities Committee of the American Academy of Neurology [3], which held a series of meetings between 2007 and 2009 to consider the question of how neurologists should respond to off-label requests by patients for neuroenhancements. Their deliberations led to a series of recommendations which can be summarized as follows:

- The prescription of drugs for neuroenhancement is not legally or ethically mandatory;
- The prescription of drugs for neuroenhancement is not legally or ethically prohibited;
- Therefore, the prescription of drugs for neuroenhancement is legally and ethically permissible.

These conclusions derive from consideration of the proper goals of medicine [4], a core domain of medical practice in which physicians are traditionally considered to be ethically obligated to act (e.g., the prevention, diagnosis, and treatment of disease). Cosmetic neuropharmacology occupies a nebulous region on the fringes of

this core domain, and thus we allow but do not require physicians to prescribe off-label cognitive-enhancement medications.

These recommendations leave the decision about prescribing enhancements firmly in control of the individual physician. The AAN committee makes one particular point that bears repeating: there are no medications specifically approved by the FDA for cognitive enhancement at the present time. It is physicians' prerogative to prescribe existing drugs off label as cognitive enhancements, but they must also grapple with all of the relevant concerns that come with off-label prescribing [5].

Providing guidance about what physicians *can* do is useful, but in the context of a busy practice, what physicians really want to know is what they *should* do. The answer, of course, depends upon the specifics of the situation, and that is why the AAN committee was correct to place the onus on physicians. What I shall do is distill some insights from the debate amongst neuroethicists regarding pharmacological cognitive enhancement in an effort to equip the practicing physician with the tools to arrive at an answer that is consistent not only with the goals of medicine but also with his or her internal moral compass.

Neuroethicists think much more about the impact of cognitive enhancement on society at large than they do about the challenges that physicians face in their day-to-day practice. Thus the four central issues that dominate neuroethical discourse are safety, noncoercion, distributive justice, and authenticity [6, 7]. While all are worthy of consideration, asking the medical profession to protect society against the social implications of cognitive enhancement seems not only quixotic but also misplaced. On the other hand, so long as cognitive enhancement is by prescription only, physicians will be the de facto gatekeepers.

Rather than recount the societal ills that may arrive with the widespread adoption of cognitive enhancement, it is worth considering the matter in the pragmatic terms that physicians require. To do so, I draw the reader's attention to a much-ignored issue that bears upon the physician's decision whether to prescribe a cognitive-enhancement drug—the distinction between restoration and enhancement. It is widely recognized that as people age, their cognitive abilities decline even in the absence of disease. Although not included in the *DSM-IV*, the nosological entity of age-associated memory impairment (AAMI) captures commonsense notions of this decline: individuals over age 50 have AAMI if they have no neurological or psychiatric disease and score one standard deviation below the mean of young adults on any test of memory [8].

Notable is the fact that this decline is specifically defined as normal—although there is a measurable change in cognitive function associated with aging, it is much the same as the panoply of age-related changes in muscle strength, endurance, and other forms of physical vigor which accompany normal aging. Prescribing a cognitive enhancement for a 60-year-old patient in good health who exhibits AAMI is restoring that individual's former function, while prescribing the same drug for a 25-

year-old, who is at the peak of his or her cognitive function, is enhancement (as the dilemma discussed elsewhere in this issue makes clear), a difference most people intuitively recognize.

The restoration-enhancement distinction becomes particularly relevant to the practicing physician in the context of safety—are the benefits afforded by the treatment sufficient to account for the attendant risks? The answer varies with the specific treatment under consideration and the overall health of the patient, and this is where the expertise of the physician comes into play most prominently. While physicians may have a great deal of experience with the risks that cognitive enhancements might have, it is harder to enumerate fully the benefits that such drugs may bring. The benefit that accrues to an aging individual experiencing age-associated memory impairment—restoration—differs from the benefit that accrues to a young adult. It is impossible to say whether one confers greater advantage than the other, but many physicians seem to find less discomfort with the prospect of restoring "impaired" memory than enhancing memory that is at its peak [9].

In some ways, the current situation, where physicians must decide for themselves whether to prescribe drugs off-label for cognitive enhancement, is at once easier and more difficult than the situation might be in the near future. At least three experimental compounds have met their phase II endpoints for age-associated memory impairment [10], and there is every reason to expect that one of these, or some similar compound, will be approved by the regulatory authorities in the coming decade. Once the rubicon of regulatory approval is crossed, physicians will find it much more difficult to deny cognitive enhancement drugs to patients who request them, at least for restoration of function eroded by AAMI. The unwelcome dilemmas that these interventions bring to the physician's practice will not be any less significant because we decide to call the intervention in people over age 50 with AAMI "restoration"; assuming this scenario plays out, prescribing cognitive enhancement for younger individuals will still be off-label use. As patient interest morphs into consumer demand, cognitive-enhancement drugs seem poised to continue to raise ethical dilemmas for increasing numbers of physicians.

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IMAGES OF HEALING AND LEARNING
Images of the Creative Brain
Glen R. Finney, MD

Creativity is a difficult concept to define. It encompasses many human endeavors, including the arts—painting, sculpting, dance, song, poetry, music, photography—and the sciences—mathematics, physics, cosmology, chemistry, geology, biology, psychology, and so on. It crops up everywhere from small innovations to acts of genius that change the way whole societies live, think, and behave. It is hard to define and harder to capture, yet creativity seems to be an essential part of human culture. Most definitions of creativity involve the element of novelty; somehow the result must be a new idea or concept (at least to the creator), generally of great perceived value or difficulty of attainment.

Graham Wallas's four-stage model of creativity is one of the most widely quoted [1]. Wallas identifies the first stage of creativity as *preparation*—a sort of prerequisite or prelude to creativity, in which the skills and knowledge required to engage in the creative act are acquired. For some activities, this preparation may take years or decades, and the information amassed can be confined to a single discipline or, as in some of the most unprecedented leaps, span disparate, even previously unconnected areas of knowledge.

Preparation shades into the second stage of creativity: *incubation*. While the creator may engage in an active search for a new answer to a question, much of this phase is performed preconsciously through the cognitive function known as parallel processing. The final phases of incubation seem to be best performed in a relaxed or low-arousal state. While only the strongest semantic connections tend to come to the attention of the conscious mind when the brain is in an excited state, relaxation may allow for weaker—which is to say, less obvious or "presemantic"—connections to rise to the fore.

The third stage is, perhaps, the briefest, but it is the key to the creative act. This is the stage of *illumination*, sometimes referred to as the "Aha!" or "Eureka!" moment. Illumination is when the aforementioned semantic connections are recognized by the conscious mind. In the third century BCE, Greek inventor Archimedes had the original "Eureka!" moment while relaxing in a bath, which served as the inspiration for his discovery: he could use water displacement to discern the volume of irregularly shaped objects, such as the crown he had been charged to discover the composition of without melting down. Popular legend has it that many other famous discoveries occurred during periods of idleness: Einstein is said to have made progress toward the theory of relativity while on the clock at a dull patent-office job;

Newton is believed to have had critical insights about gravity under an apple tree in his mother's garden; and the Nobel-Prize-winning chemist Kary Mullis reported having a breakthrough during a late-night drive down a monotonous stretch of empty highway.

Of course, it is possible to have the sensation of illumination about a connection that is actually too weak to stand, or not in fact new—a false positive, if you will. This brings us to the last stage of the creative process, *verification*, in which the product of illumination is validated, often at least in part through the creation of an artifact (e.g., an artistic work, a model, a written plan, or an equation).

What Makes a Brain Creative?

Brain scans have given us the primitive ability to measure, or at least perhaps see, the creative process at work. Carlsson et al. found cerebral blood flow differed between high- and low-creativity participants who had been separated into two groups on the basis of very high or low scores on a creativity test. The highly creative had increased blood flow in some regions during a verbal creativity task, while the lower-creativity group actually experienced a decrease in blood flow in the same regions [2]. While the dominant (left) frontal lobe was active in both groups during a primarily verbal task, blood flow to the non-dominant (right) frontal lobe increased only in the highly creative group. This may indicate more efficient but less extensive processing in the less creative group.

We know that intelligence, as measured by IQ testing, is to some degree necessary but not sufficient by itself to the creative process. Terman found that later success of children in the gifted range of intelligence quotient (IQ), at least based on the careers and later achievements they self-reported, did not demonstrate particular creativity [3]. In 1973, Guilford and Christensen used divergent thinking—the ability to break conventional thought patterns to discover a new answer—as a surrogate for creativity and compared creativity (or here, divergent thinking) to IQ. They found a triangular relation; divergence was correlated with IQ at lower IQ scores, but became less so as IQ approached 130 [4].

Some locations in the brain for some functions associated with creativity have been tentatively proposed. Feelings of illumination, for example, have been associated with right temporal lobe function in studies like Jung-Beeman's electroencephalographic observation of patients experiencing insights in problem solving [5].

Divergent thinking is often felt to be a frontal-lobe function [6]. Heilman postulates that white matter connections and general interconnectivity between disparate parts of the brain may increase the formation of novel associations and new ideas [7]. Jung et al. attempted to find links between cortical thickness and high creativity index scores assigned to a group of participants by 3 independent judges. They found that increased cortical volumes in the right posterior cingulated cortex, the right angular gyrus, and the lower left orbitofrontal cortex correlated with higher creativity index

scores [8]. Decreased cortical volumes in the lingual gyrus also correlated with greater creativity scores. While the cortical thickness results are intriguing, we do not know whether increased cortical thickness is a marker for creative potential, or a result of creative activity.

How does the classic model of the stages of creativity relate to modern findings about the neurobiological localization of function? The theoretical model predicts that, during incubation, there is increased activation of weaker semantic connections in the brain. As explained above, some of the functional neuroimaging studies showing increased non-dominant (right) frontal lobe activation in highly creative individuals, particularly those engaged in divergent thinking, may point to the right frontal cortex as a "center" for incubation.

Illumination has, surprisingly, the most solid localization of the classic stages of creativity, with several studies converging on the non-dominant (right) temporal lobe as the main region of the brain activated during moments of recognition of novelty and the illumination experience. Since the verification stage requires critical thinking and analysis, dominant (left) frontal lobe function may be important to that part of the process.

Final Thoughts

While we are just beginning to discover the neuroanatomical and neurochemical correlates of creativity, we are still at a very early stage of understanding what those correlations mean. We do not know whether the distinct qualities of the brains of highly creative people are the source of their creativity or a result of their creative activity.

One might speculate about what the world would be like if we could predict creativity based on brain structure and function. I think it would be foolish and dangerous to try to steer people into creative and noncreative tracks of endeavor based on brain correlates—indeed, such a process might diminish the creative potential of our population. Some people may be able to develop or train to become creative, and perhaps come up with important ideas that would be different from those of individuals predisposed to be naturally creative.

I think the best use for such an ability would be to help develop training strategies for those who have difficulty engaging in creative or divergent thinking. If we understand the brain-behavior relationships in creativity, we will be better able to encourage and facilitate it.

I believe strongly that we should foster creative ability in everyone. I am reminded of a story my mentor, Ken Heilman, tells, of a developmentally delayed man whose job it was to sweep up on a court. One day, he devised a new and improved way to sweep the court and was well pleased with his discovery. While this creative act may not change the world, it bettered this man's life. So may we all benefit from understanding and fostering creativity in our lives.

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OP-ED

Perspective Taking and Advance Directives

Donna T. Chen, MD, MPH

I have often wondered if we are asking patients the right question when they create advance directives. We generally ask them to focus on their own preferences and values in deciding what medical treatment choices should be made if they lose the ability to make these decisions for themselves. Then we rely heavily on surrogates to make the real-time decisions because the advance directives are not specific enough or require interpretation. And we expect their choices to reflect what the patient would choose.

Yet research consistently shows a gap between what patients say they want, and what surrogate decision makers say the patients would want. For example, a 2006 review suggests that surrogates incorrectly predict patients' end-of-life treatment preferences in one of every three cases [1]. Additionally, surrogates experience significant burdens when making health care decisions for others, particularly when they are uncertain about, or in disagreement with, what they think the patient would have chosen [2, 3].

One way we understand this is to say that surrogate decision makers do not know patients' preferences, end-of-life choices, or values as well as we thought they did and think they should. Remedies generally focus on encouraging more explicit conversation between loved ones. But this too has proven disappointing. Prior discussion fails to improve surrogates' predictive accuracy [1].

How then might we improve this situation so that patients' and surrogates' decisions line up better? Recently, I began to wonder if neuroscientific findings in cognitive, social and moral decision making might offer a different solution. I was thinking specifically about findings which suggest that decision making aimed at fulfilling a self-directed desire activates different neural networks on fMRI imaging of the brain than morally guided decision making that attends to features of interpersonal relationships. This led me to wonder what might happen if we explicitly asked patients to think about their surrogate decision makers as part of the advance care planning process and to make decisions about future treatments based on what they *would want their surrogate decision makers to decide for them*, rather than solely on what they would want for themselves. Would changing what we ask patients to consider in this regard activate different parts of the decision-making mind? Would it lead to decisions that line up better with what surrogates think they should decide for patients? Would it help close some of the gaps left after advance care planning discussions take place?

Asking individuals to make advance care planning decisions for themselves by putting themselves into the shoes of their surrogates making decisions for them may seem terribly convoluted. It may seem wrong-headed. It certainly moves us some steps away from an autonomy-based model of advance care planning that focuses largely on ensuring that one's own preferences and values are carried forward into a future when one is unable to express them.

What in the neuroscientific literature led me to wander down this path? Findings in three areas caught my eye. First, much about complex decision making occurs outside the realm of consciousness, including mental activities associated with valuing and weighing various alternatives [4, 5]. Indeed, enough good decision making seems to occur "unconsciously" to suggest, albeit controversially, that we harness the power of the unconscious mind to help us make better decisions [6, 7]. Whether or not it is preferable to optimize the role of the unconscious mind, the fact that at least some portions of valuing are not easily accessible to verbal or written communication presents a potential limit to how much explicit discussion is even possible. It may be that there is no way to communicate in writing or orally all of what is important to us. Relying, then, on more or better conversation between patient and surrogate has limited utility.

Second, findings from theory-of-mind and perspective-taking studies suggest that thinking about oneself and about a close other from each other's perspectives (e.g., I think this about me, Mary thinks this about me, I think this about Mary, Mary thinks this about herself) activates overlapping yet distinct neural networks [8]. The perspective one is asked to take matters to the brain even when the topic is the same. Individuals also recruit different neural networks when predicting future intentions of others that involve just one person satisfying his or her own particular goal versus future intentions to involve others in satisfying the goal ("social intentions") [9]. Thus, thinking about a future activity that involves just me reveals itself on fMRI differently than doing so for an activity that involves me and Mary. One wonders then, what the results would be if we asked individuals to think not about what they would choose for themselves in advance care planning but instead about what they would want someone else to choose for them.

Third, although all complex decision making necessitates the coordination of multiple mental processes, morally guided decisions tap into a distinguishable set of neural networks that do not appear to be activated by decisions based merely on personal desires [10]. Thus, it seems reasonable to wonder if asking individuals to think about what they would want for themselves in the context of advance care planning is more like asking them to think about fulfilling a personal desire or more like asking them to make a morally guided decision. Why does it matter?

Considering what you want for yourself would appear to necessitate neither perspective-taking nor the social and moral aspect of decision making. It could easily involve morally neutral, self-referential components alone. Indeed, the autonomy

model underlying advance care planning generally encourages individuals to focus on their own preferences and values.

Yet these decisions *should* activate both the moral and social mind, since asking someone else to take responsibility for making decisions on one's behalf, particularly of the nature entailed in end-of-life and other significant treatment decisions, is a deeply moral, socially embedded act. The decision about which instructions to leave for someone else to carry forward *should* be viewed in one's mind as a morally guided and socially intended decision, rather than one that merely fulfills private, self-directed values.

Certainly others, after careful normative and empirical analyses, have suggested that these relational features should be attended to more closely [11-13]. And surely it is of no surprise to anyone who has served as, or worked with, a surrogate decision maker that the relational and moral dimensions are there on the back end, when these individuals are asked to step into the shoes of another to carry forward wishes or to make significant treatment decisions. Neuroscientific findings would merely add the possibility that bringing the relational and moral aspects of surrogate decision making into the advance care planning process might more reliably activate social and moral decision-making networks up front, presenting to the mind a fuller picture of what patients actually should plan for.

Of course, the impact that bringing these social and moral aspects into advance care planning might have on the process, experiences, and outcomes of both advance care planning and surrogate decision making warrants study. There is no guarantee that bringing in these aspects up-front would necessarily improve things.

Indeed, it may not change anything. Just because different parts of the brain light up on fMRI does not mean that these differences are scientifically, functionally, or normatively significant [14-16]. That is to say, the lighting up of different parts of the brain during decision making may not change the decisional outcomes; patients' decisions may continue to align only so well with their surrogates'. Or perhaps, in spite of not being directed to do so, we might find that minds of individuals engaged in advance care planning *already* engage in perspective-taking, social intending, and moral decision making. After all, one could construe the mandate to discuss such decisions with loved ones as already bringing their perspectives into the mental process of advance care planning. After such discussions, how could individuals *not* recognize that this other person would be intimately involved in carrying out their advance care plans? And yet, the questions posed on most advance care planning documents direct individuals to think only of their own values and preferences. And maybe this is an important safeguard against losing oneself in the immensity of the social and moral complexities.

But if we have to see it to believe it (or as some might say, believe it to see it), let's get on with it and see what we see when we explore the neuroscientific underpinnings of advance care planning and surrogate decision making. I suspect we

will find that different decision-making networks are involved when we ask individuals to think explicitly about their surrogate decision makers as part of the advance care planning process and to make decisions about future treatments based on what they *would want their surrogate decision makers to decide for them*, rather than solely on what they would want for themselves. And, as long as we are careful not to over- or misinterpret our neuroscientific findings, it's worth taking a look.

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