Open access • Journal Article • DOI:10.1038/NN1102-1123

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Published on: 01 Nov 2002 - Nature Neuroscience (Nature Publishing Group)

Topics: Novelty and Public policy

11-1-2002

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Postprint version. Published in *Nature Neuroscience*, Volume 5, Issue 11, April 2004, pages 1123-1130.
Publisher URL: http://dx.doi.org/doi:10.1038/nn1102-1123

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Abstract

There is growing public awareness of the ethical issues raised by progress in many areas of neuroscience. This commentary reviews the issues, which are triaged in terms of their novelty and their imminence, with an exploration of the relevant ethical principles in each case.

Keywords

broad categories of the ethical issues, nervous system enhancement of normal function, ethical implications in enhancement, court-ordered central nervous system (CNS) intervention, ethics of court-ordered intervention, ethical issues in brain reading, long-standing issues in neuroethics

Disciplines

Neuroscience and Neurobiology

Comments

Postprint version. Published in *Nature Neuroscience*, Volume 5, Issue 11, April 2004, pages 1123-1130.
Publisher URL: http://dx.doi.org/doi:10.1038/nn1102-1123

COMMENTARY

Nature Neuroscience **5**, 1123 - 1129 (2002)
doi:10.1038/nn1102-1123

Emerging ethical issues in neuroscience

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There is growing public awareness of the ethical issues raised by progress in many areas of neuroscience. This commentary reviews the issues, which are triaged in terms of their novelty and their imminence, with an exploration of the relevant ethical principles in each case.

In less than a year, "neuroethics" has joined the vocabulary of most neuroscientists. Exactly what the word signifies may not be clear to most of us, however. Both the word and the field to which it refers come largely from individuals outside neuroscience. Newspaper columnist William Safire gave the field its name, and defining statements of the issues are found in such sources as *Brain Policy*[1] by bioethicist Robert Blank, *Our Posthuman Future*[2] by historian Francis Fukuyama and a cover story in *The Economist* magazine (May 23, 2002). Neuroscientists themselves have been relatively scarce in public discourse on neuroethics, perhaps because many of the issues under discussion seem far-fetched. Need we devote serious attention now to the needs and rights of cyborg humans with computer-augmented brains? Probably not, given the current state of technology. Yet neuroscientists are just the people to guide the discussion toward issues of current and near-term priority. How does neuroethics, as presented to us in the literature, relate to the current state of neuroscience and its foreseeable future? Here I attempt to triage the issues that have been raised, separating those that are both new and immediate from those that are not new or are likely to arise only in the distant future. Although all three categories deserve our continued attention, the first poses the most immediate intellectual and social challenges.

Three broad issues survive the triage for novelty and imminence: enhancement of normal function, court-ordered CNS intervention and 'brain-reading'. Each emerges from work in multiple areas of neuroscience, from molecular to cognitive neuroscience. The nature of the ethical issues raised are similarly varied, and include the rights to equal opportunity, privacy and freedom.

Enhancement of normal function

If drugs and other forms of central nervous system intervention can be used to improve the mood, cognition or behavior of people with problems in these areas, what might they do for normal individuals? Some treatments can be viewed as 'normalizers', which have little or no effect on systems that are already normal (for instance, the mood stablizer lithium[3]) and will not therefore figure in debates over enhancement. Other treatments can indeed make normal people 'better than normal'. Pharmacological enhancement is arguably being practiced now in several psychological domains: enhancement of mood, cognition and vegetative functions, including sleep, appetite and sex.

The enhancement potential of some psychiatric treatments is, in itself, nothing new. Until recently, however, psychotropic medications had significant risks and side effects that made them attractive only as an alternative to illness. With our growing understanding of neurotransmission at a molecular level, it has been possible to design more selective drugs with better side-effect profiles. In addition, adjuvant therapy with other drugs is increasingly used to counteract the remaining side effects. For example, the most troublesome side effect for users of selective seratonin reuptake inhibitors (SSRIs) is sexual dysfunction, which responds well to the drug sildenafil (Viagra). Other drugs specifically developed to counteract the sexual side effects of SSRIs are in development and clinical trials (Vernalis press release, May 22, 2002). The result of both new designer drugs and adjuvant drugs is the same: increasingly selective neurochemical alteration of our mental states and abilities.

Peter Kramer's book *Listening to Prozac*[4] first focused society's attention on the possibility of safe mood enhancement. The growth in sales of SSRIs clearly indicates that more people, with less severe depression, are using them. Has the threshold for SSRI use dropped below the line separating the healthy from the sick? This question is hard to answer for several reasons. First, the line between healthy and sick is a fuzzy and perhaps arbitrary one. There is no simple discontinuity between the characteristic mood of patients with diagnosable mood disorders and the range of moods found in the general population[5]. Second, diagnostic thresholds are clearly moving downward as a result of these very changes in treatment. For a given severity of illness, the better tolerated the treatment, the more likely patients are to present for diagnosis and the more likely physicians are to diagnose and treat. As a related point, other more common and less debilitating conditions are also being treated with SSRIs, such as cyclic changes in women's moods before menstruation[6]. Third, although depression is usually a remitting-relapsing disease with typically years between episodes, patients today are likely to be treated prophylactically with antidepressant medication for periods of 1−3 years, even when symptom free[7]. Thus there are many people now on antidepressant medication who are healthy, with only a vulnerability to depression as opposed to depression. These changes in psychiatric practice have resulted in many people using SSRIs and other antidepressants who would not have been prescribed these drugs ten years ago. There is no reason to predict their ranks will not continue to swell, and to include healthier and higher-functioning people.

What changes might healthy individuals hope to experience through the use of antidepressant medication? Mood enhancement belongs on the docket of new and imminent bioethical issues in neuroscience only if current and foreseeable medications can deliver pleasing results to healthy people. A handful of studies have assessed the effects of SSRIs on mood and personality in normal subjects over short periods of a few months or less (for example, refs. 8, 9). The effects are relatively selective, reducing self-reported negative affect (such as fear, hostility) while leaving positive affect (happiness, excitement) the same. The drugs also increase affiliative behavior in laboratory social interactions and cooperative/competitive games played with confederates, for example decreasing the number of spoken commands and increasing the number of suggestions. In one double-blind crossover design, subjects not only were more cooperative in a game, but showed real-world changes in behavior as well: roommates found them less submissive on citalopam, though no more dominant or hostile[9]. Much more research is needed to clarify the effects of SSRIs and other antidepressant agents on mood and behavior of normal subjects, but the evidence so far suggests subtle salutary effects.

Pharmacological manipulations of other neurotransmitter systems can alter cognitive abilities, including attention and memory. Attention, in the sense of sustained effort and resistance to distraction, is primarily modulated by dopamine and norepinephrine. Stimulant medication, such methylphenidate (Ritalin) and amphetamines (Adderol) affect both systems and are effective in treating attention deficit hyperactivity disorder (ADHD). In normal individuals, these drugs induce reliable changes in vigilance, response time and higher cognitive functions, such as novel problem-solving and planning[10]. As it turns out, thousands of normal, healthy children and adults have discovered similar effects on their own.

The question of whether and when to treat ADHD medically is a complex and contentious one for many reasons, most of which are not related to enhancement. However, as with affective disorders, it is difficult to locate a discontinuity between normal attentional functioning and ADHD (NIH consensus statement, 1998). To the extent that we intervene too 'high up' the continuum, we are practicing enhancement. According to most experts, pharmacological enhancement of children's attention is routine in some communities[11]. Parents who are eager to give their children every edge in school may press their pediatricians for medication, and teachers often welcome the greater orderliness in a classroom of attentive children. Because ADHD in children is diagnosed primarily on the basis of parent and teacher questionnaire responses, it can be difficult to free the diagnostic process from the values and standards of the respondents.

Whereas diagnostic 'over-reach' is a reason that some arguably normal children receive stimulants, many young adults with no pretense at all to a diagnosis are using stimulants to enhance their performance in college. Methylphenidate is considered by some to be the most widely used recreational drug on American campuses[12]. Students have often approached me after talks on the topic to relate their own stories about Ritalin use among their non-ADHD peers, for example recalling a hockey coach who always reminded her team to take their Ritalin before playing another school.

Loss of cholinergic neurons is responsible for many of the cognitive changes in Alzheimer's disease, including the pronounced impairment of memory. Drug therapies such as donepezil (Aricept) that increase acetylcholine can slow or reverse the loss of memory ability in the early stages of the disease. Can this or other treatments improve the memory of healthy individuals? Discussions of memory enhancement must take age into account. Although certain specialized pursuits could conceivably benefit from super-memory, the forgetting rates of normal young humans seem to be optimal for most purposes[13]. Empirically, prodigious memory is linked to difficulties with thinking and problem solving[14], and computationally, boosting the durability of individual memories decreases the ability to generalize[15]. Memory enhancement is of more interest in middle age and beyond, when the normal process of memory loss is first noticeable in healthy individuals[16]. Rejuvenation of memory function in healthy older people is a form of memory enhancement with broad appeal. Indeed, memory-enhancing nutritional supplements are a billion-dollar industry (Nutrition Business Journal, 1998), despite little evidence concerning efficacy. Ginkgo biloba, the most popular of the memory-enhancing supplements, was recently found to be equivalent to placebo[17].

How close are we to more specific and effective memory enhancement for healthy older adults? Many drug companies are now directing enormous research efforts to the development of memory-boosting drugs (Neuroinvestment, September 2001). The

candidate drugs target various stages in the molecular cascade that underlies memory formation, including presynaptic neurotransmitter release (for example, existing cholinesterase inhibitors such as donezipil) and postsynaptic effects (such as the class of drugs known as ampakines). These drugs are currently considered treatments for dementia and so-called 'mild cognitive impairment', which is more severe than normal age-related cognitive decline. No drug companies have yet targeted normal memory for enhancement, but there is reason to believe that some of the products under development would work for that purpose as well. For example, treatment of healthy human subjects with an ampakine improved performance on several memory tests[18].

Advances in the neurochemistry of sleep, appetite and sex are paving the way for better pharmacological control of these functions as well, with results that will be of interest to normal people. The drug modafinil (Provigil), approved for the treatment of narcolepsy, can prolong alert wakefulness for days[19]. Its use by healthy people is currently being explored by the military[20]. The appeal of such a drug to average people who would like more time in their lives is obvious, and media coverage of modafinil has been extensive. Weight control is a societal preoccupation, and Wallace Simpson's quip that "a woman cannot be too rich or too thin" sums up the likely attitude of most people to a safe, long-term appetite suppressant. There is currently a very limited choice of medication for weight loss, and what is available is less effective than the Fenfluramine-Phenylpropanolanine combination, withdrawn from the market in 1997 due to severe adverse effects[21]. However, findings that hormones such as leptin, ghrelin and melanocortin are involved in appetite control have given pharmaceutical researchers new avenues to explore for drug development. Men without erectile dysfunction have discovered sildenafil (Viagra) and created a new market for the drug as an enhancer of sexual performance. Although a prescription medication, sildenafil is easily obtained for such purposes after completing a short diagnostic questionnaire on the internet[22]. Pharmaceutical companies are pursuing drugs that more selectively target the neural bases of sexual function, which would have fewer cardiovascular side effects than sildenafil.

In sum, enhancement is not just a theoretical possibility. Enhancement of mood, cognition and vegetative functions in healthy people is now a fact of life, and the only uncertainties concern the speed with which new and more appealing enhancement methods will become available and attract more users.

Ethical issues in enhancement

Most of us would love to go through life cheerful and svelte, focusing like a laser beam at work and enjoying rapturous sex each night. Yet most of us also feel uneasy about the idea of achieving these things through drugs. With the necessary technology at or near hand, it is important to examine the reasons for this unease (for a more detailed discussion of enhancement in other domains, see ref. 23). Objections to enhancement can be divided into two broad categories: problems for the individual user and problems for society if use becomes widespread.

The first problem that springs to mind for many people is the possibility of serious side effects for the individual, including long-term or delayed effects that might evade current FDA safeguards. Perhaps a youth spent scaling the heights of academic and job success thanks to enhancement by Ritalin will be followed by a middle age of premature memory loss and cognitive decline. By and large, a concern with long-term or hidden side effects is not unique to enhancement but applies to therapeutic treatments as well. Its special salience in the case of enhancement may reflect an underlying wariness of

'free lunches'. There is one respect in which enhancement might deserve extra scrutiny for hidden costs, which is suggested by evolutionary considerations. We understand little about the design constraints that were being satisfied in the process of creating a modern human brain. Therefore we do not know which 'limitations' are there for a good reason. As already mentioned, normal forgetting rates seem to be optimal for information retrieval.

A concern unique to enhancement is the moral objection to, in effect, gain without pain. Most people in our society feel there is value to earning one's happiness, success, and so on. When wealthy parents make their teenage children take summer jobs to earn their spending money, they are applying this principle in a way that most of us would find reasonable. However, our judgments often deviate from this principle. Although we recognize the value of earning life's rewards, our lives are full of shortcuts to looking and feeling better. We do not disapprove of people who dislike vegetables improving their health by taking vitamin pills. Nor do we begrudge college applicants their SAT prep books or Stanley Kaplan classes. Psychopharmacological enhancement can therefore be seen as fitting in with an array of practices that are already accepted and widespread.

One variant of the 'no pain, no gain' objection is specific to our emotional lives. Many people hold the belief that one cannot experience the beauty and joy of life unless one is also acquainted with life's pain. In the words of Nietzsche, "If you take away my devils, you will take away my angels too." As an empirical claim, supporting evidence is so far lacking. Anecdotal reports of generalized emotional blunting notwithstanding, the small literature on short-term SSRI effects in normal subjects suggests no change in either direction on positive affect, only a selective decrease in negative affect. In any case, even if emotional blunting were a side effect of current mood enhancers, it is not a basis for rejecting mood enhancement in general. There is no *a-priori* reason that newer medications would have the same effect.

Other objections stem from potential harm to society. One worry is that enhancement will not be fairly distributed. It is likely that the wealthy and privileged will have the choice of self-enhancement and the less privileged will not. Is this what lies at the root of our unease with enhancement? Probably not, given that our society is already full of such inequities. No one would seek to prohibit private schools, personal trainers or cosmetic surgery on the grounds that they are inequitably distributed. Besides, consider a scenario in which the entire populace is given full and equal access to Ritalin, Prozac and other enhancers. If our qualms about enhancement were linked to equal opportunity, then this should set our minds at ease, but more than likely it does not.

Another social problem with enhancement is that widespread enhancement will raise our standards of normalcy. This in turn will put individuals who choose not to enhance at a disadvantage, in effect a form of indirect coercion. Even the enhancement of mood, which at first glance lacks a competitive function, seems to be associated with increased social ability[8], which does confer an advantage in many walks of life. Such coercion may already be felt by parents whose children attend schools with high rates of Ritalin use. Clearly coercion is not a good thing. Yet it would seem at least as much of an infringement on personal freedom to restrict access to safe enhancements for the sake of avoiding the indirect coercion of individuals who do not wish to partake.

The idea of self-enhancement through manipulations of brain function feels wrong or dangerous to many people. Yet the root cause of that feeling is difficult to find. Perhaps

it is a misleading feeling, which we will get over once we have discussed the issue of enhancement thoroughly and rationally. Or perhaps further discussion will reveal the cause of our reflexive worry.

Court-ordered CNS intervention

Another controversial use of our current psychopharmacopia is to improve the behavior of others when that behavior is medically unremarkable but socially undesirable. Rehabilitation has long been intertwined with punishment in our criminal justice system. Successful rehabilitation benefits both the offender and society, insofar as it reduces repeat offenses. It may be offered as an option or as a mandatory component of a sentence. Furthermore, court-ordered therapy or rehabilitation is not confined to medically diagnosed illnesses. Judges may require healthy individuals to undergo such interventions as parenting classes or anger management therapy.

Addiction, aggression, impulse control and even parenting behavior have been studied for several decades, and we are increasingly able to manipulate the relevant neural systems in animals by drugs and other interventions. Some of this work has been successfully generalized to humans. For example, impulsive violence has been linked to seratonergic abnormalities in patient[24], criminal[25] and healthy community populations[26]. Accordingly, SSRIs have been tried as a treatment for aggressive behavior, and found to be helpful[27]. For example, in three double-blind studies, fluoxetine (compared against placebo) reduced aggression in patients with personality disorder[25, 28, 29].

How close do our current practices come to directly altering brain function under the rubric of court-ordered rehabilitation? For any person deemed a threat to self or others, including criminal offenders, judges routinely order compliance with medication. Although the ethical issues raised by involuntary treatment are far from trivial, there is nevertheless broad consensus in favor of applying recognized treatments in such cases. A more controversial use is sentencing sexual offenders to pharmacological treatments aimed at reducing their sex drive. Several states in the US have enacted laws that either allow or require sex offenders to take the synthetic hormone medroxy-progesterone acetate, which lowers serum testosterone and significantly decreases recidivism[30]. Other pharmacological approaches involving seratonin are being explored in research studies[30].

The issue of diagnostic creep is also relevant here. Many behavioral tendencies that the layman would consider 'bad' but not medical illnesses have acquired diagnostic codes in the Diagnostic Statistical Manual of the American Psychiatric Association[31]. These diagnoses include drug abuse, compulsive shoplifting and sexual attraction to children. Psychiatrist Alvin Poussaint has even suggested that racism is a psychiatric illness and should be treated by therapy (The New York Times, August 26, 1999). The 'medical model' of condemnable behavior has been criticized when used to excuse, not simply explain, behavior[32]. In the future, the model's impact may be less friendly to offenders, by subjecting more of them to involuntary regimens of psychotropic medication.

Court-ordered CNS intervention has not been highlighted in recent discussions of neuroethics, but deserves greater attention for three reasons. First, some of the relevant technologies are already available, for example SSRIs to reduce violent behavior. Second, the practice of requiring nonpharmacological treatment aimed at changing the behavior of healthy offenders is well established. And if this, in itself, does not put us on the slippery slope toward court-ordered CNS modification of healthy offenders, then the third fact surely does, namely the use of antiadrogen treatment with

convicted sex offenders.

Ethics of court-ordered intervention

Court-ordered CNS intervention need not simply subjugate an individual's interests to those of society, in the style of Soviet psychiatry or *A Clockwork Orange*. Such uses do not challenge our moral intuitions or social policies; they are clear violations of an individual's freedom and human dignity. The harder questions arise when we consider uses of neuroscience in the criminal justice system for genuinely therapeutic purposes. For example, a judge's order to attend anger management class or a parenting support group is intended to help the offender, in addition to whatever society gains from having fewer hotheads and abusive parents among us. Substituting medications that improve anger management or parenting skills renders the effect no less therapeutic. Yet many people's intuitions raise a flag here. And if not here, then at the thought of more permanent interventions such as implanted stimulators or neurosurgery to achieve the same goals.

What moral intuition triggers this flag? Primarily an intuition about individual freedom, of a kind that we have not previously denied even to prisoners: the freedom to think one's own thoughts and have one's own personality. In anger management class, a person is free to think, "This is stupid. No way am I going to use these methods." In contrast, the mechanism by which Prozac curbs impulsive violence cannot be accepted or resisted in the same way. Offering CNS interventions in the context of a choice, with conventional therapies and incarceration as alternatives, mitigates this worry but does not eliminate it. Sentencing alternatives are rarely appealing options, introducing implicit coercion.

'Brain reading'

Mind reading is the stuff of science fiction, and the current capabilities of neuroscience fall far short of such a feat. Even a major leap in the signal-to-noise ratio of functional brain imaging would simply leave us with gigabytes of more accurate physiological data whose psychological meaning would be obscure. Nevertheless, the accomplishments of the field to date include neural correlates of many psychological traits and states. Furthermore, the demand for 'scientific' measures of personality, veracity, attitudes and behavioral dispositions in our society ensures that, ready or not, these measures will have an increasing role in our lives.

Most of our knowledge of individual variation in mental and neural function comes from biological psychiatry and concerns patterns of brain activity in mental disorders. This work has important future clinical implications, especially in a field in which the major diagnostic categories remain syndromal, that is, defined in terms of clusters of signs and symptoms. The current state of the art in functional neuroimaging does not earn it a place in psychiatric diagnosis. In general, abnormalities that characterize particular illnesses can be demonstrated when small groups of patients are compared to control subjects, but are not diagnostic at the individual patient level. Nevertheless, diagnostic imaging is currently the goal of many research groups, with encouraging results for some disorders, such as ADHD[33].

Although current imaging methods cannot reliably place most patients in a diagnostic category, this limitation does not rule out occasional revelations about an individual. Even though most patients' scans will be impossible to classify with certainty, other individual scans will deviate enough from the normal pattern to constitute a 'positive' finding. One such example comes from studies of drug craving. Drug-free cocaine

addicts experience a craving state when shown pictures of drug paraphernalia, which results in reliable group differences in PET activation of the amygdala, anterior cingulate and orbitofrontal cortex[34]. Although some of the individual scans in the patient group are indistinguishable from normal, others clearly differ from normal. In one laboratory, at least half of recently detoxified cocaine users could be identified by differential amygdala response to drug-related versus non-drug-related pictures (A.R. Childress, personal communication). Drug use is not unique in this respect; other stimuli to which individuals are strongly attracted evoke activity in similar circuits. For instance, subjects aroused by sexually explicit videos activate many of the same limbic system areas[35]. Furthermore, the conscious attempt to suppress arousal may also engender a distinct pattern of brain activation[36], suggesting an advantage of such scans over more peripheral measures capable of revealing sexual preferences.

The significance of such results for individuals is not in their use for classification or diagnosis, because of the ambiguity of most people's scans, but in the information they reveal about some fraction of the subjects (the size of which varies from study to study) whose scans fall clearly outside the normal range. Although subject cooperation is required for such scans, because of the need to remain still and focus on the visually presented stimuli, the subject need not know the scan's purpose.

Many recent studies have sought neuroimaging correlates of the dimensions of personality found in classic theories of normal personality, such as extraversion and neuroticism (see ref. 37 for a review of the social and ethical issues). These studies use small groups of subjects, but at least a small fraction of the subjects can be classified by visual inspection of the scans (T. Canli, personal communication). Other socially relevant characteristics such as racial group identity and unconscious racial attitudes also have neural correlates that can be measured in small groups of subjects. For example, a study in which four black and four white subjects viewed photographs of black and white faces found significant differences in response to ingroup and outgroup faces[38]. A correlational study of unconscious attitudes found that white subjects with more negative evaluations of black faces had more of an increase in amygdala activity to pictures of unfamiliar black than white faces[39].

One of the most sought-after uses of 'brain reading' is the detection of deception. In the wake of the 9-11 tragedy, there is renewed interest in lie detection for security purposes, to screen individuals for their attitudes and allegiances, as well as for traditional forensic purposes. The company Brain Fingerprinting Laboratories is already marketing a system that uses scalp-recorded ERPs to detect so-called 'guilty knowledge', such as familiarity with certain people, objects or scenes. Research seeking more neuroanatomically specific measures of deception using fMRI is underway[40].

Ethical issues in brain reading

One problem posed by these developments concerns privacy. As with any testing method that reveals information about an individual (such as genetic testing for breast cancer risk), it may not always be in the person's best interest to have that information available to others. However, there is an added dimension of ethical significance when the information concerns the kinds of personal traits and states that neuroimaging may reveal. The goal, in some cases already partially realized, involves breaching the privacy of a person's own mind.

Another, more immediate problem concerns the way that brain scans are interpreted outside the neuroimaging community. Physiological measures, especially brain-based

measures, possess an illusory accuracy and objectivity as perceived by the general public. One commentator, in proposing the use of Brain Fingerprinting as a screening tool at airports, wrote "Although people lie...brainwaves do not" (http://www.skirsh.com). Brain-based measures do, in principle, have an advantage as indices of psychological traits and states. Measures of brain function are one causal step closer to these traits and states than the behavioral or even peripheral autonomic signs that form the basis of more familiar measures, from responses on personality questionnaires to polygraph tracings. Imaging may therefore, one day, provide the most sensitive and specific measures available of psychological processes. For now, however, this is not the case, and there is a risk that juries, judges, parole boards, the immigration service and so on will weight such measures too heavily in their decision-making.

Long-standing issues in neuroethics

The emerging field of neuroethics is concerned with a broad array of issues beyond the three just discussed. Some are familiar, though by no means settled. Others remain hypothetical, pending future developments in neuroscience, but are fairly certain to materialize within many readers' lifetimes. In both cases, bioethicists, policy makers and society in general will benefit from having the perspective of informed neuroscientists included in their discussions.

The familiar issues can themselves be divided into those that relate to neuroscience and to other biomedical sciences as well, and those uniquely related to our growing understanding of brain function. Common biomedical issues are exemplified by questions such as the following. How safe are the new methods of neuroscience, such as transcranial magnetic stimulation or high-field MRI, and who should decide? What is the appropriate course of action when an incidental neurological abnormality is found in the course of research data collection? What considerations should guide the development of therapies for diseases such as Parkinson's based on fetal tissue or embryonic stem cells? How should promising new therapies be rationed? When and why should predictive testing be offered for future neurological or neuropsychiatric illness when no cure is available, as with Alzheimer's and Huntington's diseases? These are difficult questions, on which reasonable people can disagree. They are also questions with a history in bioethics, which offers helpful general principles and precedents.

Other ethical issues arise exclusively in neuroscience because of the particular subject matter of the field. The brain is the organ of the mind, consciousness and selfhood. Although the issues in this category are not new, they are evolving as the field evolves and in some cases developing new wrinkles.

The definition of death is one such issue. Until the 1960s, the generally accepted criterion for death was permanent cessation of respiration and circulation. The Harvard criteria for death, published in 1968, shifted the focus to brain function. This definition was refined by a presidential commission in 1981, which defined brain death as "the irreversible cessation of all functions of the entire brain, including the brain stem." This definition has, in turn, been found wanting[41]. With our growing understanding of mind–brain relationships, and our ability to assess them with functional neuroimaging, a narrower focus on the status of higher brain functions seems indicated[1, 42]. However, any such move will raise profound questions about personhood and the brain.

Informed consent for research participation or for treatment[43] is another issue that is special in neuroscience, because in many cases the subjects or patients in question have

brain disorders that affect their decision-making ability. The ethics of psychosurgery is a related issue, not least because thousands of patients ostensibly consented to the destructive and unproven method of prefrontal leucotomy[44].

Although relatively rare today, psychosurgery continues to be practiced as a last resort for patients suffering from refractory depression, obsessive-compulsive disorder (OCD) and anxiety disorders. The most common procedures are cingulotomy, stereotactic subcaudate tractotomy, anterior capsulotomy and limbic leucotomy, all of which disrupt the interconnecting pathways of the limbic system and the prefrontal cortex[45, 46]. According to one recent review, at least one third of depressed patients experience improvement as a result of these operations, with just under one third of OCD and anxiety patients improving[45]. This could be considered a favorable record with patients who have failed to benefit from multiple other treatments. Should we therefore approve of psychosurgery as a less-than-last resort?

Our notions of responsibility and blame, which guide our legal as well as personal ethics, seem at odds with deterministic views of human behavior. Whether we are moved by the 'Twinkie defense' (the apocryphal defense of a murderer based on his loss of control caused by junk-food consumption) or the 'abuse excuse' depends on how we reconcile common-sense notions of free will with mechanistic views of the causation of behavior. Although the perceived conflict between free will and determinism does not hinge on the particulars of any specific deterministic account, progress in cognitive and behavioral neuroscience certainly increases the salience of the deterministic view. The abstraction that all human behavior is explainable in terms of the laws of physics does not encroach much on our intuitions about a defendant's responsibility for his actions. In contrast, a detailed account of the mechanisms linking childhood abuse to diminished impulse control seems much more likely to temper our intuitions about responsibility and blame. As the neuroscience of intentional behavior continues to develop, it will challenge our ways of thinking about responsibility and blame.

Neuroethical questions on the horizon

The future will bring new ways of enhancing, controlling and 'reading' the brain. The current ability of TMS to improve cognition and mood[47] by the activation or inhibition of specific brain areas may be refined in the service of enhancement or control. In the more distant future, similar extensions of deep brain stimulation techniques can be envisioned, and genetic manipulations of targeted neural systems and neurosurgery could permanently modify brain function. Nanotechnology and neural prostheses might eventually create a breed of enhanced human cyborgs. Such possibilities may sound like science fiction in 2002, but consider that space travel and test tube babies were once just science fiction and seemed every bit as far-fetched in the decades before they became reality.

In addition to altering brain function, our ability to monitor and interpret it could one day achieve equally fantastic results. After all, twenty years ago it would have seemed implausible that neuroscientists would have even candidate brain indices of truth versus lie[40], veridical versus false memory[48], the likelihood of future violent crime[49], styles of moral reasoning[50], the intention to cooperate[51], and even the specific content of thoughts (visualizing houses versus faces)[52]. What might we have in another twenty years, or fifty? Our track record for predicting the rate of scientific progress has not been impressive. Gene therapy has yet to achieve the promise that seemed imminent ten or fifteen years ago, whereas the cloning of mammals took the world by surprise.

One need not project very far into the future to see the increasing role of neuroscience in our lives, and the social and ethical concerns it will bring. Like the field of genetics, neuroscience concerns the biological foundations of who we are, of our 'essence'. The relationship of self to brain is, if anything, more direct than that of self to genome, and neural interventions are more easily accomplished than genetic interventions. Yet compared to molecular geneticists, who instigated public discussion in the early days of recombinant DNA research, neuroscientists have paid relatively little attention to the social implications of their field. The time is now ripe for examination of these implications, among scientists themselves and in dialog with policy makers and the public.

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