Cosmetic neurology

The controversy over enhancing movement, mentation, and mood

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Abstract—Advances in cognitive neuroscience and neuropharmacology are yielding exciting treatments for neurologic diseases. Many of these treatments are also likely to have uses for people without disease. Here, I review the ways in which medicine might make bodies and brains function better by modulating motor, cognitive, and affective systems. These potential "quality of life" interventions raise ethical concerns, some related to the individual and others related to society. Despite these concerns, I argue that major restraints on the development of cosmetic neurology are not likely. Neurologists and other clinicians are likely to encounter patient-consumers who view physicians as gatekeepers in their own pursuit of happiness.

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Are better brains better? Advances in basic neuroscience and neuropharmacology are beginning to yield therapies for cognitive disorders. While we eagerly anticipate treatments for dementing illnesses, stroke, traumatic brain injury, and developmental abnormalities, these very treatments raise uncomfortable questions. If we can improve cognitive systems in disease, can we also do so in health? Should we?

The possibility of "better brains" has captured the attention of the press, policy pundits, and ethicists.[1–10] With few exceptions,[11] neurologists have not contributed to these discussions, despite the fact that clinicians would be centrally involved as this drama unfolds. In this paper, I review the landscape of cosmetic neurology and offer preliminary speculations about its future. While cosmetic neurology certainly includes the use of botulinum toxin to brush away wrinkles, the focus here runs deeper. I start by considering the purpose of medicine to frame the ethical dilemmas of cosmetic neurology. Then, I review three ways in which bodies and brains might be made better. This is followed by an outline of four main ethical concerns raised and my opinion on why these concerns are unlikely to serve as a restraint. The goal is *not* to evaluate the correctness of cosmetic neurology. Rather, the goal is to alert neurologists to the shape that cosmetic neurology might take and to consider our possible role.

Framing the issue: The purpose of medicine. The strength of allopathic medicine is its focus on mechanisms of disease. Understanding the biologic basis for malfunction provides insight into how to fix that malfunction. Despite the successes of this approach, it has limits. Most notably, patients' impressions of the quality of their lives do not always correspond directly to bio-markers and symptoms of disease. The cardinal symptoms of Parkinson disease (PD) most responsive to dopamine agonists are not necessarily those that bother patients most.[12] Measures of disease activity may not be the best indicator of the impact of multiple sclerosis (MS) on patients.[13] Recognizing the limits of clinical and pathologic indices, quality of life assessments of patients have become a standard practice in therapeutic trials. Such assessments seem eminently reasonable, if one believes that the point of treating a disease is to improve patients' quality of life. However, if improving quality of life is an explicit goal for physicians, and quality of life does not always correspond directly with clinical-pathologic indices, then why not consider biologic interventions for the quality of individuals' lives whether or not they have a disease?

This distinction between treating disease and improving quality of life is echoed in discussions of therapy vs enhancement.[6] Therapy is treating disease, whereas enhancement is improving normal

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abilities. Most people would probably agree that therapy is desirable. By contrast, enhancing normal abilities gives pause to many. Fukayama[14] opines that "the original purpose of medicine is to heal the sick, not turn healthy people into gods." He suggests that public policy should restrict research for enhancement.

On scrutiny, the distinction between therapy and enhancement can be vague particularly when the notion of "disease" lacks clear boundaries. For example, if individuals of short stature can be "treated" with growth hormone,[15] does it matter if they are short because of a growth hormone deficiency or because of other reasons?[16] Additionally, the idea of promoting research for therapy and restricting it for enhancement misses the point that research in one often applies to the other. Distinguishing between therapy and enhancement may avoid tackling what is perhaps a more difficult question. If one purpose of medicine is to improve the quality of life of individuals who happen to be sick, then should medical knowledge be applied to those who happen to be healthy?

Better bodies and brains. The prospects for better bodies and brains fall into three general categories: improvement of motor systems, attention, learning and memory, and mood and affect. With the current and future impact of aging in our society, these prospects are particularly germane. Some interventions like alcohol, tobacco, and caffeine have been available for a long time. Many others are on the horizon. For novel medications, the effects in clinical populations are often not known and their efficacy and safety in healthy individuals are now unexplored. However, for purposes of this discussion, we can anticipate that such interventions will eventually be available, relatively efficacious, and safe.

Movement. Medicine can make people stronger, swifter, and more enduring. While some of these interventions might not be considered "neurologic" as narrowly conceived, I mention them because neurologists treat muscle disorders, and innovative interventions for these diseases may generalize to the normal state.

Professional athletes use anabolic steroids to improve their strength and quickness. Beyond steroids, new ways of improving motor performances are being developed. Insulin-like growth factor (IGF) produced by the liver may improve the quality of life of people without disease. IGF given to men over the age of 60 for 6 months increased their muscle mass, decreased body fat, and improved skin elasticity.[17] In mice, injection of recombinant viruses containing the *IFG-1* gene directly into muscle also increased muscle mass and strength and prevented declines observed in untreated old mice.[18]

Maximizing blood oxygenation optimizes muscle activity and enhances athletic performance. In the 1970s and 1980s, athletes trained at high altitudes and used autologous blood transfusions to increase their oxygen carrying capacities.[19] Since the 1980s, human erythropoietin (EPO) has been produced to treat anemia. EPO has become a new form of athletic "doping."[19,20] Similarly, new transfusion methods, motivated by blood supply shortages and contaminants, may have implications for performance when endurance is critical.[19]

Finally, the acquisition of motor skills may be improved by medications developed to enhance neural plasticity. For example, amphetamines in small doses promote plasticity and accelerate motor learning.[21,22] Their effects are most pronounced when paired with training as seen in patients with weakness following stroke. Could amphetamines also be used in normal subjects at the time of skilled motor learning, such as learning to swim, ski, or play the piano?

Mentation. We now have unprecedented therapeutic options for degenerative and developmental cognitive disorders, with more on the way. Currently available treatments most often modulate catecholamine and cholinergic systems.

The effects of amphetamines on plasticity in motor systems may generalize to cognitive systems. Amphetamines improve the effects of speech therapy in aphasic patients.[23] Might similar effects occur in normal subjects? Modafinil improves arousal and ameliorates deficits of sustained attention associated with sleep deprivation.[24,25] Methylphenidate is used widely to improve attention, concentration, spatial working memory, and planning.[26,27] Students commonly use amphetamines despite the fact that it may also impair previously established performance.[28,29] Newer non-addictive drugs such as atomoxetine are likely to increase off-label use of such medications.

Cholinesterase inhibitors also improve attention and memory. These medications are used widely in AD, and their use in older individuals is on the rise. The reticence for enhancement and enthusiasm for therapy is reflected in the recasting of diagnostic designations of "age-associated memory impairment" to "mild cognitive impairment." The effects of cholinesterase inhibitors on normal subjects are not well studied. However, one intriguing report suggests an effect in the setting of highly skilled performance. Yesavage et al.[30] reported that commercial pilots taking 5 mg of donepezil for 1 month performed better than pilots on placebo on demanding Cessna 172 flight simulation tasks, particularly when responding to emergencies.

Two new classes of drugs for memory, ampakines and cyclic AMP response element binding protein (CREB) modulators, are on the horizon.[31] These drugs capitalize on recent advances in understanding of the intracellular events that contribute to structural neural changes associated with the acquisition of long-term memory.

Facilitation of glutamatergic transmission pro-

motes long-term potentiation, presumed to foster synaptic plasticity and memory formation. Ampakines augment AMPA-type glutamate receptors by depolarizing postsynaptic membranes in response to glutamate. Because NMDA receptors crucial to induction of long-term potentiation[32] are sensitive to this depolarization, ampakines are thought to facilitate the acquisition and consolidation of new memories (see for review).[33] Early studies show that ampakines improve memory in rats[34,35] and normal humans.[36] The NMDA receptors themselves may ultimately be a target of genetic modification. Mice genetically altered to overexpress NMDA receptors have superior learning and memory abilities.[37]

Neurogenetic studies suggest that CREB is a critical molecular "switch" in forming long-term memories.[38] Gene expression is promoted by activation of CREB, which itself is dependent on NMDA receptor activation. Specific protein kinases activate CREB. CREB then sets off a transcription cascade, which produces specific structural changes at the synapse. Drosophila genetically altered to overexpress CREB demonstrate long-term conditioning to odor-shock pairings after only one exposure, a conditioning that normally takes 10 trials.[39] Similar effects are seen in mammals.[40] Mice given rolipram, a phosphodiesterase inhibitor, which enhances CREB, form long-term memories in fewer than half the trials needed by untreated mice.[38]

Mood and affect. The aisles of almost any local drug store testify to the public's appetite for mood regulators, such as St. John's Wort, kava kava, and valerian. Anti-depressants, most notably selective serotonin reuptake inhibitors (SSRIs), are used widely for depression, but also for anxiety, obsessive compulsive, and oppositional behaviors. Some estimate between 9.5 and 20% of Americans are depressed.[41] Kramer[42] drew attention to the use of antidepressants in normal people. SSRIs may selectively dampen negative and not positive affect,[43] and they seem to increase affiliative behavior in social settings.[44] If SSRIs improve a general sense of well being, regardless of illness or health, might more than 20% of Americans wish to take them?

New approaches to treating affective illnesses will undoubtedly expand our therapeutic options.[45,46] Blocking glucocorticoids may be of benefit in a subset of depressed patients. Corticotropin releasing factor (CRF) seems to mediate long-term stress effects through the stria terminalis, a structure related to the amygdala.[47,48] Blocking CRF may selectively blunt stress effects.[45] In addition to CRF, other neuropeptides seem to play a role in depression and anxiety. These include substance P, vasopressin, neuropeptide Y, and galanin. Clinical trials of neuropeptide agonists and antagonists that cross the blood-brain barrier are just beginning.[46] The efficacy and safety of these novel treatments remain to be seen, but almost certainly new ways to alter mood and affect will be available.

Besides pharmacological interventions, other interventions, such as repetitive transcranial magnetic stimulation (rTMS), can have a therapeutic effect on depression.[49] Some patients respond to frontal rTMS that are otherwise unresponsive to medications.[50] Would TMS improve mood in normal people that are not clinically depressed, but simply have off days?

Pharmacologic agents can also modulate the way emotional events are remembered.[51] In animals, consolidation of emotional memories are strengthened by epinephrine and dampened by beta blockers injected within the amygdala. Similar effects occur in normal people. Subjects given propranolol recall emotionally arousing stories as if they were emotionally neutral.[52] Propranolol also enhances the memory of events surrounding emotionally charged events that are otherwise suppressed.[53] In one pilot study, patients in an emergency room given propranolol after a traumatic event suffered fewer post-traumatic stress disorder symptoms when assessed 1 month later.[54] Intriguingly, CREB inhibitors may have selective effects on negatively charged memories. Most would agree with treating post-traumatic stress disorder to help individuals that are paralyzed by their disturbing memories. However, these studies suggest that less disturbing memories might also be clipped, if we so desired.

Ethical dilemmas. Cosmetic neurology raises deep ethical dilemmas. These dilemmas coalesce around four concerns, two focused on the individual and two on society. While the present context for these concerns is novel, the ethical issues themselves are not without precedent. Our responses to these concerns in other settings may predict how we will deal with cosmetic cognitive neurology.

Safety. Virtually all medications have potential side effects that range from minor inconveniences to severe disability or death. In disease states one weighs risks against potential benefits. Thus a patient with glioblastoma multi-forme might be willing to endure toxic chemotherapies because the alternative is so grim. In healthy states any risk seems harder to accept because the alternative is normal health. For some interventions the risks are known or suspected. EPO improves endurance but increases the risk of stroke. Modafinil enhances alertness on some tasks but may compromise performance on others.[25] Genetically modified mice may have terrific memories[37] but are more sensitive to pain.[55]

While safety concerns are undoubtedly real, they are unlikely to have much of a practical impact. The incentives to develop new treatments with minimal side effects are in place. This is not to say that unexpected effects might not be encountered. But, in general, newer medications will continue to be safer, and the safer the medication, the less relevant this concern.

In a culture with strong libertarian undercurrents, many believe that if individuals are given ad-

equate information about potential side effects, they should be free to make their own decisions. Thus, we place warning labels on cigarette packs and beer bottles. To complicate matters further, it is not obvious that individuals make consistent use of this kind of information in making decisions.[56] Financial investment practices suggest that many Americans are willing to tolerate considerable risk to the point of "irrational exuberance," in hopes of improving their (monetary) quality of life.

Character and individuality. This concern takes two general forms, one about eroding character and the other about altering the individual. The erosion of character concern is wrapped around a "no pain, no gain" belief. Struggling with pain builds character, and eliminating that pain undermines good character. Similarly, getting a boost without doing the work is cheating, and such cheating cheapens us.[57]

While these concerns about character run deep, they are mitigated by several factors. Which pains are worth the hypothetical gains they might bring? We live in homes with central heat and air, eat food prepared by others, travel vast distances in short times, take Tylenol for headaches and H2 blockers for heartburn. Perhaps these conveniences have eroded our collective character and cheapened us. But few choose to turn back.

A fundamental concern is that chemically changing the brain threatens our notion of personhood. The central issue may be that such interventions threaten essential characteristics of what it means to be human.[9] For example, would selectively dampening the impact of our painful memories change who we are, if we are in some sense the sum of our experiences? This is a difficult issue to grapple with, and consensus on the essence of human nature may be elusive.[6,14,58] Some changes in personhood, such as sudden transformational changes in the form of religious epiphanies are not always viewed negatively. Americans often take pride in "reinventing" themselves. Is medically doing so different? For some, medicine paves the way of revealing an identity that is otherwise hidden by circumstance. People claim to "find themselves" through steroids, anti-depressants, mind-altering drugs, and amphetamines.[8] Invasive surgical procedures such as sex-change operations are used to express one's individuality. Elliott,[8] in reviewing such practices, suggests that "in America, technology has become a way for some people to build or reinforce their identity (and their sense of dignity) while standing in front of the social mirror."

Distributive justice. If we can make better bodies and brains, who gets them?[9] These interventions are expensive and there is no reason to expect insurance companies or the state to pay for them. Perhaps third-party payments for enhancements should be prioritized below more conventional treatments. Then only those who can afford to pay privately would get enhancements. The rich, in addition to becoming richer, might also become stronger, smarter, and hopefully sweeter than the rest.

A familiar counter to the worry of widening inequities is that this is not a zero sum game. With widening disparities, even those at the bottom of the hierarchy receive some benefit and improve from their previous state in some absolute sense.[9] This argument assumes that people's sense of well-being is determined by an absolute level of quality, rather than a recognition of one's relative place. However, beyond worries about basic subsistence, well-being seems mostly affected by expectations and relative positions in society (reviewed by Frank[59]).

One might argue that the critical issue is access and not availability.[60] If access to such enhancements were open to all, then differences might even be minimized. This argument may have logical merit, but in practice (in the United States) it skirts the issue. We tacitly accept wide disparities in modifiers of cognition, as demonstrated by the acceptance of inequities in education, nutrition, and shelter. Not only have we habituated to these disparities, we limit programs such as Head Start that might attenuate them. Sadly, it is hard to expect that our response to inequities in access to cognitive cosmetics will be different.

Coercion. The concern here is that matters of choice can evolve into forces of coercion. Such coercion can take two forms. One is the implicit coercion to maintain or better one's position in some perceived social order. Such pressure increases in a "winner-take-all" environment in which more people compete for fewer and bigger prizes.[61] Many professionals are familiar with Faustian trade-offs of working 60, 80, or more than 100 hours a week to the detriment of health and hearth. Athletes may feel compelled to take steroids to compete at the highest levels and children at high-end preparatory schools take methylphenidate in epidemic proportions.[31] To not take advantage of cosmetic neurology might mean being left behind.

A second form of coercion, which has not received attention, is the explicit demand of superior performance by others. Such coercion could take regulatory forms. Yesavage et al.'s[30] findings that pilots taking donepezil performed better in emergencies than those on placebo could have wide implications. If these results are reliable and significant, should pilots be expected to take such medications? Can airline executives require this of pilots? Would they offer financial incentives to pilots willing to take these medications? Will the public, fearful of flying, pay more for cholinergic copilots? Closer to home, should post-call residents take modafinil to attenuate deficits in sustained attention brought on by sleep deprivation? Will hospital administrators require this practice? Insurance companies? Patients?

Inevitability. The ethical concerns raised by cosmetic neurology are serious. However, in my view, hand-wringing of ethicists, journalists, and futurists is unlikely to have much of a restraining effect on its development. When faced with the analogous ethical concerns in other contexts, we collectively shrug our shoulders. Restraint by government regulation, journalistic consternation, and religious admonition are likely to be overwhelmed by a relatively unrestrained market and the military.

The market. Treatments to enhance normal abilities are likely to be paid for privately. Many psychiatrists in private practice only accept personal payments for conditions that fall well into the "disease" category. If social pressures encourage wide use of medications to improve quality of life, then pharmaceutical companies stand to make substantial profits and they are likely to encourage such pressures. According to Elliott,[8] in 2001 GlaxoSmithKlein spent $91 million dollars in direct advertising to consumers for its medication Paxil, more than Nike spends on its top shoes. It does not take much imagination to see how advertisements for better brains would affect an insecure public. Gingko Biloba, despite its minimal affects on cognition,[62] is a billion dollar industry. Pharmaceutical companies, undoubtedly encouraged by sales of Viagra, are not oblivious to the marketing possibilities of new "interventions" that could apply to the entire population.[31,63] Furthermore, the Academy is unlikely to restrain industry. Scientific leaders who discover new therapeutic possibilities are quick to stake biotech claims.[31] Prospecting for better brains may be the new gold rush.

Military. If we can make smart bombs, surely we can make smarter bombers. Imagine a soldier that is stronger, faster, more enduring, who learns more quickly, needs less sleep, and is not hampered by disturbing combat memories. The military has long investigated and used enhancements, dating back to "go-pills" (amphetamines) for World War II soldiers.[31] At the Defense Advanced Research Projects Agency and other military institutions, considerable research is under way using pharmaceuticals and TMS to modulate cognition.[31,49] For example, Fort Rucker investigators found that modafinil had its greatest effects in helicopter simulation performances at the combined nadir of sleep deprivation and circadian troughs.[25] Only the tip of this research may surface in the public domain. However, relevant findings from the military may trickle down to civilians. Overfed Hummer vehicles now lumber down the narrow streets of Philadelphia. Perhaps Hummer bodies and brains are around the corner.

The role of neurologists? Americans believe that the pursuit of happiness is an unalienable right. This belief assumes we have the wisdom to know what constitutes happiness, an assumption that itself is suspect.[58] Fame and fortune have been standard proxies for happiness in American culture. Better brains may very well join the list, either as a means to fame and fortune, or as a source of happiness itself.[57] Since 1997, the FDA has permitted direct marketing to consumers. Physicians are likely to face "patients" insistent on pursuing this means to happiness.

The role of neurologists and psychiatrists is likely to evolve along with the cultural zeitgeist. Some psychologists now focus on normal rather than on psychologically distressed individuals. "Positive psychology" hopes to maximize normal abilities so that individuals can fulfill themselves.[64] Therapists are now coaches in the pursuit of happiness. Can positive neurology be far behind?

Scientific, economic, marketing, and regulatory forces are likely to shape the role neurologists and psychiatrists will play in all this. The details are difficult to predict, but what is certain is the fact that clinicians will engage in cosmetic neurology. The practice of cosmetic neurology will be complicated by the fact that we cannot rely on the conventions of traditional practice or the convenience of disease markers as guides to care. As neurologists, we may have special understanding of the potential benefits and risks of quality of life therapies in so far as they work through the nervous system. But we have no special insight into the pursuit of happiness.

One plausible scenario is that neurologists will become quality of life consultants. Following the model of financial consultants, we could offer a menu of options, with the likely outcomes and the incumbent risks stated in generalities. The role would be to provide information while abrogating final responsibility for these decisions to patients. Abrogation of such responsibility is made easier by current practice norms. Financial incentives, driven by forms filled and diagnostic studies ordered, encourage less personal involvement with patients. The comfortable stance would be to let people decide for themselves. After all, isn't autonomy what patients desire? However, the degree of autonomy desired by patients when sick is not so clear.[65] Furthermore, the bewildering array of choices available to American consumers in almost every domain of life is a source of considerable anxiety.[66] If the practice of cosmetic neurology encourages the role of patients as consumers, it is in danger of compounding these anxieties.

I am not advocating that neurologists become disengaged purveyors of quality of life elixirs. I am suggesting that this role is a distinct possibility given current trajectories of medical practice. Is this what we want? While I suggest that the advent of cosmetic neurology is inevitable, the specific shape it takes may be subject to modification. I hope this paper encourages discussion of what this shape should be. Such discussions will have to center on two issues, both of which I have tried to show are not straightforward. First, we need an explicit notion of what it means to be human. How else could we motivate our

choices in enhancing movement, mentation, and mood? Second, we need to have a clear sense of the evolving role of physicians. This sense will be especially important as we wander off the familiar moorings of treating disease.

Conclusion. In this paper, I have raised issues about cosmetic neurology that our profession will encounter. We may have our personal opinions on the correctness of such "treatments," but do we have a stand as a profession? We can anticipate facing questions where separating principle from prejudice is not easy and for which there are no easy answers. To make these questions concrete, I invite readers to consider their own views on the following questions:

1. Would you take a medication with minimal side effects half an hour before Italian lessons if it meant that you would learn the language more quickly?
2. Would you give your child a medication with minimal side effects half an hour before piano lessons if it meant that they learned to play more expertly?
3. Would you pay more for flights whose pilots were taking a medication that made them react better in emergencies? How much more?
4. Would you want residents to take medications after nights on call that would make them less likely to make mistakes in caring for patients because of sleep deprivation?
5. Would you take a medicine that selectively dampened memories that are deeply disturbing? Slightly disturbing?

Such questions are not simply thought experiments. Patients and advocacy groups encouraged by direct advertising to consumers will raise them. How will you respond to these "patients" when they turn to you as the gatekeeper in their pursuit of happiness?

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