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BACKGROUND BRIEFING

NEUROETHICS

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ABSTRACT
Neuroimaging, psychosurgery, deep-brain stimulation, and psychopharmacology hold considerable promise for more accurate prediction and diagnosis and more effective treatment of neurological and psychiatric disorders. Some forms of psychopharmacology may even be able to enhance normal cognitive and affective capacities. But the brain remains the most complex and least understood of all the organs in the human body. Mapping the neural correlates of the mind through brain scans, and altering these correlates through surgery, stimulation, or pharmacological interventions can affect us in both positive and negative ways. We need to carefully weigh the potential benefit against the potential harm of such techniques. This paper examines some of these techniques and explores the emerging ethical issues in clinical neuroscience.

INTRODUCTION

Some of the most innovative and exciting work in contemporary medicine is being done in the clinical neurosciences of psychiatry, neurology, and neurosurgery. Advances in basic and clinical neuroscience during the last 25 years, combined with advances in radiology, have provided new insight into the relation between the human brain and mind. They have also contributed to a better understanding of the differences between normal and abnormal brain activity, as well as to the etiology and progression of diseases of the brain. The significance of these advances is illustrated by the fact that psychiatric and neurological disorders affect roughly 400 million people globally. In June 2004, the *Journal of the American Medical Association* published results from the world's largest survey on mental health. From 1–5% of the populations of most countries surveyed have serious mental illness, much of it untreated or undertreated.[1]

Neuroimaging in the form of computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and functional magnetic resonance imaging (fMRI) can reveal the neurobiological bases of both normal mental activity and various psychopathologies. Brain scans may detect early signs of neurological

[1] WHO World Mental Health Survey Consortium. Prevalence Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys. *J Am Med Assoc* 2004; 291: 2581–2590.

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and psychiatric disorders well before their characteristic symptoms appear. Psychosurgery can alleviate or even eliminate the symptoms of obsessive-compulsive disorder (OCD), severe depression, and other conditions that are refractory to all other treatments. Electrical and magnetic stimulation of the brain may relieve these symptoms in a non-invasive way. Stimulating electrodes implanted deep in the brain can enable people with motor disorders such as Parkinson's disease to regain some control of their body. Antidepressant and antipsychotic drugs may restore or regenerate neurons and neuronal connections disrupted or destroyed by depression and schizophrenia. It may even be possible to use psychotropic drugs to enhance normal cognition and mood.

But the ability to map, intervene in, and alter the neural correlates of the mind raises important ethical questions. Indeed, these questions are arguably weightier and more momentous than any other set of questions in any other area of bioethics. This is because techniques that target the brain can reveal and modify the source of the mind and affect personal identity, the will, and other aspects of our selves.[2] The mind consists of interrelated cognitive, affective, and conative capacities, which include beliefs, desires, emotions, and volitions that are generated and sustained by the brain. These core features of the philosophy of mind overlap with the ethical notions of benefit and harm, since whether an action benefits or harms one depends on whether and how it affects one's mind. Our identities as persons, our experience of agency, and our first-person phenomenological experience as conscious beings consist in the unity and integrity of our mental states. Mapping or intervening in the brain can reveal and affect the nature and content of our minds and thus who we essentially are.

[2] Certain genes and the proteins they encode can influence the structure and function of the brain and in turn the nature and content of the mind. Yet these genes only shape the broad outline of mental and behavioral functions and therefore do not determine the mind. Moreover, some actions of the endocrine and immune systems can influence our mental states. Stress hormones such as adrenaline and cortisol released by the adrenal glands can affect structures of the central nervous system that sustain our mental states. A certain class of cytokines released by the immune system can also disrupt critical functions of the central nervous system and can causally contribute to or exacerbate the negative moods symptomatic of major depression. So the biological basis of the mind is mainly but not entirely neurobiological.

I will explore some of the ethical issues in five broad areas of clinical neuroscience: diagnostic neuroimaging, predictive neuroimaging, psychosurgery, neurostimulation, and cognitive and affective enhancement. There are other areas of neuroscience that raise additional ethical issues.[3] But I will limit the discussion to the issues that are or will become the most prominent and controversial in this rapidly developing field.

DIAGNOSTIC NEUROIMAGING

The main purpose of CT, PET, SPECT, MRI, and fMRI scans in medicine has been and will continue to be to confirm a diagnosis based on behavioral symptoms and established clinical criteria. As more sophisticated and higher-resolution versions of this technology develop, pharmacological and surgical interventions will more precisely target damaged regions of the brain and thereby enable more effective treatments for neurological and psychiatric disorders. For example, more refined images of glucose metabolism in the prefrontal cortex may help psychiatrists to administer antidepressants that more directly affect serotonergic and noradrenergic receptors in the brain. This could at once relieve depressive symptoms and minimize adverse side effects. The potential therapeutic value of neuroimaging for this and related purposes is obvious. There are other potential uses of diagnostic brain imaging that are more ethically contentious, however.

Suppose that one person kills another in a fit of rage and is charged with second-degree murder. The offender claims that his action resulted from a violent impulse he could not control. He undergoes MRI and PET scans, which show structural damage and abnormal function in the prefrontal cortex of his brain. This brain region is the seat of executive

[3] For general discussion of a full range of neuroethical issues, see R. Blank. 1999. *Brain Policy: How the New Neuroscience Will Change Our Lives and Our Politics.* Washington, D.C. Georgetown University Press; S. Marcus, ed. 2002. *Neuroethics: Mapping the Field*. New York. Dana Press; M. Farah & P.R. Wolpe. Monitoring and Manipulating Brain Function: New Neuroscience Technologies and their Ethical Implications. *Hastings Cent Rep* 2004; 34: 35–45; Steven Rose. 2005. *The Future of the Brain: The Promise and Perils of Tomorrow's Neuroscience*. Oxford: Oxford University Press; and J. Illes, ed. 2005. *Neuroethics: Defining the Issues in Theory, Practice and Policy*. New York: Oxford: Oxford University Press.

functions regulating decisions and actions and is crucial for rational planning and impulse control. The offender and his defense lawyer argue that the brain damage undermined his capacity for moral reasoning and his ability to control his behavior. To be morally and legally responsible for one's behavior, one must have the capacity to control that behavior. Because the offender lacked this capacity, he could not be responsible for killing his victim and thus should be exonerated. Would this defense be convincing in a court of law? To answer this question, we need to look at empirical studies in brain science and what they indicate about the neurobiological basis of behavior.

Studies conducted by neurologist Antonio Damasio and colleagues have shown that lesions in the orbitofrontal cortex of the brain correlate with impulsive and antisocial behavior.[4] Despite being intellectually unimpaired, individuals with damage to this region seem unable to conform to social and moral norms when they act. Adults and children who sustained this damage presented with a syndrome resembling psychopathy. Similarly, brain-imaging studies by psychologists Adrian Raine and Richard Davidson have also shown that some violent people have diminished activity in the prefrontal region of the brain.[5] At the same time, these individuals have increased activity in the amygdala, the most important region of the limbic system that regulates emotions. Specifically, an overactive amygdala often correlates with heightened negative emotions such as fear and anger. PET and fMRI scans measure the rate of glucose uptake by brain cells. Diminished glucose metabolism is a marker for diminished functioning in regions such as the prefrontal cortex. Heightened glucose metabolism can be a marker for overactive functioning in limbic structures such as the amygdala. The studies by Damasio, Raine, and Davidson suggest that structural and functional abnormalities in the brain regions underlying the mental states leading to actions can undermine one's ability to control these states and actions.

The prefrontal cortex, amygdala, and other interacting brain regions constitute a complex neural circuit that controls interacting cognitive and emotional systems. By generating and sustaining these systems, the brain generates and sustains the mind. This model of the mind is monistic rather than dualistic because it conceives of brain and mind as interdependent aspects of a human organism. Cognitive information processing in the prefrontal cortex regulates emotional processing in the limbic system. Emotional processing in the limbic system regulates planning, decision-making, and other cognitive and executive functions in the prefrontal cortex. Each of these brain regions modulates the other in a feedback loop. Normal functioning of these two interdependent systems ensures a healthy balance between cognition and emotion. Damage to either of these regions of the brain can disrupt this balance and cause a person to lose control of his motivational states and actions. Given the damage to his prefrontal cortex, the individual in my hypothetical case presumably would lack control of his emotions and impulses and would not be responsible for his behavior. But in many cases brain dysfunction by itself does not explain violent behavior or prove that a person cannot control his actions and cannot be responsible for them.

In the *Nicomachean Ethics*, Aristotle defends the default assumption that a person acts freely and is morally responsible for his behavior barring evidence of compulsion, coercion, or ignorance of the circumstances of action.[6] The first two of these conditions are metaphysical, or freedom-relevant, while the third condition is epistemological, or knowledge-relevant. A person can be excused from responsibility for his behavior when any of these

[4] A. Damasio et al. Impairment of Social and Moral Behavior Related to Early Damage in Human Prefrontal Cortex. *Nat Neurosci* 1999; 2: 1032–1037. Also, A. Damasio. A Neural Basis for Sociopathy. *Arch Gen Psychiatry* 2000; 57: 128; A. Damasio. The Neural Basis of Social Behavior: Ethical Implications. In Marcus, ibid, pp. 14–19; and P.S. Churchland. Neuroscience: Reflections on the Neural Basis of Morality. In Marcus, ibid. pp. 20–26.

[5] A. Raine et al. Reduced Prefrontal Gray Matter Volume and Reduced Autonomic Activity in Antisocial Personality Disorder. *Arch Gen Psychiatry* 2000; 58: 119–127; R. Davidson et al. Dysfunction in the Neural Circuitry of Emotion Regulation – A Possible Prelude to Violence. *Science* 2000; 289: 591–594. Also, K.A. Kiel et al. Limbic Abnormalities in Affective Processing by Criminal Psychopaths as Revealed by Functional Magnetic Resonance Imaging. *Biol Psychiatry* 2001; 50: 677–684.

[6] *The Complete Works of Aristotle*. 1984. Volume II, Book III, J. Barnes trans. and ed. Princeton, Princeton University Press. Hart defends a similar default position in H.L.A. Hart. 1968. *Punishment and Responsibility*. Oxford. Clarendon Press.

conditions is present. Impulsive violent behavior correlating with structural or functional brain abnormalities would appear to meet Aristotle's excusing conditions. Yet free will is often not an all-or-nothing capacity. Instead, it is a capacity that comes in degrees along a spectrum of control.[7] At one end of the spectrum, persons are in complete control of their behavior and are completely responsible for what they do. At the other end of the spectrum, persons have no control of their behavior and should be completely excused from responsibility for what they do. Many cases involving violent criminal behavior fall in a gray area between the two extremes. Just as there are degrees of control of behavior, so too there are degrees of responsibility for behavior.

There are differences between moral and legal responsibility. For example, strict liability has no equivalent in the moral domain. In general, though, both moral and legal conceptions of responsibility presuppose certain mental capacities. The Model Penal Code version of the Not Guilty By Reason of Insanity defense has cognitive and volitional components. According to the first component, a person is not guilty if he suffers from a mental illness causing him to be ignorant of what he is doing. According to the second component, a person is not guilty if he suffers from a mental illness causing him to lose control of his impulses.[8] These same legal conditions apply to judgments about moral responsibility.

The degree of control one has over one's motivational states and actions is obviously influenced by the brain. But it can be influenced by factors in the social and physical environment as well. In addition, some people may put more mental effort than others into exercising the control they have over their behavior. Just because one displays weakness of will does not mean that one lacks free will. Except for cases of severe damage to regions of the brain directly regulating the capacity for moral reasoning and choice, how much control one has over one's behavior, and how responsible one is for it, will not be determined by measuring brain function or dysfunction alone.

Most brain-damaged people are not violent. So it is implausible to claim that structural and functional abnormalities in the brain always cause violent behavior. Nor does brain dysfunction constitute a sufficient reason to excuse people from responsibility for what they do. Perhaps the best illustration of this point is psychopathy. This is a disorder characterized by callousness, diminished capacity for empathy and remorse, and poor behavior controls.[9] Impaired moral reasoning may be due to deficits in emotional processing or in arousal to fear-inducing stimuli. A deficit in the ability to feel remorse and empathy may explain why psychopaths fail to consider the interests of others when they act. A deficit in the ability to experience fear may explain why they act impulsively. In imaging studies similar to those conducted by Damasio, R.J.R. Blair has shown that children with psychopathic tendencies have structural and functional abnormalities in the orbitofrontal cortex and the amygdala.[10] Interestingly, unlike violent individuals, psychopaths tend to have a hypoactive rather than hyperactive amygdala. Nevertheless, psychopaths do not completely lack the capacity to control their impulses. Moreover, although they act without concern for the needs and interests of others, they have some understanding of what it means to harm someone and that other people can be harmed by their actions. On this basis, psychopaths seem to have

[7] Churchland discusses this concept of free will in Neuroscience: Reflections on the Neural Basis of Morality, and in 2002. *Brain-Wise: Studies in Neurophilosophy*. Cambridge, MA. MIT Press: Chapter 5. See also John Martin Fischer. 1994. *The Metaphysics of Free Will: An Essay on Control*. Cambridge, MA. Blackwell; J.D. Greene et al. The Neural Basis of Cognitive Conflict and Control in Moral Judgment. *Neuron* 2004; 44: 389–400, and W. Glannon. Neurobiology, Neuroimaging, and Free Will. *Midwest Studies in Philosophy* 2005; 29: 68–82.

[8] *Model Penal Code*. 1985. Official Draft and Revised Commentaries. Philadelphia. American Law Institute. Compare this with the *M'Naghten Rules* 1843. Cited in the *Report on the Committee on Mentally Abnormal Offenders*. 1975. London. Her Majesty's Stationery Office. For discussion of the similarities and differences between philosophical and legal notions of responsibility in the light of neuroscience, see Stephen Morse. 2004. New Neuroscience, Old Problems. In *Neuroscience and the Law: Brain, Mind, and the Scales of Justice*. Brent Garland, ed. New York. Dana Press: 157–198; and Michael Gazzaniga & Megan Steven. Free Will in the Twenty-First Century: A Discussion of Neuroscience and the Law. In Garland, ibid, pp. 51–70.

[9] R.D. Hare. 1994. *Without Empathy: The Strange World of the Psychopaths Among Us*. New York. Pocket Books; and Hervey Cleckley. 1967. *The Mask of Sanity*. St. Louis. Mosby.

[10] R.J.R. Blair and L. Cipolotti. Impaired Social Response Reversal: A Case of 'Acquired Sociopathy'. *Brain* 2000; 123: 1122–1141; R.J.R. Blair. Neurological Basis of Psychopathy. *Br J Psychiatry* 2003; 182: 5–7. Also, N. Camille et al. The Involvement of the Orbitofrontal Cortex in the Experience of Regret. *Science* 2004; 304: 1167–1170.

some control over their behavior and can be at least partly responsible for it.[11] In these and other cases, brain images alone will not enable us to draw a clear distinction between responsibility and excuse.

Another difficulty with brain imaging is that regions other than the orbitofrontal cortex may play a role in cognitive processing. Focusing on this region alone may be an oversimplified way of explaining the link between the brain and behavior. An abnormality in this region does not necessarily mean that the balance between cognitive and emotional processing has been entirely disrupted. The parietal cortex may also play a role in maintaining this balance. Reasoning and executive functions are probably distributed across multiple regions of the cortex.[12] Even the subcortical cerebellum appears to play a role in cognition in addition to regulating motor function. In a deeper sense, scans of the prefrontal cortex or other regions of the brain will not tell us *how* our actions are willed. They cannot explain how actions issue from intentions and decisions. Nor can they explain the phenomenology of free will, or why we *feel* in control (or out of control) of our actions. This is because the relation between the structure and function of the prefrontal cortex and our motivational states and actions is one of correlation rather than causation.

A similar problem besets those who would insist on using brain scans to test for damage to brain systems controlling declarative, or explicit, memory. This consists in the capacity for conscious recollection of specific facts and events. Negligent acts or omissions that result in harm to others may be due to damage or dysfunction in the network involving the hippocampus and neocortex that regulates memory retrieval.[13] But a scan of one brain region will not decisively tell us whether a mother whose child dies from hyperthermia in an overheated car was unable to remember leaving her in the car because of brain dysfunction, or whether she was able to remember but failed to exercise her capacity to do so.[14] Several regions in the brain regulate the formation, storage, and retrieval of memory. Dysfunction in one region does not necessarily mean that other regions are also dysfunctional. There are redundancies in the brain. Some systems can compensate for others that have been damaged and can perform the same tasks.

The main reason for questioning the use of neuroimaging to make ethical or legal judgments is that it involves a move from empirical claims about the brain to normative claims about how people ought to behave. Free will and responsibility are not primarily empirical but normative notions reflecting social conventions and expectations about how people can or should act. Although our understanding of free will and responsibility is informed to some extent by brain science, normative claims cannot be reduced to empirical ones. This is the principal reason why questions about control and responsibility cannot be answered by appeal to brain imaging alone. What complicates this problem is that brain-based measures of psychological traits have an illusory accuracy and objectivity. An fMRI scan showing anomalous brain function is not necessarily diagnostic, because it can be modulated by the experimental tasks taken to mimic actual functions in the scanner. There is also the potential for bias in the design of functional imaging experiments using brain-damaged patients, which can influence how data from these experiments are analyzed. If this bias can be eliminated, and if brain scans can be perfected, then we may have a more accurate picture of the link between the brain and the mind. This would minimize the risk of abuse of information about the brain. Yet, as American cognitive neuroscientist Martha Farah points out, 'for now, however, this is not the case, and there is the risk that juries, judges, parole boards, the immigration service and so on will weigh such measures too heavily in their decision-making'.[15] Even if functional

[11] C. Elliott. Diagnosing Blame: Responsibility and the Psychopath. *J Med Philos* 1992; 17(2): 199–214.

[12] M.L. Platt & P.W. Glimcher. Neural Correlates of Decision Variables in Parietal Cortex. *Nature* 1999; 400: 233–238; M.L. Platt. Neural Correlates of Decisions. *Curr Opin Neurobiol* 2003; 13: 141–148. LeDoux defends the distributive view of cognitive, emotional, and executive functions in J. LeDoux. 2002. *The Synaptic Self: How Our Brains Become Who We Are*. New York. Viking: 187 ff.

[13] See D. Schacter. 1996. *Searching for Memory: The Brain, the Mind, and the Past.* New York. Basic Books.

[14] This refers to Schacter's account of the case of Carrie Engholm in his testimony before the US President's Commission on Bioethics, Seventh Meeting, 17 October 2002. Session 3: Remembering and Forgetting: Physiological and Pharmacological Aspects. Transcript: 14–15. At http://www.bioethics.gov/transcripts/oct02/session3/html.

[15] M. Farah. Emerging Ethical Issues in Neuroscience. *Nat Neurosci* 2002; 5: 1127.

neuroimaging is perfected, it will not necessarily translate into simple answers to normative questions such as when and to what degree people are responsible. These will always be influenced by social norms.

More sophisticated higher-resolution brain scans may enable researchers to identify features of the brain that play an important role in moral reasoning and the execution of intention in action. Moreover, they may enable researchers to distinguish between true and false memory and thus improve the science of lie detection.[16] Ideally, the combination of this technology and established clinical criteria will contribute to a clearer distinction between complete responsibility, on the one hand, and excuse or mitigation, on the other. The information derived from functional neuroimaging will be a helpful tool indeed. But it should supplement, not supplant, existing criteria of responsibility and liability in the criminal justice system. Because it is still an imprecise science, it will be some time before diagnostic brain imaging is or should be used as evidence in criminal law, in the same way that DNA evidence is now used.

More ethically controversial is whether we should intervene in the neural circuitry or biochemistry of people whose structural and functional brain images display abnormalities that strongly correlate with violent behavior. Even if this intervention were done with the best of intentions, surgical manipulation of the brain as a form of forced behavior control would be morally objectionable to most people. Would we think the same way about pharmacological intervention that could restore normal cognitive processing in the prefrontal cortex and normal emotional processing in the amygdala? This would not be as objectionable as psychosurgery because it would not entail permanent modification of the brain. Nor would drug treatment be as invasive. Doses of selective serotonin reuptake inhibitors (SSRIs) might increase serotonin levels in the prefrontal cortex and in turn might decrease aggression by modulating a hyperactive amygdala. What if forced pharmacological intervention could modulate violent impulses and thereby prevent violent actions from being committed? Although they would not be as objectionable as psychosurgery, would there still be reasons against using pharmacological agents for this purpose?

The question is especially contentious in the case of children with severe abnormalities in the prefrontal cortex and no moral sensibility. A bleak future of psychopathy and violence may be written into their neurons. Unless they had structural or functional brain damage that was beyond repair, intervening pharmacologically at an early age to correct or ameliorate brain dysfunction might prevent a lifetime of criminal behavior. The personalities of these individuals would be altered, and they could not give informed consent to this intervention. But would this be morally objectionable if their pathological personalities entailed a high risk of harm to themselves and others? Even if one answered this question affirmatively, the prospect of personality change would have to be weighed against the prevention of harm that could result from the intervention. Philosopher Patricia Smith Churchland's views on this issue are instructive:

> Certainly, some kinds of direct intervention are morally objectionable. So much is easy. But *all* kinds? Even pharmacological? Is it possible that some forms of nervous-system intervention might be more humane than lifelong incarceration or death? I do not wish to propose specific guidelines to allow or disallow any form of direct intervention. Nevertheless, given what we now understand about the role of emotion in reason, perhaps the time has come to give such guidelines a calm and thorough reconsideration.[17]

PREDICTIVE NEUROIMAGING

Diagnostic and predictive brain scans involve very different patient populations. In recently published studies, brain scans of adolescents considered at

[16] D. Langleben et al. Brain Activity During Simulated Deception: An Event-Related Functional Magnetic Resonance Study. *Neuroimage* 2002; 15: 727–732. L. Tancredi explores these and other possible legal applications of brain imaging in Neuroscience Developments and the Law. In Garland, *op. cit.* note 8, pp. 71–113. See also H. Greely. Prediction, Litigation, Privacy, and Property: Some Possible Legal and Social Implications of Advances in Neuroscience. In Garland, *op. cit.* note 8, pp. 114–156; and Neuroscience, Ethics and the Law. In Illes, *op. cit.* note 3.

[17] Churchland, *op. cit.* note 7, pp. 235–236.

high risk for schizophrenia showed structural and functional abnormalities in certain regions of their brains.[18] The abnormalities became even more marked once they went on to develop psychotic symptoms and were diagnosed with schizophrenia. These subjects had less gray matter in the frontal and temporal lobes, as well as in the cingulate gyrus. Diminished gray matter in these brain regions is associated with the disrupted cognitive processing symptomatic of schizophrenia. Most significant about this study was that the images predicted this mental disorder before the subjects developed full-blown symptoms. This suggests the possibility of using structural MRI scans to predict later-onset neurological and psychiatric disorders. Schizophrenia is one of the most debilitating of these disorders. Once symptoms of cognitive impairment appear, brain images showing critical neurological markers could enable physicians to administer antipsychotic drugs that could better control the progression of the disease. Early pharmacological intervention might also prevent or delay the onset of psychosis. The earlier this and other mental disorders are treated, the better is their prognosis. This is especially important because of the rapidly changing neural circuitry in adolescents.

Imaging techniques can also show diminished glucose metabolism in the hippocampus. As noted, this is one of the brain regions that regulate memory. These techniques may be developed to the point where they can reveal a loss of cholinergic neurons in this and other brain regions. Brain scans can also display the first signs of amyloid plaques and neurofibrillary tangles. All of these are signature characteristics of Alzheimer's disease, which is by far the most common form of dementia. Significantly, brain scans already may reveal indicators of this disease years before memory loss and other symptoms appear. Neuroimaging may therefore enable neurologists to predict who will develop Alzheimer's. Periodic brain scans can reveal subtle changes in the brains of Alzheimer's patients as the disease progresses over time. The scans can enable neurologists to evaluate and monitor the effects of cholinesterase inhibitors such as donepezil on cholinergic neurons in the hippocampus. This drug can slow memory loss in the early stage of the disease by slowing the progression of atrophy in this region of the brain.[19] Brain scans can also test the efficacy of nonsteroidal anti-inflammatory drugs, which have shown some promise in possibly preventing the neurodegenerative processes associated with Alzheimer's.[20]

The combination of brain imaging and drug therapy can be especially beneficial to people with the mutation on the APOe4 allele of the gene coding for the beta-amyloid precursor protein. They have a high risk of developing Alzheimer's at around age 40. Knowing that there is a strong genetic component to this early-onset form of the disease provides a reason for using brain imaging to detect and monitor its early signs. A smaller number of cholinergic neurons might predict Alzheimer's and warrant early pharmacological intervention, which might retard the progression of the disease. Similarly, brain scans can be used for adolescents with a high genetic risk of schizophrenia who display subtle cognitive symptoms of the disorder. Scans showing abnormalities in the frontal lobes, temporal lobes, and cingulate gyrus may predict schizophrenia and provide a reason for early pharmacological intervention as well.

It remains unclear which structural or functional brain abnormalities can accurately predict disorders before symptoms appear. Although there may be a correlation between earlier brain abnormalities and later cognitive abnormalities, this is not equivalent to a causal relation between them. Having less gray matter in the brain, for example, by itself does not necessarily mean that one will become psychotic. This can have ethical implications for those suspected of developing schizophrenia. Chronic use of antipsychotic drugs can result in tardive dyskinesia, a movement disorder associated with dopamine-

[18] P.M. Thompson et al. Mapping Adolescent Brain Change Reveals Dynamic Wave of Accelerated Gray Matter Loss in Very Early-Onset Schizophrenia. *Proc Natl Acad Sci USA* 2001; 98: 11650–11655; C. Pantelis et al. Neuroanatomical Abnormalities Before and After Onset of Psychoses: A Cross-Sectional and Longitudinal MRI Comparison. *Lancet* 2003; 361: 281–288; A.L. Spong et al. Progressive Brain Volume Loss During Adolescence in Childhood-Onset Schizophrenia. *Am J Psychiatry* 2003; 160: 2181–2189.

[19] B. Seltzer et al. Efficacy of Donepezil in Early-Stage Alzheimer Disease. *Arch Neurol* 2004; 61: 1852–1856; M. Hashimoto et al. Does Donepezil Treatment Slow the Progression of Hippocampal Atrophy in Patients with Alzheimer's Disease? *Am J Psychiatry* 2005; 162: 676–682.

[20] C. Martyn. Anti-Inflammatory Drugs and Alzheimer's Disease: Evidence Implying a Protective Effect Is As Yet Tentative. *Br Med J* 2003; 327: 353–354.

blocking agents. A newer generation of these drugs that was introduced in the 1990s lacks some of these side effects. But like any psychotropic medications, these drugs may have other significant long-term adverse effects. Administering these drugs on predictive rather than definitive diagnostic grounds might mean that an iatrogenic disorder would result from treatment for a possible disorder that never would have developed. The risk of using these drugs must be weighed against the risk of not using them for those who are at high risk of developing schizophrenia.

In the case of Alzheimer's, should predictive neuroimaging be offered for a future neurological illness when no cure is available? The crux of the discussion should be whether such imaging offers benefits to those who undergo it. Currently, there is no clear benefit. Predictive neuroimaging would be beneficial if it led to cholinesterase inhibitor therapy that delayed the onset of Alzheimer's disease. Informing a person that scans of her brain showed early signs of the dread disease may harm her by causing anxiety about her future. This is analogous in many respects to predictive presymptomatic genetic testing for Huntington's disease. Yet knowing early on that one would subsequently develop Alzheimer's could enable one to plan one's future more prudently. Moreover, acetylcholine-boosting drugs might slow the memory loss and cognitive decline associated with this disease. This is more than what a person with predicted Huntington's disease can hope for, since there are presently no drugs that might even retard the progression of its symptoms. Nevertheless, the emotional fallout of information from predictive neuroimaging can be devastating, regardless of the condition in question.

Predictive neuroimaging is still in the experimental stage. Its applications are not yet proven. Clinical trials have been designed where subjects are separated into experimental and control arms. The first group includes people who are considered to have a significant risk of developing one of the disorders I have been discussing. The adolescents with early signs of schizophrenia in the study mentioned at the beginning of this section were in the experimental arm of that study. Risk is determined by family history or by the presence of a known genetic cause. Suppose that some of the controls in one of these trials are healthy but have brain scans showing less gray matter than normal in the prefrontal cortex. As we have seen, this feature of the brain may be a risk factor for developing psychopathology. What should the researcher do with these incidental findings?[21] Should he tell the subjects, or the parents who consented to allow their children to participate in the trial, that their brains indicate a predisposition to psychopathology? Given the possibility that less gray matter may lead to mental illness, is the researcher obligated to disclose this information? Or is he obligated not to inform them, given the uncertainty about what the findings can predict and the likelihood of causing anxiety in the subjects or their parents? If the risk of developing psychopathology is uncertain, then would there be more harm than benefit in informing people of the results of brain scans?

It is crucial that the researcher inform subjects of the aim of a predictive neuroimaging clinical trial, what brain scans might reveal, and the uncertainty about what these findings might suggest for late-onset neurological and psychiatric conditions. The researcher is obligated to do this before the trial begins. Only in this way can subjects give valid informed consent to participate in such a trial. This applies both to those assigned to the experimental group and those assigned to the control group. Even in the best of circumstances, information about clinical trials can easily be misunderstood. The problem is more acute in predictive neuroimaging because of people's general difficulty in assessing probability and risk, combined with the uncertainty surrounding the medical significance of structural and functional brain abnormalities. Researchers have an obligation to point out to subjects and patients that predictive brain scanning is not an exact science. This can minimize the risk of harm in interpreting the information derived from scans. It can help to prevent distress in individuals who might otherwise think that their brains were not so 'normal' after all.

How a subject interprets information about the brain, or how a researcher presents this information to the subject, are not the only problems with

[21] These and related issues are addressed in J. Illes et al. Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging. *Brain Cogn* 2002; 50: 358–365, and by Illes, *op. cit.* note 3, chapter 11.

predictive brain scans. Analogous to genetic information indicating a predisposition to a disease, potential insurers or employers may use information from brain scans to discriminate against people seeking employment or medical insurance. With the exception of monogenic diseases, just because one is genetically predisposed to a disease does not mean that one will have that disease. Similarly, just because an asymptomatic individual has some structural or functional brain anomaly does not mean that this individual will develop a neurological or psychiatric illness. Unless there is a known causal connection between a brain scan and subsequent mental illness with a high risk of violent or otherwise harmful behavior, information about the brain should remain confidential and should not be disclosed or made available to third parties. In these days of managed care and the move toward electronic medical records, however, this standard for confidentiality is becoming increasingly difficult to ensure.

Predictive neuroimaging may become a useful tool in locating the first signs of neurological and psychiatric diseases. It could enable earlier pharmacological intervention to prevent or control the progression of these diseases. But what imaging can predict about future medical conditions is fraught with uncertainty and could lead to considerable abuse, discrimination, and harm. Accordingly, these brain scans should be used only to track nervous-system disorders with a known family history or genetic cause. Subjects in the control arm of a predictive imaging clinical trial should have the right to not have information about incidental brain findings disclosed to them. There should be general agreement within the research and clinical community about the medical rationale for and medical significance of these scans. This should reflect what is currently based on evidence, what might be possible, and what should be done in populations at risk. Indeed, whether and how this technology should be used must be framed and discussed as broader social questions. In the words of neuroscientist Joseph LeDoux:

> Such studies force us to confront ethical decisions as a society. How far should we go in using brain imaging to read minds, and how should we use the information we discover? It is testimony to the progress being made that these questions need to be asked.[22]

PSYCHOSURGERY

The Portuguese neurologist Egas Moniz coined the term 'psychosurgery' to describe the procedure of prefrontal leucotomy for the treatment of certain psychoses. The procedure consisted in injecting alcohol into the white matter of the frontal lobes. Moniz received the Nobel Prize for Medicine in 1949 for the 'therapeutic' value of leucotomy. But the most enthusiastic proponent and practitioner of psychosurgery was the American neurologist Walter Freeman, who performed some 3,500 frontal lobotomies in the United States in the 1940s and 1950s. This involved inserting an instrument through the skull just above the eyes and then swinging it back and forth to disconnect white matter tracts in the frontal lobes. Although lobotomies relieved some symptoms of severe psychiatric illnesses, they often resulted in severe neurological and psychological sequelae. These included seizures, significant personality changes, apathy, loss of social control, and in some cases death.

The notorious history of psychosurgery has generated revulsion in some people to the very thought of it. In spite of this, it continues to be practiced as a defensible medical treatment of last resort for OCD and severe depression and anxiety disorders that are refractory to all other treatments. Although it is relatively rare, most forms of psychosurgery are not experimental. More selective MRI-guided stereotactic techniques have improved the safety and efficacy of surgically intervening in the brain and ablating certain circuits or pathways. Nevertheless, the risk of permanent damage to brain circuits, and severe adverse psychological effects of this damage, cannot be ignored. It is precisely for this reason that psychosurgery remains an intervention of last resort.

Cingulotomy has been the surgical procedure of choice to treat severe OCD. A dysfunctional anterior cingulate gyrus has been implicated as the cause

[22] Le Doux, *op. cit.* note 12, p. 221.

of patients' obsession with contamination and compulsion to wash their hands. This procedure may be used experimentally to treat intractable pain as well, since the anterior cingulate plays a role in modulating pain sensation and pain affect. In a cingulotomy, bilateral burr holes are drilled in the skull, and two small holes are then made in the cingulate. The goal is to alter the main pathway between the limbic system and the prefrontal cortex and thereby correct the imbalance between cognitive and emotional processing due to the dysfunctional cingulate. This same procedure has been performed on severely depressed patients as well. Subcaudate tractotomy and limbic leucotomy are similar procedures targeting different regions of the brain. They have been performed to treat severe anxiety disorders. As in cingulotomy, the goal of these procedures is to correct the dysfunctional region or system of the brain in order to restore normal cognitive and emotional functioning. Data from cingulotomies performed over the last 30 years at the Massachusetts General Hospital indicate that 30% of patients experienced significant improvement, while 60% experienced mild to moderate improvement.[23]

Curing or relieving uncontrolled pathological obsessions, compulsions, anxiety and mood through psychosurgery is clearly an important therapeutic achievement. But for the patients who experience significant memory loss or personality change as a result of the procedure, the cure may come at the cost of their identities, their selves. In these metaphysical terms, the cure may seem worse than the disease. Some philosophers and neuroscientists equate personal identity and the self. Others treat them as related but different concepts. For the latter, the self pertains to the first-person phenomenological feel of conscious experience.[24] Identity is a unity relation pertaining to the connectedness and continuity of mental states over time. Core features of the self may be altered by neurological and psychiatric illness. Or they may be altered by psychosurgery to control or cure these illnesses. This alteration could occur if the surgery damaged the somatosensory system in the brain, which regulates one's orientation in space, or the temporal lobe, which regulates one's orientation in time. These changes would not necessarily undermine personal identity. Yet if the connections between memory of past experience and anticipation of future experience were severed as a result of surgical intervention in the brain, then the unity of these mental states over time would also be severed. The person after the surgery intuitively would be different from the person before the surgery. A good example of this is severe retrograde amnesia resulting from damage to the hippocampus and the temporal lobe. The loss of episodic memory can disrupt the psychological continuity that extends from the past to the present.

Some patients who have undergone unilateral temporal lobotomy to control the seizures in severe epilepsy have exhibited impaired fear conditioning after the surgery.[25] This is due to damage to the amygdala, which regulates fear and other emotions. Excessive fear is often a symptom of depression and anxiety disorders. Antidepressant medication and psychotherapy are means of enabling patients to restore a balance between too much and too little fear. Brain surgery resulting in the loss of the capacity to fear can be more harmful to a patient than excessive fear. This capacity is necessary for survival, and losing it can make one unable to recognize and protect oneself from real threats. Despite the possibility of these serious side effects, when a neuropsychiatric disorder is so severe that it interferes with a person's ability to have a normal life, the potential benefits of psychosurgery appear to outweigh the risks. Yet it is because these risks may have significant medical, ethical, and metaphysical implications that psychosurgery is justified only to treat severe conditions.

[23] G.R. Cosgrove. Surgery for Psychiatric Disorders. *CNS Spectr* 2002; 5: 43–52. D. Dougherty et al. Prospective Long-Term Follow-Up of 44 Patients who Received Cingulotomy for Treatment-Refractory Obsessive-Compulsive Disorder. *Am J Psychiatry* 2002; 159: 269–275.

[24] For one philosophical account, see G. Strawson. The Self. In S. Gallagher & J. Shear, eds. 1999. *Models of the Self*. Exeter. Imprint Academic: 1–24. From a neuroscientific perspective, see A. Damasio. 1999. *The Feeling of What Happens: Body and Emotion in the Making of Consciousness*. New York. Harcourt; T. Feinberg. 2001. *Altered Egos: How the Brain Creates the Self*. New York. Oxford University Press; and T. Kircher and A. David, eds. 2003. *The Self in Neuroscience and Psychiatry*. Cambridge. Cambridge University Press. The most widely discussed philosophical defense of the psychological continuity view of personal identity is that of D. Parfit. 1984. *Reasons and Persons*. Oxford. Clarendon Press.

[25] See, for example, K.S. LaBar et al. Impaired Fear Conditioning Following Unilateral Temporal Lobectomy on Humans. *J Neurosci* 1995; 15: 6846–6855.

Whether valid informed consent can be obtained from patients undergoing these procedures is another ethically contentious question.[26] Although the fact that certain conditions do not respond to any other treatments would seem to justify psychosurgery, patients may agree to undergo such a procedure out of a desperate desire for relief from their symptoms. This desperation may impair their ability to rationally weigh the benefits against the risks. To be sure, there are other conditions in which patients have a desperate desire for relief from symptoms. What is distinctive about psychosurgery is that the dysfunctional region of the brain that is the target of the intervention is often the cause of the patient's impaired competence or incompetence. This suggests that there should be a higher threshold of consent for psychosurgery than for most, if not all, other procedures. Another reason for a higher threshold of consent for psychosurgery is that the procedure could have significant and permanent adverse effects on personality.

For these reasons, a careful psychological evaluation of the patient must be part of the selection of candidates for surgery. A family member or other person who knows the patient well should be part of the consent process, together with the patient. The problem of consent is especially acute in cases of severe depression, where the patient may have little or no capacity to consent. An appropriately designated surrogate acting in the best interests of the patient can consent to the treatment on the patient's behalf. This can be justified when the patient poses a significant risk of harm to himself or others. Proxy consent might also be justified when there is no risk of suicide or harm to others, but when the patient's quality of life is so poor that the potential benefit of surgery to the patient clearly outweighs the risk. This would apply to depression, anxiety, or OCD. Similar justification could be given for proxy consent on behalf of patients with brain tumors causing significant cognitive or affective impairment. Even in these cases, though, the potential neurological and psychological side effects of psychosurgery require that consent be a sustained deliberative process involving the neurosurgeon, the supporting medical team, the patient, and the surrogate.

Proxy consent for psychosurgery should be held to a higher standard than proxy consent for other procedures. In the light of the risk of serious changes to thought and behavior from psychosurgery, a group of neurosurgeons in Scotland recently formulated and defended 'a policy of not offering ablative neurosurgery for mental disorders to anyone who is incapable of providing sustained, informed consent'.[27] Yet if a patient's condition is severe, does not respond to any other therapy, and the potential benefit of psychosurgery outweighs the potential harm, then proxy consent for this procedure can be justified. The requirement of consent would rule out forced psychosurgery even for therapeutic reasons.

NEUROSTIMULATION

Neurostimulation can be a medically and ethically preferable alternative to the brain lesioning in psychosurgery. This form of brain intervention is in its early stages and is still experimental. Neurostimulation often involves stimulating a dysfunctional area of the brain using implanted electrodes connected to a battery. Because the electrodes are usually implanted in subcortical regions deep in the brain, it has also been described as 'deep-brain stimulation' (DBS). This procedure has helped to restore coordinated movement in patients affected by the rigidity or tremors of Parkinson's disease. The same technology could also be used to prevent or treat epilepsy by inhibiting hyperactive neural circuits causing the seizures that are symptomatic of the disorder. A device implanted in the brain could automatically release a very low dose of an anti-epilepsy drug or deliver an electrical signal that could block seizures. In 2002, an ethics commission in France approved clinical trials using neurostimulation for OCD.[28] In contrast to the lesioning in psychosurgery, neurostimulation has the advantage of being reversible. The electrodes can be removed

[26] J. Kleinig. 1985. *Ethical Issues in Psychosurgery*. London. Allen & Unwin. Also, S. Stagno, M. Smith & S. Hassenbusch. Reconsidering 'Psychosurgery': Issues of Informed Consent and Physician Responsibility. *J Clin Ethics* 1994; 5: 217–223.

[27] K. Matthews & M. Eljamel. Status of Neurosurgery for Mental Disorder in Scotland. *Br J Psychiatry* 2003; 56: 404–411.

[28] A. Abbot. Brain Implants Show Promise Against Obsessive Disorder. *Nature* 2002; 419: 658.

and patients can control the function of the electrodes by switching them on or off. This also makes it easier to justify conducting blind controlled clinical trials and to obtain informed consent from research subjects.

Still, implantation and stimulation of electrodes in the brain must be precise. Implanting or stimulating one millimeter off target may cause unforeseeable adverse neurological sequelae. In these instances, a patient could develop seizures. Or the patient's emotional processing could be affected, causing the patient to become emotionally flat or even suicidal. Even when the target area is stimulated as intended, activating one brain circuit in isolation from other circuits that play a role in movement could adversely affect the patient's capacity for motor control. This could defeat the purpose for which the technique was designed. Accordingly, the commission overseeing the OCD study in France set strict experimental conditions for it. This included careful selection of subjects (only those whose OCD was refractory to all other treatments), obtaining informed consent, and evaluation of results. Belgian neurosurgeon Bart Nuttin and colleagues drafted and published general ethical guidelines for the use of deep-brain stimulation to treat psychiatric illness in August 2002.[29]

Neurostimulation can be expanded to treat severe depression and anxiety disorders. In patients who fail to respond to antidepressant medication, stimulating the prefrontal cortex may help to modulate a hyperactive amygdala and restore the balance between cognitive and emotional processing. One recent study has shown that DBS modulated elevated activity in the subgenual cingulate region and produced some benefit in six patients with refractory depression.[30] DBS can function as a 'pacemaker' for the brain in treating motor and mood disorders. The behavioral symptoms of affective and anxiety disorders are more subtle than those of Parkinson's or OCD, however. This complicates drawing a direct link between brain stimulation and behavior. Locating the organic cause or causes of mood and anxiety disorders is also more complicated. This is because the etiology of these disorders may include psychological factors such as beliefs and emotions that have a widely distributed neurological underpinning. These mental states may also be influenced by factors in the physical and social environment. So the efficacy of DBS as a treatment for a broad range of neurological and psychiatric disorders may be limited.

Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS), and Vagus Nerve Stimulation (VNS) may seem more attractive as treatments for severe depression and other psychiatric disorders because they avoid surgical intervention in the brain altogether.[31] In ECT, electrodes are applied to the head, and a series of electric shocks are delivered to the brain to induce seizures. The technique appears to restore the proper balance of neurotransmitters and neuronal connections in the pathway between the prefrontal cortex and limbic system. TMS also aims at restoring the cortical-limbic balance. It involves delivering a localized magnetic pulse to the brain through the scalp by application of hand-held coils. VNS has been used to treat epilepsy, as well as severe depression and bipolar disorder. It involves stimulating the left vagus nerve in the neck with a series of electrical pulses. These pulses travel through a surgically implanted wire attached to a pulse generator in the chest. The vagus nerve has connections to the limbic structures and the thalamus, which play an important role in regulating affective states.

The fundamental problem with these techniques, as with the other techniques I have discussed, is that their long-term effects are not known. Despite being less invasive, ECT, TMS, and VNS may prove to be no more medically or ethically acceptable than the other procedures. ECT has been known to result in significant memory loss in some patients. TMS can excite only the cortex because the strength of the magnetic field falls off sharply beyond the distance of only a few centimeters. Yet dysfunction of both cortical and subcortical regions of the brain has

[29] B. Nuttin et al. Ethical Guidelines for Deep-Brain Stimulation. *Neurosurgery* 2002; 51: 519.

[30] H. Mayberg et al. Deep-Brain Stimulation for Treatment-Resistant Depression. *Neuron* 2005; 45: 651–660.

[31] See, for example, R. Abrams. 2002. *Electroconvulsive Therapy*. 4th ed. New York. Oxford University Press; S.V. Eranti & D.M. McLoughlin. Electroconvulsive Therapy – State of the Art. *Br J Psychiatry* 2003; 174: 8–9; A. Pascual Leone. 2002. *Handbook of Transcranial Magnetic Stimulation*. New York. Oxford University Press; S. Lisanby, ed. 2004. *Brain Stimulation in Psychiatric Treatment.* Washington, DC. American Psychiatric Publishing.

been implicated in most psychiatric disorders. Also, the effects of TMS may be of only short duration. Clinical trials aiming to increase the depth and duration of TMS to treat depression are under way in the United States, though it remains to be seen whether these trials will achieve the desired effects.[32] Like internal and external electrical stimulation, external magnetic stimulation of the brain may adversely affect circuits other than those targeted by the procedure. Neural stimulation can either excite or inhibit neurons. Some of these techniques involve both excitation of some neurons and inhibition of others. This can make it difficult to control the effects of stimulation. These effects also depend on the frequency used and on which areas of the brain are stimulated.

This does not mean that TMS and other procedures should be banned. Rather, more long-term studies are needed to adequately assess their benefits and risks. Given the uncertainty about the effects of these techniques, the same strict experimental conditions should be applied to all forms of neurostimulation, regardless of the degree of invasiveness. In addition, informed consent from patients or subjects, or from appropriate surrogates, must be obtained. This requires that the researcher explain the potential benefits and risks of these techniques and point out the uncertainty about these benefits and risks. Finally, the medical uncertainty of these experiments indicates that they are ethically justifiable only when the neuropsychiatric conditions they are designed to treat are refractory to pharmacological or other proven treatments.

COGNITIVE AND AFFECTIVE ENHANCEMENT

Unlike techniques designed to monitor or treat neurological and psychiatric disorders, some drugs are being used to enhance normal cognition and mood. Perhaps the most intriguing of these drugs is modafinil. This drug was approved for the treatment of narcolepsy in 1998 and is now prescribed to treat sleep apnea and shift-work sleep disorder. All of these conditions are caused by dysregulated circadian rhythm/sleep-wake cycles in the central nervous system. Studies have shown that modafinil reduces daytime sleepiness among shift workers, reducing the incidence of motor vehicle accidents caused by people who otherwise would have fallen asleep at the wheel.[33]

The benefits of modafinil are clear. But this drug is also being used to promote alertness in people with regular sleep-wake cycles. In fact, roughly 90% of prescriptions for the drug are for this and other off-label uses. Those taking the drug could have prolonged periods of alertness and could function at a sustained high cognitive level on much less sleep than is considered normal. Experiments involving B-2 Bomber and commercial airline pilots on transcontinental flights have shown that modafinil can keep them alert and engaged in mental activities despite sleep deprivation. In some respects, modafinil would function like methylphenidate (Ritalin) and other stimulants that can improve people's cognitive capacity for focusing attention on specific tasks. Would there be any medical or ethical reason to object to the use of this drug for cognitive enhancement?

Researchers believe that modafinil does not produce the hyperactive and addictive effects of stimulants like amphetamines and cocaine because of its selectivity in targeting the dopamine pathway that controls wakefulness and blocking the hypothalamus from promoting sleep. Yet sleep plays an important role in maintaining neural plasticity. Limiting sleep through pharmacological means could impair the brain's ability to adapt to changing environments or to adjust to injury. Moreover, people who are chronically sleep-deprived generally are at greater risk of hypertension, as well as metabolic disorders such as obesity and diabetes. More recent studies suggest that sleep is important for consolidation of newly acquired memories.[34] Constant manipulation of the natural alertness system could have harmful consequences. The main issue with modafinil and other alertness-enhancing drugs is

[32] Y.Z. Huang et al. Theta Burst Stimulation of the Human Motor Cortex. *Neuron* 2005; 45: 201–206.

[33] D.C. Turner et al. Cognitive Enhancing Effects of Modafinil in Healthy Volunteers. *Psychopharmacology* 2002; 165: 260–269.

[34] M. Nicolelis et al. Global Forebrain Dynamics Predict Rat Behavioral States and Their Transitions. *J Neurosci* 2004; 49: 11137–11147. Also, R. Huber et al. Local Sleep and Learning. *Nature* 2004; 430: 78–81.

that their exact biochemical mechanisms and long-term effects are not known. Chronic use of these drugs could remodel synapses, alter neural circuits, and result in permanent changes in the brain.[35] A sufficient number of longitudinal studies are needed to ascertain these effects and determine whether the benefits of the drugs outweigh the risks.

Another form of psychopharmacological enhancement involves drugs that would increase memory storage and expedite memory retrieval. These drugs most likely would target working memory, which enables us to perform cognitive tasks and executive functions like reasoning and decision-making. Working memory can be described as a short-term form of declarative memory. Declarative memory consists of semantic memory, which involves the ability to consciously recall concepts, facts, and numbers, and episodic memory, which involves the ability to consciously recall events. Declarative memory is distinct from procedural memory, which enables us to unconsciously perform such skills as riding a bicycle or driving a car. The prefrontal cortex regulates working memory. Drugs that are already under development aim to increase memory storage by acting on the transcription factor cyclic AMP (cAMP) and the protein it modulates, CREB (cyclic AMP response element binding protein). This protein is responsible for switching on and off the genes involved in memory formation and storage. Memory-enhancing 'smart drugs' would increase the supply of CREB inside neurons and thereby strengthen memory consolidation.[36]

It is not clear that increasing the brain's ability to store memories would not impair its ability to retrieve these memories. This point is motivated by an evolutionary interpretation of memory. The limits we have in our capacity to remember only so many facts or events may be part of a natural design that is critical for our survival. Ideally, we would want to use drugs that both increased memory formation and storage and made memory retrieval more efficient. But increased storage would not necessarily mean quicker retrieval. More facts stored in the brain might result in an overloaded working memory, which could impair the ability to execute cognitive tasks. It might also impair our ability to learn new things, which depends on a certain degree of forgetting.

These considerations suggest that there may be an optimal amount of CREB in our brains for memory. Too much CREB could result in an overproduction and oversupply of memory, which could result in our brains and minds becoming cluttered with memories of facts or events that served no purpose. If there is an optimal balance between remembering and forgetting, then it seems plausible to hypothesize that increased semantic memory storage and decreased forgetting could result in impaired semantic memory retrieval, as well as impaired ability to learn new things. Farah supports this point:

> We understand very little about the design constraints that were being satisfied in the process of creating a human brain. Therefore, we don't know which 'limitations' are there for a good reason . . . normal forgetting rates seem to be optimal for information retrieval.[37]

Farah further warns of 'hidden costs' of trying to enhance memory, and that evolutionary considerations should make us wary of the prospect of general cognitive enhancement as a 'free lunch'. We should be wary of making the inference that, if a certain amount of memory is good, then more memory is better.[38]

There may be important social implications of drugs that enhanced alertness, attention, memory, or other cognitive capacities. Some might argue that cognitive enhancement should aim to reduce unfairness, but without eliminating beneficial options.[39] The cognitive capacities that constitute intelligence are a competitive good that can give some people an advantage over others in gaining employment, income, wealth, and a higher level of wellbeing. If

[35] S. Hyman & W. Fenton. What Are the Right Targets for Psychopharmacology? *Science* 2003; 299: 350–351.

[36] T. Tully et al. Targeting the CREB Pathway for Memory Enhancers. *Nat Rev Drug Discov* 2003; 2: 267–277, and G. Lynch. Memory Enhancement: The Search for Mechanism-Based Drugs. *Nat Neurosci* 2002; 5: 1035–1038.

[37] M. Farah. Emerging Ethical Issues in Neuroscience. *Nat Neurosci* 2002; 5: 1125. Also M. Farah et al. Neurocognitive Enhancement: What Can We Do and What Should We Do? *Nat Rev Neurosci* 2004; 5: 421–425.

[38] J. McGaugh made this point in his testimony to the US President's Council on Bioethics on 17 October 2002. See note 14.

[39] For example, A. Caplan. No Brainer: Can We Cope with the Ethical Ramifications of New Knowledge of the Human Brain? In Marcus, *op. cit.* note 3, pp. 95–106.

we could ensure universal access to drugs that enhanced cognitive capacities and intelligence, then presumably this would reduce social inequality and unfairness. It would give everyone an equal opportunity for access to the education and employment that would guarantee a moderate to high level of wellbeing for everyone. But this would not necessarily follow. Equal access to a competitive good, or to the means that would facilitate such access, would not imply equal outcomes from the use of these means.

Differing parental attitudes to competitive goods such as an elite education and lucrative jobs could mean substantial differences between children regarding how enhancement drugs would be utilized. Some parents would be more selective than others in sending their children to better schools or in arranging for private tutors. In these respects, equality in access to cognitive enhancement would not imply equality of achievement among children, adolescents, and adults. Furthermore, some adolescents and adults would use cognitive enhancement drugs to engage in trivial or even pathological tasks, such as gambling. Not everyone would use these drugs in a beneficial way. There would be inequality of outcomes of cognitive enhancement with respect to the competitive goods at issue. Any beneficial options of enhancement would probably come on top of existing social inequality and would more likely exacerbate than ameliorate it.

Cognitive enhancement must be distinguished from mood enhancement. The latter has been associated with exaggerated claims that many people use SSRIs to overcome shyness or to create a general feeling of wellbeing. These claims are due in part to Peter Kramer's popular 1993 book *Listening to Prozac*, which includes some discussion of using SSRIs such as Prozac to boost self-confidence and self-esteem. But this view makes light of the fact that the majority of the people who take these drugs do so because of the debilitating affective, cognitive, and physical symptoms of major depression.[40] The aim of these drugs is not to make people feel better about themselves, but to restore them to normal levels of mental and physical functioning. Some people may take these drugs to enhance mood; but most do not. In fact, for those whose affective symptoms fail to meet criteria of major clinical depression, the positive effects of these drugs are minimal. American psychiatrist Greg Sullivan explains:

> If someone is pleased with the effects of an SSRI, that usually is an indication that the drug has had a significant impact on serious symptoms, including those caused by a chronic low-level depression (dysthymia) . . . But SSRIs are not 'happy pills', and people without significant mood or physical dysfunction do not generally get much benefit from them, certainly nothing that would make them sustain their use.[41]

Even if the risks of using psychopharmacology to enhance cognition or mood were minimal, the potential of these drugs to alter personality raises a metaphysical question. If one's cognitive ability or emotional capacity changed substantially, then would one retain one's identity and remain the same person, the same self? Or would one become a different person or self? If one's psychological connectedness and continuity were disrupted by these changes, then it is unclear *who* would have benefited from the drug intervention. The change could preclude a comparison of two states of affairs in which the same person existed, which would be necessary for there to be any benefit for that person. All of the issues raised in this section indicate the need for broad public discussion of the rationale for psychopharmacological enhancement. They also indicate the need for studies to determine the safety and efficacy of these interventions.

CONCLUSION

As brain imaging, psychosurgery, neurostimulation, and psychopharmacology become more refined and more available, researchers will become more able to map and modify the neural basis of the human mind and behavior. This will enable doctors to more accurately predict, prevent, diagnose, and treat neurological and psychiatric disorders. But the brain is by far the most complex and least understood organ in the

[40] Kramer's *Against Depression* is in many respects a sobering antidote to his earlier book. Peter Kramer. 2005. *Against Depression*. New York: Viking.

[41] Cited in LeDoux, *op. cit*. note 12, p. 276.

human body. We still do not know precisely how all of the different systems of the brain interact, or what a particular brain abnormality can predict about future psychopathology. Nor do we know precisely how intervening in these systems can affect the beliefs, desires, intentions, and emotions that constitute the human mind. The measures and interventions I have discussed have the potential to affect our minds and alter who we are in both positive and negative ways. Thus we need to carefully weigh the potential benefits against the potential harms of the different measures and interventions in clinical neuroscience.

Neuroscience is perhaps the fastest growing and most exciting area of medicine and biotechnology. Although it is in some respects still an emerging field, in other respects it is already being practiced in clinical and experimental settings. The ethical issues emerging from clinical neuroscience are as significant as those associated with stem-cell research, genetic testing, or any other area of bioethics. Acknowledging the differences between actual and possible applications of these techniques, we need to appreciate the dilemmas that already exist and those that will arise in the future. It is because neuroscience is developing at such a rapid pace and can affect us so directly and deeply that we should now be paying attention to and debating the important ethical issues arising from it.

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