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INTRODUCTION

It was my great pleasure to give the Tanner Lecture on Human Values at Clare Hall, Cambridge University, in October 2007. In this lecture, I focused on the landscape of ethical, legal, and social challenges in neurosciences—"neuroethics"—using brain biomarkers for behavior and pathology as models. That lecture and this chapter use predictive information as a foundation to explore the deep intersections between ethics and neuroscience, and the values and wisdom of Grace and Obert Clark Tanner, whom we honor through the annual Tanner Lecture events. The Tanners were strong believers in intellectual freedom, in human joy, and in the pursuit of knowledge both for its own inherent value and for the practical benefits it may bring to people. The modern field of neuroethics embodies these values, and it serves well to frame a discussion of the benefits and risks—and many aspects of the ethics overall—of predicting brain health and disease using technological means.

I will begin this chapter with an introduction to the modern discipline of neuroethics. Thereafter, I will apply neuroethics to the specific discussion of prediction and brain imaging. The conclusion will focus on special *neuro*challenges in our society today and prospects for moving and valuing *neuro*innovation ahead.

Neuroethics: A Modern Context

Borrowing from the writings of Professor Albert Jonsen and Van Rensselaer Potter (Jonsen 2003), I have defined neuroethics as *"a discipline that combines neurobiological knowledge with knowledge of human value systems"* (2006a). It also has been given definition by cognitive neuroscientists such as Professor Michael Gazzaniga, who has written, *"Neuroethics is more than just bioethics for the brain. [It] is the examination of how we want to deal with the social issues of disease, normality, mortality, lifestyle, and the philosophy of living informed by our understanding of underlying brain mechanisms. It is—or should be—an effort to come up with a brain-based philosophy of life"* (2005), and from champions of neuroscience such as William Safire of the Dana Foundation, who commented, *"Neuroethics [is] the examination of what is right and wrong and good and bad about the treatment of, perfection of, or unwelcome invasion of and worrisome manipulation of the human brain. . . . It deals with our consciousness—our sense of self—and as such is central to our being"* (in Marcus 2002). These convictions bring all people interested in this topic to a common message:

neuroethics is for everyone—theoreticians, philosophers, researchers, clinicians, lawyers, engineers, and, in fact, all citizens of science.

Why do we need these definitions and a discipline dedicated to their examination? Why would *Nature* publish an editorial titled "Neuroethics Needed" (2006)? Why would Cambridge University professor Barbara Sahakian, others, and I establish an organization called the Neuroethics Society (http://www.neuroethicssociety.org)? The answers lie in the deep thought about mind and brain that dates well back to the ancient philosophers, to discoveries of neurologists and physiologists of the seventeenth and eighteenth centuries, to the phrenologists of the nineteenth, and to events of human abuses in research in the early twentieth century (Marshall and Fink 2003; Illes and Bird 2006).

One key event in history, for example, is the Nuremberg War Crimes Tribunal following World War II (Weindling 2001). Another is the Tuskegee Experiment in Alabama during which poor black men with syphilis were left untreated for the benefit of later neuropathological studies of the disease. Such a legacy of human abuse has not only shaped our thinking but fundamentally transformed ethical behavior within the discipline (Roy 1995).

Much work has already been done over the past three decades to explicitly create bridges between the two disciplines of neuroscience and ethics. This has been achieved through work of the International Bioethics Council in 1996, for example, and of the U.S.-based Society for Neuroscience's former Social Issues Committee, currently the Dialogues Series.

We are in a new era now, however. Bridges are not enough. With the explosion of methods for probing human thought in health and disease, a true unity of ethics and neuroscience is needed to provide the full range of the moral and intellectual space for decision making.

This was a call first formalized at a meeting, "Neuroethics: Mapping the Field," in 2002 in San Francisco, during which Mr. Safire made the remarks to which I referred earlier. A recent study of publications in the peer-reviewed literature by Lombera and Illes (2008) provides evidence that his challenge to the professional community is being met. Growing attention to modern neuroethics is signaled by significant increases in the number of papers, journals publishing them, and countries engaged since the 2002 landmark year. The meeting also gave the discipline four first pillars upon which to build a future and to have an enduring impact:

- education through dissemination of information

- brain and the self
- brain and social policy
- brain and clinical practice

The Lombera and Illes study shows that the entry point into neuroethics is initially in the area of clinical practice, the focus of the greatest number of publications. The study further demonstrates that rates of publications on the theme of social policy, the next focus, are highly correlated with economic investment in science and technology in the respective countries.

Who are the people engaged and publishing in neuroethics? Drawing upon the writing of Professor Daniel Wikler (1997), one might view "neuroethicists" both as scholars and as reformers. The *scholars* look for uncertainties and challenge them in a value-free perspective. The *reformers* move issues forward, such as patients' rights—especially those with limited decisional capacity—and just access to and cultural acceptability of innovations in health care. Data from the Lombera and Illes study suggest that these hybrid scholars and reformers are emerging both in the developed and in the developing world. It is the special status of the brain as the integrating machinery of who we are as persons, with identities, personal capacities, and convictions, that brings neuroethicists together in a borderless pursuit of answers to questions in brain research and clinical neurological medicine of *what can be done,* and *what ought to be done.* This special *neuro*challenge is reflected in the increasing capacity to predict disease and behavior, and indeed, to peer into the brain, as described next.

Predictions, Risks, Certainties

I would like to examine three types of predictive information. Predictive information gives measures of (1) risks with relative certainty: certainty at least to the extent that the sensitivity of the test and its specificity to a specific disease can be calculated with some degree of accuracy; (2) risks with relative uncertainty: uncertainty in that environmental conditions heavily interface with biologic ones so that even the best calculations of specificity and sensitivity are difficult to interpret; and (3) information whose meaning is presently uncertain: specificity and sensitivity are unknown at the present time.

The theme of uncertainty was captured in the journal of the European Molecular Biology Organization, in an article by Tannert, Elvers, and

Jandrig (2007). Fundamental questions posed by Immanuel Kant about knowing, doing, hoping, and being are beautifully visualized by these authors as gradations of knowledge and ignorance in their schemata of personal choice. On this continuum illustrated as an "igloo," an absence of knowledge, or "closed ignorance," results from rejecting or ignoring available evidence, sometimes as a measure of self-preservation or survival (recall Galileo's quest for survival). Changes in attitudes can transform closed ignorance into open limitations in knowledge, even in the face of objective or epistemological uncertainties and ongoing gaps in information. The potential for this transformation underlies the position that research is a moral duty.

For research on predicting brain function, we rely heavily on surrogates. Recall a classic film from the 1960s called *Charly* (ABC Pictures, 1968), a screenplay based on the book *Flowers for Algernon* (Keyes 1959). The film portrays a mouse—Algernon—whose intelligence as measured by maze running is improved significantly by an experimental neurosurgical procedure. The tremendous success of the mouse predicts a great improvement of intelligence to near-genius levels in a developmentally delayed protagonist, "Charly," who undergoes the same procedure in an N of 1 study. The eventual decline of Algernon's stellar performance accurately predicts a return to limited intelligence in this poignant tale of Charly.

Aside from mouse models provided to us by a sometimes visionary entertainment industry, what other tools for prediction do we have?

The strength of clinical observation was brought to us by Professor Alexander Luria, for example, whose post–World War II studies of traumatic brain injury formed the basis for fundamental theories of brain function. His theories led to methods for the remediation of focal brain lesions and to a systematic approach to brain and cognition later known as the core discipline of neuropsychology (Luria 1978).

Genes are predictive, naturally, representing, as Hariri and Weinberger (2003) would say, the GO square on the Monopoly Board of life. Modern neuroscience has given us many different tools for prediction by capturing the electrical and metabolic activity of the brain through imaging. These include electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and its single-photon variant (SPECT) (reviewed in Illes and Racine 2005). A most recent technique is the ubiquitous functional magnetic resonance imaging (fMRI) that provides measures of hemodynamic—blood flow—change in selected regions of the brain as they become oxygenated in response to specific stimuli. The

results are activation maps reflecting the difference in brain states between control and experimental conditions, usually represented as group averages although increasingly in individuals, as we will see shortly.

I will use fMRI as my primary case modality in this chapter (Illes 2004b), but different kinds of markers of prediction have much in common with this particular neurotechnology. In fact, we are brought back both to the concept of uncertainty and to what I have called the *Flowers for Algernon Problem.* Simply stated, the problem describes variability in what a surrogate can predict. It may closely track performance, or less successfully predict decline or improvement that is not concurrently or perhaps ever manifested. There are implications in these latter cases, for science and for the selection of populations for research. Once predictions can be made reliably in the clinical setting, the challenges involve the timing of disclosure to patients, allocation of precious resources, and even maintenance of intervention when the surrogate may predict impending therapeutic failure.

With this background, let us now turn to specific examples. We will begin with risk and relative certainty as exemplified by certain forms of neurodegenerative disease.

Valuing Risk with Relative Certainty

Discovery of the Huntington's gene in the mid-1980s was clearly a landmark for neurodegenerative disease research (Gasser and Meitinger 1993; Harding 1993) and set in motion a cascade of gene-hunting activity that has had a profound impact on the understanding of a wide range of diseases and brought with it a new hope for cures (Eldridge 1980; Gasser and Meitinger 1993; Greenstein and Bird 1994; Martin 1994).

Over the past decade, tremendous resources have been allocated to modern methods for biomarking disease with imaging. Alzheimer's disease (AD) has been a major focus. Numerous studies have been published using functional imaging as a marker for AD, and millions of dollars have been invested in public and private research. One partnership known as the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www.loni.ucla.edu/ADNI) is a five-year public-private endeavor to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to mark and measure the progression of mild cognitive impairment and early Alzheimer's disease. Results of studies from this cohort and others suggest, for example, that disrupted connectivities between regions of the brain such as the posterior

cingulate and hippocampus may mark an impending breakdown of memory and other cognitive functions in even the most mild stages of the disease (Greicius et al. 2004; Bookheimer et al. 2000; Burggren and Bookheimer 2002; Hale et al. 2007).

As we learn more about the genetics of frontotemporal dementia (FTD), the second most frequently occurring neurodegenerative disease, we are also gaining knowledge from imaging. Honig, Bell, and Chin (2003), for example, demonstrated decreases in blood perfusion and metabolism in frontal and mesiotemporal regions in early FTD that exceed the decreased function predicted by the atrophy in these regions evident on structural MRIs.

What are some of the considerations as we move forward to understand and predict dementia-causing diseases of the brain, especially in individuals who today are seemingly robust and healthy?

In the context of medical and policy implications, we must appreciate that the entry points of this category of brain disease are variable and continuous, and that cognitive, linguistic, and personality factors change over time and according to the biology of the degeneration. The timing of the onset of disease is a major factor, certainly whether the disease will manifest noticeably in mid- or late life, as well as the projected rate of decline. Sensitivity and specificity also are clearly key. Reflect on the Algernon problem: How often can a technique capture disease early and with what accuracy? How often does it miss or yield a false positive? Will we have new clinical subtypes requiring redefinition of the categories of diseases or the diseases themselves once the technology is fully validated? How will different types of therapeutic interventions—drugs, devices, stem cells—be received by patients and providers in the absence of a cure? How will tolerance for toxicity interface with vulnerability, and at times desperation? What strategies can be introduced for prevention? For privacy protection? In genetics, the influence of one gene on multiple phenotypic traits is a known risk (Wachbroit 1998). There is every reason to be proactive and to anticipate both comorbidities as well as the potential for pleiotropies for all types of predictive information—imaging or otherwise.

All these questions further come into play as the professional community is mindful of distributive justice and access to health care. These challenges exist in the face of health care disparities that have been a hallmark of societies in which universal medical care has not yet been realized, and even in those with universal health care but in which privatized medicine is emerging as a competitive force.

Given these medical, social, and policy factors, how then do we view and value predictive information for neurodegenerative disease? We must consider the information in the context of life and end-of-life planning, benefits versus risks, hope and hopelessness, stigma and discrimination, behavioral and psychological change—either for better self-care or worse.

It is a reasonable hypothesis that the cognitive domain of these illnesses will affect a person's desire to know his or her risk of disease. Although we have not witnessed a race to know in people at risk for Huntington's disease and Alzheimer's disease, a shift in this pattern may be seen in the future for FTD. As fundamental aspects of personhood, personality, and the ability to inhibit inappropriate behavior are affected in this form of neurodegenerative disease, early knowledge may lead directly to heightened attention to and prolonged strategies for self-monitoring and maintenance of executive function.

Risk with Relative Uncertainty

With advances and increasingly sophisticated neurotechnology, there is a push in many Western countries to screen children earlier than ever before, even when there is no overt symptomatology for behavioral abnormalities or learning difficulties. There are good markers now for attention deficit hyperactivity disorder (ADHD), for example, with notable disruptions in frontal and parietal-striatal regions associated with mental tasks such as rotating complex objects (Silk et al. 2005; Vance et al. 2007). Given the significant influence of the environment on the manifestation of this disorder in children, however, predicting the course of attention deficit hyperactivity disorders is more difficult. This challenge becomes even greater as justification is sought for prescribing medication. ADHD prescription medications are rampant in primary and secondary schools in North America, in the UK, and across Europe, as studies by Ilina Singh from the London School of Economics, for example, have described (2007).

Even more difficult is how we will use imaging information that predicts emotional intelligence and reasoning, as shown in a study by Reis and colleagues (2007), or of risk-taking behavior in adolescents, as shown in a study by Galvan and her colleagues (2007), with activation of the nucleus accumbens correlated with the perceived consequences of engaging in risky behavior.

What are the medical, social, and policy implications of such predictive imaging in our youth? At least these: sensitivity and specificity, certainly definition or absence of immediate and long-term therapeutic goals, and,

beyond distributive justice, the sheer existence of appropriate resources to respond to the kind of new information that we may be gathering and ultimately allocating to it. The human value questions are profound. They span interactions between parents and their children, children and their environment, "neuroprofiling" and labeling, stigma, and altered behavior or even fatalism, especially in adolescents at risk for sociopathy and suicide (Brook et al. 1992; Sass, Herpertz, and Houben 1994; Blair 2001; Illes and Raffin 2005).

Good solutions to these difficult questions will be found with cautious approaches to information gathering, and to truly robust methods for dissemination and translation of knowledge. This includes potentially a new generation of "neuroeducators," a term coined by Howard Gardner and his colleagues (Sheridan, Zinchenko, and Gardner 2006) to describe experts needed to manage the complex and unique information emerging at these crossroads. This is a proposal of great merit and potentially a model for other applications as well.

True Uncertainty

There is information we can gather using brain imaging today that I believe is still of great uncertainty. I would like to describe two examples: one from the clinical realm and one from the nonmedical world.

We turn first to experimental uncertainty in the medical realm. Landmark studies have been performed by Cambridge University professor Adrian Owen, a 2007 Tanner Lecture respondent, and his colleagues both in Europe and in the United States on patients in limited states of consciousness. These studies have shown similar brain fMRI activation patterns in the somatosensory, temporal, and parietal cortices between healthy persons and brain-injured patients responding to stimuli such as familiar voices and imagined navigation through familiar space (Schiff et al. 2005; Owen et al. 2006).

Although much remains to be understood about these data, as advances are made in this domain of research, we may learn that consciousness may not be as impaired or immutable after brain injury as traditional clinical tests and observation suggest. Until then, the medical and policy questions that surround these studies and their implications are considerable. First, in thinking about brain injury, unlike neurodegenerative diseases, the entry point is acute and discrete. The etiology of injury is heterogeneous; although definitions (Royal College of Physicians 2003) and degrees of minimally conscious, persistent vegetative states vary, an

international agreement on diagnostic criteria is still elusive. This uncertainty raises questions about how neuroimaging results will complement clinical assessment. The implications for intervention and for prediction of recovery and outcome remain to be determined.

The human values questions, and therefore the benefits of imaging in this context, are challenged by the still relatively early state of studies. Moreover, we must anticipate that the specificity of neuroimaging findings may lead to a new nosology of disease and conscious intention, and that individual values and culture may further shape how we view intentionality as well as altered states of consciousness.

To this end, there is a clear need for more data and reports of them on large patient numbers. Perspectives from family and physician stakeholders from a diverse range of ethnicities are needed to inform the cultural sphere. Caution and restraint are needed, despite any iatrogenic risks that caution brings to the fore. This innovation touches people who are among the most vulnerable in our society.

We now turn to uncertainty in the nonmedical realm. Groundbreaking imaging neuroscience also has the potential to predict conscious intention under conditions of brain health. In an increasingly wide range of applications, activation patterns have been reported to be associated with phenomena such as moral and existential judgments (Greene et al. 2001; Moll, Oliviera-Souza, and Bramati 2002), choices by people with introverted and extroverted personalities (Canli et al. 2001), decision making or "neuro-economics" (De Martino et al. 2006), and truth telling versus lying (reviewed in Illes 2004a). The greatest medical risk in these research studies that are, by all known measures, experimentally benign and noninvasive is a finding of a clinically important abnormality that may have an immediate or potentially future health impact. The data suggest that these serendipitous findings should be expected in 2-8 percent of the population recruited to imaging studies as normal controls (Kim et al. 2002; Illes, Rosen, et al. 2004). How to manage these findings is not an insignificant problem (Illes et al. 2006). Many imaging investigators are Ph.D.-trained, not M.D.-trained, and many studies take place in laboratories not affiliated with medical centers. Therefore, duty of care, clinical incidence, and the right to know and not know—a true Pandora's box of ethical and moral questions—are important variables in the analysis of this issue (Grossman and Bernat 2004; Illes 2006b).

The social and policy considerations are equally significant and rich. Most important is the reductionist notion of framing human experience

or "personhood" in biological terms (Roskies and Petersen 2001; Illes and Racine 2005). Next are the risks of premature, overambitious, or frank misuse of technology for classifying people based on brain patterns acquired in laboratory settings that can only marginally mimic the real world (Illes, Racine, and Kirschen 2006). These patterns may conceivably—eventually—become predictive of socially dysfunctional though not necessarily pathological behaviors. This could become a particularly vexing problem if capabilities for covert monitoring appear on the horizon using infrared imaging or other methods, and do not actually require human responses or consent.

There are inherent risks to the credibility of the research enterprise if it moves too fast in the nonmedical world. There are risks to social structures as society hungers for a biology of human compatibility between and within genders for lifelong partnership, guilt and innocence, moral fortitude, and even trustworthiness among its political and financial leadership. There is a great deal to think about.

Be that as it may, integrated, organized brain phenomena reflect the plasticity of the brain and its ability to override genetic hardwiring. Combined methods will maximize the meaningfulness and certainty of our measurements, and for that we have imaging genomics. Imaging genomics enables a direct assay, like fMRI, to identify phenotypes in the brain related to functional polymorphisms in genes likely important for human behavior and neuropsychiatric illness (Pezawas et al. 2005). We can fully expect the still evolving combined-modalities approach to be extremely powerful and likely the future for brain science, neurology, and neuropsychiatric disease. We must prepare not only for the information but also for the truly revolutionary knowledge that imaging and other technological innovations are likely to yield. As we move from *information* to *knowledge,* therefore, the pursuit of ethics guidelines and frames becomes ever more important in the context of modern brain research.

Conclusion: The Neuroethics Challenge

As the late Peter Lipton remarked in his response to my Tanner Lecture, "'Knowing' is not a unitary phenomenon as it cannot be equated with 'understanding'" (2007). Dedicated ethics work is needed right alongside neuroscience to promote understanding, and understanding within the context of value systems. This, in fact, defines the neuroethics challenge. To this end, scholars from a wide range of disciplines in the natural and social sciences must join together to do the following:

- Identify pragmatic starting points at the intersection of neuroscience and ethics. This will be achieved by integrating culturally and socially relevant neuroethics into neuroscience training programs worldwide.
- Align the disciplines closely for ongoing interaction. This will be achieved by encompassing advances in neuroscience into programs that encompass philosophy of mind, health law, sociology, and medical anthropology.

These measures, along with the growth of a dedicated new professional organization and funding for both theoretical and empirical research, can yield approaches to and resolution of difficult ethical challenges pertaining to research on brain health and brain disease through a negotiated scientific-social process.

Unlike the natural progression from basic research to translational neuroscience, the transition from science and traditional health care to the commercialization of personal genomics and personal "brainomics" (Kennedy 2003, 2006) is less well worked out. The voice of an increasingly literate and culturally diverse public is critical to advancing this process, and there is ample scientific evidence that the public wishes to be involved (Gaskell et al. 2005). Empirical studies are needed to determine how best to leverage all the strengths of the community while, in parallel, the professions model a new kind of responsiveness and responsibility for thinking beyond the boundaries of scientific intent. The wide use of drugs for off-label purposes provides ample precedent for proactive considerations of this nature. For the entrepreneurial community, initial validity, quality control, and privacy are foreground challenges, especially as innovation is advanced by small businesses with uncertain longevity (Eaton and Illes 2007). In the long term, sustained validity, changing doctor-patient relationships, and off-label and unintended uses are at the heart of neuroethics analyses of these matters. For any term, guidelines are absolutely needed to protect the most vulnerable from falling prey to aggressive advertising campaigns (Illes, Kann, et al. 2004).

The media are closely tracking both the increase in numbers of peer-reviewed studies and the commercial applications involving neuroimaging of all types, combined with and independent of genetics. The press brings enormous value to the scientific enterprise. Sometimes, however, it throws caution to the wind (Racine, Bar-Ilan, and Illes 2005). The well-being and welfare of people are at stake when certainty is overstated and

tempered, realistic limitations are not conveyed. It is incumbent on the scientific community to work more closely with both the press and the public to ensure scientific accuracy and the cultural relevance of how new findings about the brain are disseminated. It is incumbent on the media to reconfigure publication strategies so that they favor accuracy above all, even in the face of the pressures of publication deadlines.

Obert Clark Tanner took inspiration from Socrates in his belief that the *"unexamined life is not worth living."* Neuroscience goes forth with its many methods and at an extraordinarily rapid rate of discovery of both already examined phenomena needing more inquiry as well as the "previously unexamined." With neuroethics at our side, we can embrace new ways of thinking about these discoveries. Within its framework we have a rich array of tools:

- We must think critically about the means with which we pursue knowledge about the brain.
- We must assess when uncertainty converts to information, information to knowledge, and value that knowledge in culturally relevant ways.
- We must integrate that new knowledge into our internal and external schema.
- We must ethically examine the contours of life that have previously been out of reach.

Notes

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References

Blair, R. J. 2001. "Neurocognitive Models of Aggression, the Antisocial Personality Disorders, and Psychopathy." *Journal of Neurology, Neurosurgery, and Psychiatry* 71, no. 6: 727–31.

Bookheimer, S. Y., M. H. Strojwas, M. S. Cohen, A. M. Saunders, M. A. Pericak-Vance, J. C. Mazziotta, and G. W. Small. 2000. "Patterns of Brain Activation in People at Risk for Alzheimer's Disease." *New England Journal of Medicine* 343, no. 7: 450–56.

Brook, J. S., M. Whiteman, P. Cohen, and J. S. Tanaka. 1992. "Childhood Precursors of Adolescent Drug Use: A Longitudinal Analysis." *Genetic, Social, and General Psychology Monographs* 118, no. 2: 195–213.

Burggren, A. C., and S. Y. Bookheimer. 2002. "Structural and Functional Neuroimaging in Alzheimer's Disease: An Update." *Current Topics in Medicinal Chemistry* 2, no. 4: 385–93.

Canli, T., J. D. Desmond, E. Kang, J. Gross, and J. D. E. Gabrieli. 2001. "An fMRI Study of Personality Influences on Brain Reactivity to Emotional Stimuli." *Behavioral Neuroscience* 114, no. 1: 33–42.

De Martino, B., D. Kumaran, B. Seymour, and R. J. Dolan. 2006. "Frames, Biases, and Rational Decision-Making in the Human Brain." *Science* 313, no. 5787: 684–87.

Eaton, M. L., and J. Illes. 2007. "Commercializing Cognitive Neurotechnology: The Ethical Terrain." *Nature Biotechnology* 25, no. 4: 1–5.

Eldridge, R. 1980. "Clinical Neurogenetics: Needs versus Resources." *Neurology* 30, no. 8: 860–63.

Galvan, A., T. Hare, H. Voss, G. H. Glover, and B. J. Casey. 2007. "Risk-Raking and the Adolescent Brain: Who Is at Risk?" *Developmental Science* 10, no. 2: F8–F14.

Gaskell, G., E. Einsiedel, W. Hallman, S. H. Priest, J. Jackson, and J. Olsthoorn. 2005. "Communication: Social Values and the Governance of Science." *Science* 310, no. 5756: 1908–9.

Gasser, T., and T. Meitinger. 1993. "Neurogenetics. Part 3: New Developments in Gene Mapping and Diagnosis." *Nervenarzt* 64, no. 6: 353–59.

Gazzaniga, Michael. 2005. *The Ethical Brain*. New York: Dana Foundation Press.

Greene, J. D., R. B. Sommerville, L. E. Nystrom, J. M. Darley, and J. D. Cohen. 2001. "An fMRI Investigation of Emotional Engagement in Moral Judgment." *Science* 293, no. 5537: 2105–8.

Greenstein, P., and T. D. Bird. 1994. "Neurogenetics: Triumphs and Challenges." *Western Journal of Medicine* 161, no. 3: 242–45.

Greicius, M. D., G. Srivastava, A. L. Reiss, and V. Menon. 2004. "Default-Mode Network Activity Distinguishes Alzheimer's Disease from Healthy Aging:

Evidence from Functional MRI." *Proceedings of the National Academy of Sciences* 101, no. 13: 4637–42.

Grossman, R. I., and J. L. Bernat. 2004. "Incidental Research Imaging Findings: Pandora's Costly Box." *Neurology* 62, no. 6: 849–50.

Hale, T. S., S. Bookheimer, J. J. McGough, J. M. Phillips, and J. T. McCracken. 2007. "Atypical Brain Activation during Simple and Complex Levels of Processing in Adult ADHD: An fMRI Study." *Journal of Attention Disorders* 11, no. 2: 125–40.

Harding, A. E. 1993. "The Gene for Huntington's Disease." *British Medical Journal* 307: 396–97.

Hariri, D., and D. R. Weinberger. 2003. "Imaging Genomics." *British Medical Bulletin* 65: 259–70.

Honig, L. S., K. Bell, and S. S. Chin. 2003. "Frontotemporal Dementia." *Science of Aging, Knowledge, and Environment* 13.

Illes, J. 2004a. "A Fish Story: Brain Maps, Lie Detection, and Personhood." In *Cerebrum: Special Issue on Neuroethics.* New York: Dana Foundation Press.

———. 2004b. "Medical Imaging: A Hub for the New Field of Neuroethics." *Academic Radiology* 11, no. 7: 721–23.

———. 2006a. "Neuroethics, Neurochallenges: A Needs–Based Research Agenda." Paper read at the Society for Neuroscience, Atlanta, Georgia, October 13–18.

———. 2006b. "On the Contents of Pandora's Box of Incidental Findings in Brain Imaging Research." *Nature, Clinical Practice, Neurology* 2, no. 2: 60–61.

Illes, J., and S. J. Bird. 2006. "Neuroethics: A Modern Context for Ethics in Neuroscience." *Trends in Neuroscience* 29, no. 9: 511–17.

Illes, J., D. Kann, K. Karetsky, P. Letourneau, and T. A. Raffin. 2004. "Advertising, Patient Decision–Making, and Self-Referral to CT and MR Imaging." *Archives of Internal Medicine* 164: 2406–8.

Illes, J., M. P. Kirschen, E. Edwards, L. R. Stanford, P. Bandettini, M. K. Cho, P. J. Ford, G. H. Glover, J. Kulynych, R. Macklin, D. B. Michael, and S. M. Wolf. 2006. "Incidental Findings in Brain Imaging Research." *Science* 311, no. 5762: 783–84.

Illes, J., and E. Racine. 2005. "Imaging or Imagining? A Neuroethics Challenge Informed by Genetics." *American Journal of Bioethics* 5, no. 2: 5–18.

Illes, J., E. Racine, and M. P. Kirschen. 2006. "A Picture Is Worth 1000 Words, but Which 1000?" In *Neuroethics: Defining the Issues in Theory, Practice, and Policy,* edited by J. Illes. Oxford: Oxford University Press.

Illes, J., and T. A. Raffin. 2005. "No Child Left without a Brain Scan? Toward a Pediatric Neuroethics." In *Cerebrum: Special Issue on Neuroethics.* New York: Dana Foundation Press.

Illes, J., A. C. Rosen, L. Huang, R. A. Goldstein, T. A. Raffin, G. Swan, and S. W. Atlas. 2004. "Ethical Consideration of Incidental Findings on Adult Brain MRI in Research." *Neurology* 62, no. 6: 888–90.

Jonsen, A. 2003. *The Birth of Bioethics.* New York: Oxford University Press.

Kennedy, D. 2003. "Neuroethics: An Uncertain Future." Annual meeting of the Society for Neuroscience, New Orleans, Louisiana.

———. 2006. "Neuroethics: Mapping a New Interdiscipline." In *Neuroethics: Defining the Issues in Theory, Practice, and Policy,* edited by J. Illes. Oxford: Oxford University Press.

Keyes, D. 1959. *Flowers for Algernon.* Orlando: Harcourt, Brace.

Kim, B. S., J. Illes, R. T. Kaplan, A. Reiss, and S. W. Atlas. 2002. "Incidental Findings on Pediatric MR Images of the Brain." *American Journal of Neuroradiology* 23, no. 10: 1674–77.

Lipton, P. 2007. "Response: The Tanner Lectures on Human Values." Clare Hall, Cambridge University.

Lombera, S., and J. Illes. 2008. "International Dimensions of Neuroethics." *Developing World Bioethics.*

Luria, A. R. 1978. "The Localization of Function in the Brain." *Biological Psychiatry* 13, no. 6: 633–35.

Marcus, S. J., ed. 2002. *"Neuroethics: Mapping the Field" Conference Proceedings.* New York: Dana Foundation Press.

Marshall, J. C., and G. R. Fink. 2003. "Cerebral Localization Then and Now." *NeuroImage* 20: S2–S7.

Martin, J. B. 1994. "Neurogenetics: Now and the Future." *Transactions of the American Clinical and Climatological Association* 106: 114–22; discussion 122–23.

Moll, J., R. de Oliviera-Souza, and I. Bramati. 2002. "Functional Networks in Emotional and Nonmoral Social Judgments." *NeuroImage* 26: 696–703.

"Neuroethics Needed." 2006. *Nature* 441, no. 7096: 907.

Owen, A. M., M. R. Coleman, M. Boly, M. H. Davis, S. Laureys, and J. D. Pickard. 2006. "Detecting Awareness in the Vegetative State." *Science* 313, no. 5792: 1402.

Pezawas, L., A. Meyer-Lindenberg, E. M. Drabant, B. A. Verchinski, K. E. Munoz, B. S. Kolachana, M. F. Egan, V. S. Mattay, A. R. Hariri, and D. R. Weinberger. 2005. "5-HTTLPR Polymorphism Impacts Human Cingulate-Amygdala Interactions: A Genetic Susceptibility Mechanism for Depression." *Nature and Neuroscience* 8, no. 6: 828–34.

Racine, E., O. Bar-Ilan, and J. Illes. 2005. "fMRI in the Public Eye." *Nature Reviews of Neuroscience* 6: 159–64.

Reis, D. L., M. A. Brackett, N. A. Shamosh, K. A. Kiehl, P. Salovey, and J. R. Gray.

2007. "Emotional Intelligence Predicts Individual Differences in Social Exchange Reasoning." *NeuroImage* 35: 1385–91.

Roskies, A. L., and S. E. Petersen. 2001. "Visualizing Human Brain Function." In *Frontiers of Life.* Vol. 3, *The Intelligent Systems.* Pt. 1, *The Brain of Homo Sapiens,* edited by P. C. E. Bizzi and V. Volterra. New York: Academic Press.

Roy, B. 1995. "The Tuskegee Syphilis Experiment: Biotechnology and the Administrative State." *Journal of the National Medical Association* 87, no. 1: 56–67.

Royal College of Physicians. 2003. *The Vegetative State: Guidance on Diagnosis and Management.* London: Royal College of Physicians.

Sass, H., S. Herpertz, and I. Houben. 1994. "Personality Disorders: Conceptual Issues and Responsibility." *Japanese Journal of Psychiatry and Neurology* 48 (supp.): 5–17.

Schiff, N. D., D. Rodriguez–Moreno, A. Kamal, K. H. Kim, J. T. Giacino, F. Plum, and J. Hirsch. 2005. "fMRI Reveals Large-Scale Network Activation in Minimally Conscious Patients." *Neurology* 64, no. 3: 514–23.

Sheridan, K., E. Zinchenko, and H. Gardner. 2006. "Neuroethics in Education." In *Neuroethics: Defining the Issues in Theory, Practice, and Policy,* edited by J. Illes. Oxford: Oxford University Press.

Silk, T., A. Vance, N. Rinehart, G. Egan, M. O'Boyle, J. L. Bradshaw, and R. Cunnington. 2005. "Fronto-Parietal Activation in Attention-Deficit Hyperactivity Disorder, Combined Type: Functional Magnetic Resonance Imaging Study." *British Journal of Psychiatry* 187: 282–83.

Singh, I. 2007. "Clinical Implications of Ethical Concepts: The Case of Children Taking Stimulants for ADHD." *Clinical Children's Psychology and Psychiatry* 12, no. 2: 167–82.

Tannert, C., H-D. Elvers, and B. Jandrig. 2007. "The Ethics of Uncertainty: In the Light of Possible Dangers, Research Becomes a Moral Duty." *EMBO Reports* 8, no. 10: 892–96.

Vance, A., T. J. Silk, M. Casey, N. J. Rinehart, J. L. Bradshaw, M. A. Bellgrove, and R. Cunnington. 2007. "Right Parietal Dysfunction in Children with Attention Deficit Hyperactivity Disorder, Combined Type: A Functional MRI Study." *Molecular Psychiatry* 12, no. 9: 826–32.

Wachbroit, R. 1998. "The Question Not Asked: The Challenge of Pleiotropic Genetic Tests." *Kennedy Institute of Ethics Journal* 8, no. 2: 131–44.

Weindling, P. 2001. "The Origins of Informed Consent: The International Scientific Commission on Medical War Crimes, and the Nuremburg Code." *Bulletin of the History of Medicine* 75, no. 1: 37–71.

Wikler, D. 1997. "Presidential Address: Bioethics and Social Responsibility." *Bioethics* 11, nos. 3–4: 185–92.