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Monitoring and manipulating the human brain: new neuroscience technologies and their ethical implications

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Abstract

Discusses the use of new neuroscience technologies in monitoring and manipulating brain function, as of May 2004. History of modern brain imaging; Implications of neuroimaging for medical ethics; Factors that contributed to brain enhancement.

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Monitoring and Manipulating Brain Function

New Neuroscience Technologies and Their Ethical Implications

by Martha J. Farah and Paul Root Wolpe

The eye may be window to the soul, but neuroscientists aim to get inside and measure the interior directly. There's also talk about moving some walls.

Congress christened the 1990s "the decade of the brain," and this was apt from the vantage point of the early 21st Century. Great strides were made in both basic and clinical neuroscience. What the current decade may, in retrospect, be remembered for is the growth of neuroscience beyond those two categories, "basic" and "clinical," into a host of new applications. From the measurement of mental processes with functional neuroimaging to their manipulation with ever more selective drugs, the new capabilities of neuroscience raise unprecedented ethical and social issues. These issues must be identified and addressed if society is to benefit from the neuroscience revolution now in progress.

Like the field of genetics, cognitive neuroscience raises questions about the biological foundations of who we are. Indeed, the relation of self and personal identity to the brain is, if anything, more direct than that of self to the genome. In addition, the ethical questions of neuroscience are more urgent, as neural interventions are currently more easily accomplished than genetic interventions. Yet compared to the field of molecular genetics, in which ethical issues have been at the forefront since the days of the 1975 Asilomar meeting on recombinant DNA, relatively little attention has been paid to the ethics of neuroscience.

This situation is changing, as bioethicists and neuroscientists are beginning to explore the emerging social and ethical issues raised by progress in neuroscience. In the Society for Neuroscience's recently formulated mission statement, bioethical issues figure prominently.[1] Numerous articles, meetings, and symposia have appeared on the subject.[2] The term "neuroethics," which originally referred to bioethical issues in clinical neurology, has now been adopted to refer to ethical issues in the technological advances of

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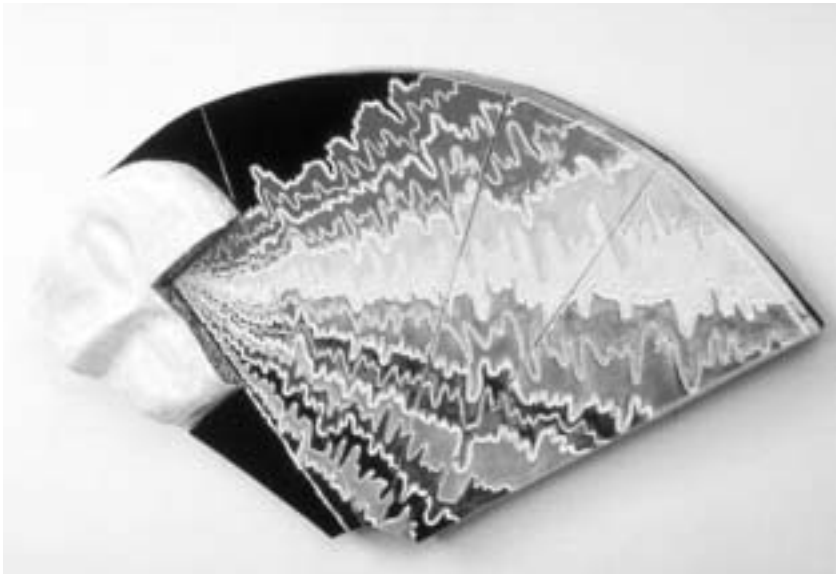
neuroscience more generally.[3] (Unfortunately, the term is also used to refer to the neural bases of ethical thinking, a different topic.[4])

Neuroethics encompasses a broad and varied set of bioethical issues. Some are similar to those that have arisen previously in biomedicine, such as the safety of new research and treatment methods, the rationing of promising new therapies, and predictive testing for future illnesses when no cure is available (as with Alzheimer's or Huntington's disease). Other neuroethical issues, however, are unique to neuroscience because of the particular subject matter of that field. The brain is the organ of the mind and consciousness, the locus of our sense of selfhood. Interventions in the brain therefore have different ethical implications than interventions in other organs. In addition, our growing knowledge of mind-brain relations is likely to affect our definitions of competence, mental health and illness, and death. Our moral and legal conceptions of responsibility are likewise susceptible to change as our understanding of the physical mechanisms of behavior evolves. Our sense of the privacy and confidentiality of our own thought processes may also be threatened by technologies that can reveal the neural correlates of our innermost thoughts.

Many of the new social and ethical issues in neuroscience result from one of two developments. The first is the ability to monitor brain function in living humans with a spatial and temporal resolution sufficient to capture psychologically meaningful fluctuations of activity. The second is the ability to alter the brain with chemical or anatomical selectivity that is sufficient to induce specific functional changes. For each of these developments, we will review advances in the enabling technology and provide examples of ethically challenging uses of the technology and an analysis of the ethical issues they raise.



Brain Scan Fan, by Christine Pendergrass, clay on wood, 11" x 20" x 2"

Neuroimaging

The history of modern brain imaging began in the 1970s with computed axial tomography or CAT scans and proceeded at a rapid and accelerating rate for the remaining decades of the twentieth century. The idea of passing X-rays through the head from multiple directions and reconstructing a three-dimensional structural image, revolutionary at the time, was quickly adapted to radiological signals other than X-rays. These included radiation from exogenous tracers to enable imaging of brain function, as in positron emission tomography (PET) and single photon emission computed tomography (SPECT), and endogenously generated magnetic fields to image either structure or function, as in magnetic resonance imaging (MRI). Pioneering research on cognition and emotion was undertaken with PET and SPECT in the 1980s, and by the 1990s MRI, the noninvasive alternative to PET, became commonplace in research.[5]

In an MRI, atoms are first aligned by a strong static magnetic field, then knocked out of alignment by a radio frequency pulse, and then allowed to realign. The fluctuating field created as the atoms "relax" to the aligned state is the signal that is measured. Although early functional MRI used an injected contrast agent, current methods use the magnetic properties of the blood itself as a tracer, and are therefore entirely noninvasive. In blood oxygen level dependent (BOLD) MRI, the different magnetic susceptibility of oxygenated and deoxygenated hemoglobin provides a measure of regional brain activity.[6] In arterial spin labeling (ASL) MRI, the atoms are aligned by a magnetic field at the neck, and relax as they circulate through the brain, indicating regional perfusion.[7] The spatial and temporal resolution of functional MRI (fMRI) is limited by haemodynamics rather than by the physics of the method; blood flow changes over seconds in response to neural activity, and these changes extend into nearby tissue. In practice, fMRI has a spatial resolution of one millimeter and a temporal resolution of about one second, which is adequate to distinguish among at least some psychologically meaningful differences in brain activity.[8] A few additional methods figure in the cognitive neuroimaging revolution. One is structural MRI, from which precise measurements of brain size and shape can be made. Combined with reliable methods for delineating and measuring particular brain structures, this

has opened up the field of brain morphometry, in which slight anatomical variations are correlated with psychological traits.[9] The venerable techniques of electroencephalography (EEG) and event-related potentials (ERP) have acquired new capabilities by the application of signal processing techniques that allow better localization of brain activity and analysis of temporal patterns of activity.[10] Optical methods, such as near infrared spectroscopy (NIRS), provide another noninvasive measure of regional brain activity based on the absorption of different wavelengths of light as it passes through the head.[11]

By and large, these methods have been developed for long-standing clinical and scientific goals, from localizing seizure foci to studying the neurochemical abnormalities in psychiatric illness. These uses are associated with ethical issues of a familiar nature: for example, the risks of radiation, obtaining adequate informed consent (especially from the mentally ill), and the possibility of discovering incidental brain anomalies. However, neuroimaging also yields information that can be used for different purposes, raising new ethical issues. In principle, and increasingly in practice, imaging can be used to infer people's psychological traits and states, in many cases without the person's cooperation or consent. It can be used, in effect, as a crude form of mind reading.

Imaging of Personal Information

Our society's attitude toward mental illness has come a long way since 1972, when Senator Thomas Eagleton was forced to withdraw his vice presidential candidacy after his history of depression became known. Nevertheless, psychiatric illness continues to carry a stigma, and a currently healthy individual might well wish to avoid disclosing a psychiatric history. The finding that depression, schizophrenia, and other illnesses leave their marks on the brain raises the possibility that psychiatric history and risk could be inferred from a brain scan without an individual's knowledge or consent. For the most part, the currently available markers are morphometric, relying on structural rather than functional imaging.[12]

Although the abnormalities that characterize particular illnesses can be demonstrated when small groups of patients are compared to control subjects, they are not currently diagnostic at the individual patient level. Nevertheless, diagnostic imaging is currently the goal of many research groups, with encouraging results for some disorders, for example ADHD.[13] Should diagnostic imaging become reliable, the possibility of inferring current or prior psychiatric illness from images taken for other purposes will also become a concern.

Imaging of personality

A number of recent studies have sought neuroimaging correlates of personality found in classic theories of normal personality, including extraversion/ introversion, neuroticism, novelty seeking, harm avoidance, and reward dependence.[14] Most of the studies employed resting scans (that is, scans that were obtained while subjects were simply resting, rather than performing any particular task) of groups of twelve to thirty healthy subjects, not selected for being especially extreme on any dimension, and they performed correlations between personality scale scores and brain activation in regions of a priori interest throughout the brain. Despite the seemingly low power of such designs, a number of positive results have been reported, with both converging and diverging results among the studies. The areas that distinguish normal people with differing personality at rest include a large number of cortical and subcortical areas, particularly paralimbic cortical areas such as the insula, orbital frontal cortex, and the anterior cingulate, as well as subcortical structures, such as the amygdala and putamen.

Canli and colleagues have sought correlates of personality in the brain's response to emotionally evocative stimuli. Given that many aspects of personality are most apparent in the context of frightening, happy, sad, or tempting stimuli, such an approach has the potential to identify important differences not apparent in resting scans. In one study, Canli focused on two personality traits: extraversion, which is the tendency to seek out and enjoy social contact and maintain an upbeat outlook, and neuroticism, which is the tendency to worry and focus on negative information.[15] They found that extraversion was correlated with brain response in several areas to pictures with positive emotional valence such as puppies, ice cream, and sunsets. The effect was specific to positive and not negative stimuli, and this was confirmed in a later study with pictures of happy and fearful faces.[16] Neuroticism, in contrast, is associated with differences in response to negative but not positive

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stimuli. Photographs of spiders, cemeteries, crying people, and other negatively valenced images evoked more response in certain brain areas the more neurotic the subject. Positive pictures did not show such an effect.

Imaging of Social and Moral Attitudes

In a now well-known study, Phelps and colleagues studied white subjects' attitudes toward unfamiliar black faces, using both behavioral measures and fMRI.[17] Using previously developed behavioral measures, they were able to estimate the degree of unconscious negative evaluation of unfamiliar black as opposed to white faces. They then measured brain response to unfamiliar black and white faces and found a moderately strong correlation between individuals' amygdala activation and the degree of negative evaluation of black faces.

Racial group identity also has neural correlates that are roughly measurable with current brain imaging methods. In a study of black and white subjects viewing photographs of black and white faces, significant differences in response to in-group and out-group faces were found.[18]

Differences in the way people view particular actions as right or wrong, across specific moral dilemmas and across individuals, have measurable neural correlates. In particular, Greene and colleagues used fMRI to demonstrate different patterns of brain activation associated with the logical weighing of rights and wrongs. For example, they found that the emotional centers of the brain were more active when subjects made moral decisions based more on their visceral reactions than on a rational weighing of costs and benefits.[19]

Imaging of Preferences

The objects of a person's desires may also be discernable in some cases with functional neuroimaging. The first experiments to demonstrate this concerned 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 limbic and paralimbic areas, including the amygdala, anterior cingulate cortex, and orbitofrontal cortex.[20]

Drug use is not unique in this respect; other stimuli to which individuals are strongly attracted have been found to evoke activity in these neural circuits. Subjects aroused by sexually explicit videos activate many of the same limbic system areas as drug craving does.[21] Furthermore, the conscious attempt to suppress arousal may also engender a distinct pattern of brain activation.[22] For this reason neuroimaging may be more informative than peripheral measures that are capable of revealing sexual preferences.

Objects that are feared or disliked may also be discerned by brain imaging. Amygdala responses to photographs of upsetting scenes and unpleasant facial expressions are among the most reliable findings in the imaging literature on emotion.[23] Indeed, the amygdala response to such stimuli is detectable even when the photographs have been presented at subliminal exposure durations and subjects are not aware of having seen them.[24]

Forensic Imaging

The ability to know a person's attitudes and thoughts and to predict their actions would be particularly useful within the criminal justice, intelligence, and immigration enforcement communities, where interviewees are often motivated to lie or to withhold desired information. Several different applications of functional neuroimaging are being explored with support from these communities.

Lie detection is one of the most sought-after applications. The work of Langleblen and colleagues attracted tremendous media attention when it showed differences in subjects' brain activation when bluffing versus telling the truth about symbols on playing cards.[25] Lee et al. mapped the differences in brain activation in a memory task between honest test performance and simulated malingering.[26] Such research has a long way to go before it can be used to detect spontaneous, genuine deception. The forms of deception being detected in these studies involve highly constrained questions and may reflect nothing more than the additional cognitive effort required to deceive.

The "guilty knowledge test," used for decades with peripheral measures of autonomic response, has been adapted for use with scalp-recorded event-related potentials (ERPs) and marketed by ERP researcher Lawrence Farwell. The method is based on the difference in the P300 ERP evoked by familiar and unfamiliar stimuli. In Farwell's "brain fingerprinting," people, objects, or scenes associated with a crime are presented to an individual to determine whether the brain recognizes the image as familiar (such as whether a crime scene appears "familiar" to the brain despite the subjects claim he has never been there). The Brain Fingerprinting company's web site describes the method as "a new paradigm in criminal investigations and counterterrorism,"[27] and indeed it has been admitted as evidence in court[28] and is being promoted as a means of screening for terrorists, despite the reservations of leading ERP researchers such as Emmanual Donchin.[29]

In addition to the problem of discriminating intentional lies from truth, brain imaging is potentially applicable to a related problem of great legal significance: the problem of discriminating false memory from veridical memory. A false memory is a kind of memory error that occurs when a person mistakenly believes that he or she remembers an event that did not actually take place. When false memories are induced in the laboratory, they evoke patterns of

activity in memory-related areas of the brain that are distinctive from both veridical memories and correct judgments that an event did not happen. Whereas both veridical and false memories activate the hippocampus, the parahippocampal region is activated more strongly by veridical memories.[30]

Finally, the effort to predict future violent crime may eventually be aided by functional neuroimaging. Some offenders commit one violent crime and live the rest of their lives without harming anyone, whereas others continue to be violent. Personality factors correlate to some degree with these tendencies, but more recently PET and fMRI have been used on an experimental basis to distinguish these two populations.[31]

Imaging Specific Thoughts

Perhaps the most science-fictionesque example of brain imaging as mind reading comes from studies of high-level vision. Although visual processing does not have the obvious personal and social relevance that we associate with social attitudes, emotions, or tendencies to violence, the striking thing about work in this area is the specificity of the mental content that can be recovered by analyzing a brain image. Haxby and colleagues scanned subjects while they viewed numerous pictures each of faces, cats, houses, chairs, scissors, shoes, and bottles.[32] They found that the overall pattern of activation in the ventral extrastriate cortex enabled them to classify the stimulus category been viewed by the subject with 96 percent accuracy.

Working with a reduced set of stimulus categories, O'Craven and Kanwisher accomplished a similar feat with subjects' purely mental images, formed from memory in the absence of a visual stimulus.[32] After first showing subjects pictures of faces and houses and noting the locations of maximum activation to each type of stimulus, they instructed the same subjects to imagine faces and houses. For a majority of the scans, the researchers were able to tell whether a subject was thinking about a face and a house just by explaining the scan.

Ethical Issues in Neuroimaging

The main ethical problem that the scientific trends just reviewed pose concerns privacy. As with any testing method that reveals new kinds of information about an individual (genetic testing for breast cancer risk, for example), it may not always be in the individual's best interest to have that information available to others. There is an added dimension of ethical significance when the information concerns the kinds of personal traits and states that neuroimaging may reveal. The current technology can, in some cases, breach the privacy of a person's own mind, for example laying bare a disavowed attitude toward particular races. It may eventually be possible for employers, juries, parole boards, or law enforcement to examine your brain in order to answer: Are you prone to depression? How neurotic are you? To whom are you sexually attracted? How do you feel about other races? What scares you? Have you abused illegal drugs?

An individual need not know when images are used to obtain personal information. Images used for one purpose, for example medical diagnosis, may nevertheless reveal unrelated private information to whatever party evaluates (or subpoenas) the image. The experimental paradigm used by Phelps and colleagues to correlate amygdala activation with racial attitudes simply required subjects to view pictures of faces, and it could be administered in the guise of a face perception study. Brain activation can reveal attitudes and feelings that the subject may not be aware of having. For example, although subjects in Whalen's study were not aware of having seen fearful facial expressions when the expressions were presented subliminally, and cortical brain regions did not react to them, the amygdala nevertheless responded.

What obstacles lay between the present state of imaging technology and the ability reliably to read personality, psychiatric history, truthfulness and so on from an individual's brain scan? One important limitation of the current technology is the need to aggregate data over multiple observations. When the individual subject is the unit of analysis, the need for multiple trials of data collection may be impractical. Although fears or cravings can be evoked repeatedly if necessary, the recall of a specific memory cannot be repeated without changing the nature of the memory itself. For most of the examples cited here, subject groups must be compared in order to obtain reliable differences between groups (between formerly depressed and never-depressed individuals, for example), or to detect a relation to a trait (such as extraversion).

Nevertheless, even a scanning protocol that is incapable of reliably classifying all individuals may be able to classify individuals with relatively extreme patterns of brain activity, and

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so may be seen as a useful screening tool in certain circumstances. In one lab, for example, at least half of recently detoxified cocaine users could be identified by differential amygdala response to drug-related versus nondrug-related pictures.[34] In another, simple visual examination of whole brain activity patterns allowed at least a fraction of the subjects to be sorted by personality trait.[35] Even when patterns of brain activation are not extreme, they provide information sufficient to narrow the range of an individual's likely values on psychological traits of interest. Using only the published data in reports of imaging correlates of personality traits, a new individual's trait level could be bracketed within a range of 2.0 to 3.5 standard deviations (depending on the study), compared to the 4.0 standard deviation range of the population.[36]

Illusory Accuracy

In addition to privacy concerns, neuroimaging is liable to over-reliance on, or misapplication of, information from brain scans. The ability to assess personality, attitudes, and desires would be of interest in screening for employment, school tracking, or military service. The ability to distinguish between truth and falsehood, or veridical and false memory, would find wide use in the legal system. The demand for these abilities, coupled with the inevitable misunderstandings of brain imaging among the lay public, sets the stage for misuse. Physiological measures, especially brain-based measures, possess an illusory accuracy and objectivity as perceived by the general public. In proposing the use of brain fingerprinting as a screening tool at airports, one commentator wrote, "Although people lie . . . brainwaves do not."[37]

Although brainwaves do not lie, neither do they tell the truth; they are simply measures of brain activity. Whether based on regional cerebral bloodflow or electrical activity, brain images must be interpreted like any other correlate of mental activity, behavioral or physiological. Brain images and waveforms give an impression of concreteness and directness compared to behavioral measures of psychological traits and states, and high-tech instrumentation lends an aura of accuracy and objectivity. Nevertheless, the psychological interpretations of these measures are far from direct or intrinsically objective. As the foregoing review suggests, progress has been made in the use of such measures, and some inferences to socially relevant traits and states can now be made with a degree of certainty under specific and highly controlled conditions. However, the current state of the art does not allow reliable screening, profiling, or lie detection.

There is no reason to doubt that the state of the art will improve in the coming years. Brain-based measures do, in principle, have an advantage as indices of psychological traits and states over more familiar behavioral or autonomic measures. They are one causal step closer to these traits and states than responses on personality questionnaires or 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 use these technologies prematurely.

Brain Enhancement

The psychopharmacology of the mid-twentieth century depended entirely on serendipity. The antihistamine chlorpromazine was accidentally found to calm agitated schizophrenic patients and reduce their psychosis. Another early drug investigated for its antipsychotic properties, imipramine, turned out to be ineffective for that purpose, but was observed to lift the mood of some of the patients taking it. When a small number of patients with major depression tried it, the therapeutic effect was dramatic, and imipramine continues to be used as an antidepressant today. The second antidepressant to be discovered, iproniazid, was hitherto used as an antibiotic for treating patients with tuberculosis when its mood-elevating properties were observed. Similar accidental discoveries led to the identification of amphetamine as a stimulant in the course of refining a treatment for asthma, and meprobamate as an anti-anxiety treatment in the course of testing an antibiotic.[38]

Such lucky accidents were then augmented by trial and error tests with other molecules of similar structure. Parallel to this development, researchers began to understand the effects of these drugs on brain function, identifying the specific neurotransmitter systems affected by the drugs and the mechanisms by which the drugs interacted with these systems. The advent of direct-binding assays in the 1960s provided the first direct approach to testing and comparing the affinity of a drug for different

The military's substantial support for brain-machine interfaces suggests that some think normal healthy individuals might someday be enhanced by neural prostheses.

neurotransmitter receptors, and the tools of the molecular biology revolution, including the cloning of rare subtypes of receptors, allowed for the design of highly selective agonists, antagonists, and other molecules to influence selectively the process of neurotransmission.

The continual improvement in side-effect profile of modern psychotropic medications is due to the increasing selectivity of drug action made possible by the methods of molecular neuroscience. "Selective" is the first S in SSRI, the class of drugs to which fluoxetine (Prozac) belongs. New drugs with ever more selective actions on the neurochemistry of mood, anxiety, attention, and memory are under development. Although intended for therapy, many of these drugs affect brain function in healthy people, raising the possibility of their use for enhancement of normal function rather than remediation of dysfuntion.

The enhancement potential of some medications is, in itself, nothing new, and the attempts of human beings to use chemical substances to alter normal affective and cognitive traits is as old as the drinking of alcohol. Until recently, however, psychotropic drugs had significant risks and side effects that limited their attractiveness. This situation is changing as side-effect profiles become more tolerable. In addition, therapy in conjunction with other drugs is an increasingly common strategy for counteracting the remaining side effects. For example, the most troublesome side effect for users of 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. The result of both new designer drugs and adjuvant drugs is the same: increasingly selective alteration of our mental states and abilities through neurochemical intervention, with correspondingly less downside to their use by anyone, sick or well.

Technical advances in non-pharmaceutical methods for altering brain function are also creating potential enhancement tools. Transcranial magnetic stimulation (TMS) and, more rarely, vagus nerve stimulation and deep-brain stimulation have already been used to improve mental function or mood in patients with medically intractable neuropsychiatric illnesses.[39] Research on the effects of non-pharmaceutical methods on brain function in normal individuals has been limited to the relatively less invasive TMS. Mood effects on normal healthy subjects have been investigated in the context of basic research on mood and brain function,[40] and at least one laboratory is devoted to the development of TMS methods for enhancing normal cognition.[41] Finally, there is growing research interest in computer augmentation of brains. Most research on brain-machine interfaces currently focuses on capturing and using movement command signals from the brain and carrying sensory inputs to the brain, for example from a video camera.[42] One research program is tackling memory augmentation by developing a prosthetic hippocampus that can be interfaced with a rodent brain.[43] The motivation for this research is partly scientific, to better understand neural coding of sensory, motor, and memory information, and partly clinical, to help patients with paralysis and peripheral sensory impairments.

Nevertheless, the military's substantial support for this research suggests that some think normal healthy individuals might someday be enhanced by neural prostheses.[44]

Enhancement of Normal Mood

Amphetamines, barbituates, benzodiazepenes, and other "mother's little helpers" have long been used to improve the moods of healthy people. However, the high potential for addiction and tolerance with these drugs dissuades most people from using them. Pre-SSRI antidepressants, while presenting no such risks, have unpleasant side effects that limit their appeal only to those faced with clinical depression as the alternative. The SSRIs, in contrast, have relatively narrower neurochemical effects and consequently fewer side effects. The result, as Peter Kramer described in Listening to Prozac, is that many people who would never have taken a tricyclic antidepressant are taking SSRIs.[45]

Of course, most people using SSRIs meet DSM IV criteria for some psychiatric disorder, although not necessarily major depression: dysthymia (a mild depression), social phobia (an extreme form of shyness and self-consciousness), premenstrual dysphoric disorder (a recurrent negative mood associated with PMS) and various eating disorders respond well to SSRIs. It nevertheless remains controversial whether some of these diagnostic categories are medicalized labels for normal variants of human personality, which do not necessarily require pharmaceutical treatment. In addition, some people using SSRIs have no recognized illness. These include people who have suffered from depression in the past and choose to continue medication prophylactically, as well as people who, in Peter Kramer's words, feel "better than well" when taking an antidepressant.

What is the effect of SSRIs on normal, healthy individuals? While no systematic studies have examined individuals who choose to take these medications, a handful of studies have assessed the effects of SSRIs on mood and personality in randomly selected healthy subjects over short periods of a few months or less.[46] Effects on mood are relatively selective, reducing self-reported negative affect while leaving positive affect neither increased nor decreased. The drugs also increased affiliative behavior in laboratory social interactions and cooperative/competitive games played with confederates. For example, subjects on the drug spoke fewer commands and instead made more suggestions. In one double-blind crossover design, subjects were not

only more cooperative in a game, but showed real world changes in behavior as well: Flatmates found the subjects less submissive on citalopam, though no more dominant or hostile.[47] Although more research is needed to clarify the effects of SSRIs and other antidepressant agents on mood and behavior of normal healthy subjects, and long-term studies are needed on those who choose to take SSRIs in real-life settings, the evidence so far suggests subtle but salutary effects without significant short-term side effects.

Enhancement of Cognition

Our current ability to enhance cognition through the direct alteration of brain function involves two types of cognitive function: attention and memory. "Attention" is used here in its broadest sense, including active use of working memory, executive function, and other forms of cognitive self-control. These are the cognitive abilities most obviously deficient in the syndrome of Attention Deficit Hyperactivity Disorder (ADHD). These same abilities vary in their strength within the normal population. Indeed it seems likely that ADHD represents the lower tail of the whole population distribution rather than a qualitatively different state of functioning, discontinuous with the normal population.[48]

Drugs targeting the neurotransmitter systems dopamine and norephinephrine are effective in treating ADHD, and have been shown to improve normal attentional function as well. Methyphenidate (Ritalin) and amphetamine (Adderal), as well as modafinil (Provigil, a newer drug approved for regulating sleep) have been shown to enhance attention across a variety of different tests in healthy young volunteers.[49]

Do these laboratory-measured improvements translate into a noticeable improvement of real world cognitive performance? No experimental evidence is available, but the growing illicit use of ADHD medications on college campuses suggests that many young adults believe their cognition is enhanced by the drugs.[50] Parents also appear to find real world benefits for their normal children with ADHD medication: In certain school districts the proportion of boys taking methylphenidate exceeds the most generous estimates of ADHD prevalence.[51]

Memory is the other cognitive ability that can, at present, be manipulated to some degree by drugs. Interest in memory enhancement has so far been confined to the middle-aged and elderly, whose memory ability undergoes a gradual decline even in the absence of dementia. The most commonly used method involves manipulation not of memory circuits per se but of cerebrovascular function. Herbal supplements such as Gingko Biloba affect memory mainly by increasing blood flow within the brain. However, the effectiveness of this treatment is questionable.[52] How close are we to more specific and effective memory enhancement for healthy older adults?

As the molecular biology of memory progresses, it presents drug designers with a variety of entry points through which to influence the specific processes of memory formation. A huge research effort is now being directed to the development of memory-boosting drugs.[53] The candidate drugs target various stages in the molecular cascade that underlies memory formation, including the initial induction of long-term potentiation (LTP) and the later stages of memory consolidation. There is reason to believe that some of the products under development would work for enhancement as well as therapy. For example, treatment of healthy human subjects with an ampakine, which enhances LTP, improved performance in a dose-dependent manner.[54]

Few consider memory enhancement for the young to be a goal. Although some specialized pursuits such as certain competitive card games could conceivably benefit from super-memory, evidence suggests that the forgetting rates of normal young humans are optimal for most purposes.[55] Empirically, prodigious memory has been linked to difficulties with thinking and problem solving,[56] and computationally, the effect of boosting the durability of individual memories is to decrease the ability to generalize.[57]

Indeed, in some circumstances reduced learning would confer benefit. Memories of traumatic events can cause lifelong suffering in the form of post traumatic stress disorder (PTSD), and methods are being sought to prevent the consolidation of such memories by intervening pharmacologically immediately following the trauma.[58] Drugs that interfere with the consolidation of memories in general, such as benzodiazepines, are well known.[59] Extending these methods beyond the victims of trauma, to anyone wishing to avoid remembering an unpleasant event, is yet another way in which the neural bases of memory could be altered to enhance normal function.

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Ethical Issues in Enhancement

Although the promise of enhancement is easy to identify—smarter, more cheerful, and more capable people—the risk is harder to articulate. Most people feel at least some ambivalence about neuropsychological enhancement, but distinguishing realistic or compelling arguments from generalized fear is often difficult.

Many of the ethical issues raised by neuropsychological enhancement also arise with other types of enhancement.[60] Cosmetic surgery and the use of human growth hormone for healthy children who are naturally short, for example, are medical enhancements that do not affect brain function, and though both are controversial, both are generally accepted. Enhancement techniques that affect brain function through more familiar and non-neuroscience-based interventions such as biofeedback, meditation, tutoring, or psychotherapy are not seen as objectionable, and, in fact, are often seen as laudable. What, then, are the objections to using pharmaceutical or other neurotechnological means to achieve the same ends as behavioral techniques? Much recent discussion has focused on this question.[61] Although few if any ethical concerns arise uniquely in connection with neuroscience-based methods, two concerns seem particularly salient in the context of neural interventions for enhancement compared with other biomedical interventions whose targets are not psychological, on the one hand, and behavioral interventions for psychological enhancement, on the other.[62]

The first of these concerns is safety. Safety is a concern with all medications and procedures, but in comparison to other comparably elective treatments such as cosmetic surgery or growth hormone treatment, neuroscience-based enhancement involves intervening in a far more complex system. We are therefore at greater risk of unanticipated problems when we tinker. Would endowing learners with supermemory interfere with their ability to understand what they have learned and relate it to other knowledge? Might today's Ritalin users face an old age of premature cognitive decline? These are empirical questions, of course, which can only be answered in time. So far, medications such as SSRIs and stimulants have good safety records, and their long-term effects may even be positive. For example, SSRIs have been shown to be neuroprotective over the long term.[63] A recent study of the effects of Ritalin on rat brain development showed both desirable and undesirable effects on later adult behavior.[64] Nevertheless, drug safety testing does not routinely address long-term use, and relatively little evidence is available on long-term use by healthy subjects. It remains an open empirical issue whether the net effects of these or other yet-to-be developed drugs are positive or negative.

The second concern about neuroscience-based enhancement is more complex and difficult to state succinctly. This is actually a group of related concerns resulting from the many ways in which neuroscience-based enhancement intersects with our understanding of what it means to be a person, to be healthy and whole, to do meaningful work, and to value human life in all its imperfection. The recent report of the President's Council on Bioethics emphasized these issues in its discussion of enhancement. At the heart of this group of concerns is the problem of reconciling our understanding of persons and brains.[65]

Among the widely shared intuitions about persons are the following: Persons have a kind of value that is independent of any commodity or capability they bring to the world. Persons are responsible for their actions and deserve blame or respect depending on those actions. Persons lead lives that have meaning, and although it is difficult to say exactly what is meant by "meaning" in this context, most of us would agree that accomplishments in life are made meaningful partly by the effort they require. Finally, persons endure over time; although some of their characteristics may change, there is a self that remains constant for as long as the person can be said to exist.

Brains are physical systems and as such do not share any of the foregoing qualities. Of course, neuroscience-based enhancements work because changes to the brain result in changes to the person. To use such enhancements, without infringing on our personhood, can seem a contradiction, or at least perplexing, and raises a number of concerns. Maximizing the performance capabilities of an already healthy, functional person can be viewed as commodifying human abilities. Improving behavior pharmacologically seems to detract from the responsibility of the person for his or her own actions. Reducing the effort needed for personal accomplishments by neurochemical means may reduce their meaning as well. And the changing of abilities, memories, and moods at will by swallowing a pill may undermine the idea of a constant "self."

Pending Challenges

Technologies for monitoring and manipulating the brain have developed rapidly over the last few decades and are poised for continued growth. Some of the ethical problems posed by these developments have immediate practical consequences. Examples of such problems include the illusory accuracy of brain images in forensic contexts and the unknown safety of long-term stimulant use by healthy adults and children. Other ethical problems are on the horizon, pending further technological progress. For example, brain imaging will not pose a serious threat to privacy until scanning methods can reliably deliver useful information about individual subjects. Although this is not the case at present, the development is foreseeable and could have enormous practical consequences.

Another way in which developments in neuroscience will influence

society is less tangible than those just mentioned, but no less consequential. Both brain imaging and brain-based enhancement are forcing us to confront the fact that we are physical systems. If specific abilities, personality traits, and dispositions are manifest in characteristic patterns of brain activation and can be manipulated by specific neurochemical interventions, then they must be part of the physical world. Our intuitions about personhood do not mesh easily with this realization. At the very least, the realization calls for a considerably more nuanced idea of personal responsibility in law and morality.[65] More generally, it will prove challenging to traditional ideas regarding the soul, or the nonmaterial component of the human mind.

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