Article

The Speculative Neuroscience of the Future Human Brain

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Abstract: The hallmark of our species is our ability to hybridize symbolic thinking with behavioral output. We began with the symmetrical hand axe around 1.7 mya and have progressed, slowly at first, then with greater rapidity, to producing increasingly more complex hybridized products. We now live in the age where our drive to hybridize has pushed us to the brink of a neuroscientific revolution, where for the first time we are in a position to willfully alter the brain and hence, our behavior and evolution. Nootropics, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) and invasive brain mind interface (BMI) technology are allowing humans to treat previously inaccessible diseases as well as open up potential vistas for cognitive enhancement. In the future, the possibility exists for humans to hybridize with BMIs and mobile architectures. The notion of self is becoming increasingly extended. All of this to say: are we in control of our brains, or are they in control of us?

Keywords: hybridization; BMI; tDCS; TMS; DBS; optogenetics; nootropic; radiotelepathy

Introduction

Newtonian systems aside, futurecasting is a risky enterprise at the best of times. To manage the risk, forecasts can be divided into near-term (next 10 years), mid-term (next 25 years) and long-term (next 50–100 years), with the potential of getting it wrong increasing exponentially as the long-term asymptote is approached. The challenge of predicting the brain from a neuroscience perspective suggests a narrowing of the field of possibilities; however neuroscience is an extremely broad field in itself, collaborating with such diverse areas as psychology, anthropology, pharmacology, physiology, sociology, genetics, computer science, engineering, mathematics, physics, philosophy and ethics. A neuroscientist can specialize in any one of these fields, and consequently if asked about the future will

no doubt propose a view commensurate with the history and developments of their field, while glossing over other areas so as to avoid turning the question into a book-length project. One essay on the topic justified the undertaking by saying: "… it seems necessary to explore possible directions of the evolution of human brains simply to be able to prevent maladaptive developments" ([1], p. 3). This rather academic claim may be true for the near-term, but for mid- to long-term scenarios, it smacks somewhat of grandiosity. Even in the present, policy makers and ethicists are constantly playing catch-up with evolutionary developments, and with the current rate of change, no one in all honesty can say that society is in a position to preempt what the future has in store when it comes to the brain. A program to prevent maladaptive developments requires very specific and targeted prescriptions, none of which a futurist essay is in a position to concretely provide. Curiosity and pleasure count as more realistic motivations. Curiosity is a powerful force. Ideas put forward can influence thinkers in ways impossible to predict. To a scientist, this is what makes the endeavor pleasurable, and as such, better informs the current discussion.

When talking about the brain, there is a tendency to forget that it is embedded in our bodies and gives rise to a social life with values and desires that shape our every action. An essay on the future of the human brain that does not couch the discussion in terms of human experience, therefore, would seem to be negating its very reason for existence. We would like to know, for example, if we changed the human brain, what impact would it have on ordinary life? Is it possible that we might change the human brain so much that what we currently consider ordinary life might become a thing of the past, a mere curiosity? This is the sociological angle. To this we could add the anthropological view—how the human brain evolved from the past to present, and its interrelationship with culture. This invokes the genetic view, how culture and genes interacted over our long history to produce the neocortex and its altered neurochemical profile when compared to our closest neighbors, the nonhuman primates. Pharmacology could follow, ending with computer science, giving us a reasonably broad view from which to entertain speculations on how any one, or all combined, could potentially influence the future of the human brain.

Ironically, if you count artificial intelligence scientists out, neuroscientists have published few speculative writings on the future of the human brain (Steven Rose is a notable exception [2]). The topic seems to have been taken up more enthusiastically by futurists [3] and transhumanists [4–6]. Transhumanists encourage the modification and augmentation of the human body. They suggest we are not far away from hybridizing our brains with nanotechnology and downloading our brains into computers. This places them in the near- to long-term predictive category, which to most neuroscientists who deal with the wet and messy reality of the brain on a daily basis makes their predictions seem more like fringe science, not worthy of scholarly consideration. At a deeper level, the transhumanists, like all humans, are fascinated with prolonging life and extending adaptive capabilities, and in their own way are no different from the first builders of flying machines who dared dream to fly. Technical realities aside, the sociological question begs: is a life that has been downloaded into a computer worth living? If we could see in the dark and read small text from a thousand yards, would that improve the quality of our life beyond what we currently experience? Perhaps the answer lies in what is already around us. Today we rely (almost obsessively) on mobile technologies such as cell phones, laptops, PDAs, GPS, pagers, wristwatches—even glasses. Does having these items make our lives any more fulfilling? From a utilitarian point of view, the answer

would appear to be "yes" in most cases. Information, it seems, is the base currency of our existence. Mobile technologies, in one way or another, all contribute to increasing, as well as helping us analyze the information in our environment. The deeper question appears to be how much is enough? Considering that transhumanists propose we increase our processing capacity through neural augmentation, the goal post will inevitably creep forward, rendering the answer relative. Ultimately, it all depends on the individual. This raises ethical considerations, not just for the mid- to long-term future, but the present and near-term as well. A case in point is the recent upswing in use of nootropics [7]—drugs that facilitate cognitive enhancement from mood to intelligence—but for which there is a paucity of studies examining long-term effects. Clearly, people want to neuroenhance themselves. The fact that it is already happening at the population level means that it will more than likely increase in the future [8].

The term "converging technologies" [9] has been coined to describe the trend where nanotechnology, biotechnology, information technology and cognitive science intersect and synergize to amplify or extend "core capacities" of the brain to produce a "post human" state [10]. It is not out of the realm of possibilities that converging technologies will enable human beings to tinker with their own evolution, a step that may affect natural selection. Indeed, some argue that the human brain is still evolving, and ever more rapidly because of modern technology [11,12]. Given this situation, the aim of this essay is to survey the literature in the areas cited above (not necessarily in that order) and tie the discussion together in a meaningful way leaving the reader with a clearer understanding of what possibilities might lie ahead. In broad brush strokes, the discussion can be divided into four areas: recent evolution of the human brain (our separation from the common ancestor, comparative psychology between nonhuman primates and humans); brain-machine-interfaces (BMIs: neural implants for therapeutic applications, possible cognitive enhancements); cognitive enhancements via pharmacological agents, and finally, mid- to long-term possibilities, such as genetic modification, nanotechnologies and artificial intelligence (e.g., mind "uploading" and interaction with neural networks).

Evolution of the Human Brain

A survey of the recent evolution of the human brain will provide a reference background for extrapolating its evolution into the future. Biologists argue that human evolution occurred through the mutation of genes, creating a potential for natural selection through successful or failed adaptations to the environment. Convention holds that the human transition began with a split away from the chimpanzees (*Pan troglodytes*) approximately 6–10 mya [13,14] and makes its presence fully felt in *Homo erectus* and so-called archaic *Homo sapiens*. Given the long time-span of our evolution, it is generally accepted that humans evolved slowly, with modern humans (who act, behave, look just like we do) emerging at around just 50 ka [15]. This emergence is closely followed by what has been euphemistically referred to as the "big bang of consciousness" occurring around 30 ka and is associated with cave art and figurine sculptures, with the second big bang occurring around 10–12 ka with agriculture and the domestication of animals. While no one argues about the sudden appearance of sophisticated cave art as indicative of a major shift in consciousness, there is a vigorous debate over the nature of human consciousness leading up to it. There is strong evidence that humans engaged in sophisticated behaviors long before 50 ka, including use of fire as early as 1.7 -1 mya [16–18], seafaring by 850 ka [19], settlements by 400 ka [20,21], beadwork circa 250 ka [22], and of course the

diverse and complex lithic industries that began with the Oldowan period (2.6 mya) and transitioned through to the first symmetrical hand axes around 1.7 mya to the manufacture of stone-tipped hunting weapons around 500 ka [23].

The stone-tipped weapons are crucial indicators of the development of human cognitive development (such as the conscious manipulation of symbolic thought) because they demonstrate empirical evidence of hybridization behavior in our species. In the early stages of our evolution, hybridization manifested itself as the merging of two separate categories of the world—form and function. While other perishable materials may have preceded it, the hand axe is the first concrete evidence of this development [24]. Hominids demonstrated it by knapping stone into a quasi-symmetrical shape while maintaining a cutting edge. Symmetry was imposed on the stone when it did not require it (a non-symmetrical flaked stone with sharp edges is just as functional as a symmetrical one). Why did we impose a symmetrical form onto an already functional object? The answer varies depending on whom you talk to. But the fact remains that for the first time, form and function were merged—hybridized. When we examine our closest genetic relatives, the nonhuman primates, we find that what separates us from them at the most basic level is hybridization behavior.

In almost all other areas of investigation, nonhuman primates have demonstrated diverse cognitive abilities that have forced researchers to reconsider how unique humans are. Thus, nonhuman primates use tools [25–27], display mirror self-recognition [28–30], employ basic theory of mind [31–33], engage in certain types of causal reasoning [34–36], imitate [37–39], cooperate [40–42], and to a reasonable degree use language [43–49], display symbolic ability [50,51] and engage in mental time travel [52–54] and metacognition [55,56]. They also display a form of pedagogy, which one researcher has called "education by master-apprenticeship" [57] and contextual volitional control [58,59]. This last ability is perhaps the most important in terms of brain evolution since the brain can be considered a control system for the body. Christensen proposes that the core trait under selection in the evolution of cognition is high order control capacity, rather than more specific abilities such as spatial cognition, tool use or theory of mind [60]. Many specific abilities have played a role in the evolution of cognition, but the deepest level of organization is shaped by problems of control that are common across many abilities. The major functional benefit of control is behavioral flexibility, and this is where humans stand out amongst primates, in that control has allowed us to *willfully* hybridize our world. This last point cannot be overstated, as the evolution of human behavior can be seen as one of leveraging increasingly more complex hybridizations of thought and action.

As a process, hybridization describes the evolution of humans away from the common ancestor, and accounts for the gradual to increasingly rapid changes in culture that our species has traversed. As more internal ideas and worldly objects became hybridized, a positive feedback loop developed. At first, the slope of development was gradual, but as more and more hybridized events interacted, the slope steepened. Thus, for first five or so million years after splitting away from the common ancestor, progress was slow, almost glacial. The first stone tools around 2.6 mya leave little trace of hybridization behavior. However, around 1.7 mya, the symmetrical hand axe appeared in the archeological record in Southern Africa. Even though this hybridization event probably occurred unconsciously, it established a link between symbolic thought and behavior that would set us on the path that we are still on now.

In a revealing experiment, chimpanzees were tested using a reverse contingency paradigm [61]. They had to select one of two dishes containing candy. One of the dishes always contained more candy than the other. Upon their selection, the chosen dish was removed and they were given the remaining dish. Since chimpanzees always selected the dish containing the most candy, they always ended with the least number of candies. This pattern reversed when Arabic numerals were switched in place of candy. The researchers concluded that, "the Arabic symbols appeared to capture the requisite numerical information of the stimuli, without encompassing the incentive properties that subserved the interfering response bias" ([61], p. 83). In other words, the apes were perfectly capable of symbolic behavior, but were unable to *link* this behavior with their appetitive, reward-seeking drive. This is precisely what hybridization in the brain means. That one sub-system is able to link up with another and form a new behavioral output. It appears that when we broke away from the common ancestor, for whatever reason, be it environmental or genetic—or both, something changed in our brains such that we were able to link together symbolic processing with other functional areas, such as appetitive drive and motor output. Neurologically, this amounts to the formation of new brain circuits. The hybridization hypothesis therefore allows us to posit that the brain must not only carry within it the history of the evolution of hybridization behavior, but also clues as to its possible future.

In terms of history, the Bruce Lahn laboratory recently sought to associate two genes, MCPH1 (microcephalin) and ASPM (abnormal spindle-like microcephaly associated), with the two big bangs of consciousness [62,63]—MCPH1 with cave art around 37 ka, and ASPM with writing and complex civilization around 5.8 ka. They suggested a selection for intelligence or language, specifically reading and writing, as possible drivers of a selective sweep coinciding with these two periods of growth. However, a more recent study that attempted to correlate spoken and written language, working memory, IQ—even brain size—with these two genes failed to find any relation [64]. Thus it is more than likely that these two genes do not reflect recent cognitive selection in humans. In further support of this, two separate studies independently demonstrated that ASPM, among other genes, had undergone accelerated evolution in primates, especially in man, beginning over 2 mya [65,66]. The analyses suggested that brain-size related changes in ASPM were complete well before the development and migration of modern humans out of Africa, with the derived allele reaching fixation around 2–400 ka, with evidence for stabilizing selection since that time. Evolution of the human ASPM gene then, may have played a major role in the increase of brain size onwards from the common ancestor of humans and chimpanzees, but not for more recent changes related to modern humans.

A more promising gene is Forkhead box protein P2 (FOXP2) [67]. FOXP2 is a member of FOX group of transcription factors and is involved in the regulation of gene expression. Mutations of the FOXP2 gene cause a severe form of language impairment and orofacial dyspraxia [68]. It was first discovered after analyzing the genome of an English family that exhibited a common pattern of severe speech and language deficits [69]. Many of its target genes have since been found to be important for neural connectivity in the central nervous system [70]. With the exception of bats [71]—perhaps due to the sensorimotor demands of echolocation—FOXP2 is relatively well conserved in mammalian species; it differs in humans and chimpanzees by only two amino acids. When a humanized version of FOXP2 was inserted into the mouse genome, the transgenic animals displayed practically completely opposite traits to those carrying a nonfunctional FOXP2 allele modeled on the human mutation associated with speech impairment [72]. They displayed *decreased* exploratory behavior, *decreased*

levels of dopamine throughout their brains, increased dendritic length, increased long-term synaptic depression affording them increased synaptic plasticity, a factor important for flexible learning. The indices of all these traits were reversed in the mutant FOXP2 mice.

The decrease in exploratory behavior in mice with the humanized variant of FOXP2 is a curious finding, since one would think that increased exploratory behavior of novel stimuli, while increasing potential life risk, would also confer increased behavioral flexibility, and therefore improved adaptability to the environment. Further complicating the finding is the increased synaptic plasticity which, once again, one would assume would make mice more open to learning novel stimuli. Perhaps, because of the increased ability to break previous learning bonds through long-term synaptic depression, the mice were overwhelmed by the novel environment causing a reduction in exploratory behavior? Paradoxically, it might be the heightened sensitivity to novel stimuli that increases opportunities for learning novel associations, something that could facilitate the acquisition of hybridization behavior in humans.

Fred Previc's work on dopamine raises the distinct possibility that it was a significant factor in the "humanization" of the cerebral cortex [73]. Previc suggests that dopamine is important in "promoting generativity" and improves human "fluency" ([73], p. 314). In other words, increased hybridized output. In a recent study, dopamine was found to play a significant role in the cortical evolution of apes, and contributed to further changes in the descent of humans [74]. If true, this potentially makes dopamine the neurotransmitter of behavioral hybridization. But it also makes the FOXP2 mice all that more difficult to understand, particularly with respect to decreased dopamine in the cortico-basal ganglia circuits. Altered dopamine regulation in humans is associated with a number of disorders and behavioral deficits, including Parkinson's disease [75], Huntington's disease [76], phenylketonuria [77], depression [78] and attention-deficit/hyperactivity disorder (ADHD) [79]. That the FOXP2 mice did not display any of these symptoms despite having low levels of dopamine suggests that much more work needs to be done on this model of human brain evolution.

Brain size, of course, has been one of the most researched areas of human evolution [80]. From the appearance of *Homo erectus* around 1.7 mya to the present, brain size increased nearly twofold: from around 800 mL to 1,500 mL in the Late Pleistocene (circa 30 ka) [80]. No doubt this increase in size provided the neural volume and mass for increased intelligence. However, while brain size has been positively correlated with intelligence, a more nuanced interpretation would argue that neural integration plays an equally, if not more important role [81]. The linking between symbolic reasoning with other functional areas is a case in point. For example, the number of cortical neurons and conduction velocity (as the basis for information-processing capacity) [82], as well as increased complexity and capacity for neural plasticity in neural centers [83], has been proposed as a more meaningful measure of intelligence. From the Late Pleistocene onward brain size then decreased again [84,85]. However, this decrease can be deceiving. Measures of *internal* frontal bone profiles have shown that the prefrontal areas have changed very little over the last half-a-million years [86]. Considering the importance of the frontal areas for social reasoning and organized behaviors, this would seem to correlate well with evidence of sophisticated behavior found in human variants across the globe dating through this period. Moreover, when brain size was examined over our entire evolution, it was found to correlate isometrically with body size, suggesting that the "exceptional mental ability of humans may be a result of functional rather than anatomical evolution" ([87], p. 745). On this basis, if we were

to extrapolate into the future, we might hypothesize less change in absolute size but more change in neural integration. What might account for such changes? The trend over the last 500 ka has been one of increased externalization of symbolic processing, of external storage and manipulation of information [88]. In the future, we must expect a continuation of this trend, particularly increases in mobile technologies and their hybridization, where previously brain-based processes are taken over by external processors, either externally attached to the body, or integrated into it. This opens up the discussion for brain-machine-interfaces (BMI).

Brain Machine Interface (BMI)

In 1999, researchers implanted a 64 × 64 electrode array directly into the lateral geniculate nucleus of a cat and recorded from 177 neurons [89]. Over repeated presentations of movies to the cat they were able to reconstruct with sufficient resolution images that the cat saw. Also in 1999, researchers demonstrated that a robotic manipulator could be directly controlled by an ensemble of rat cortical neurons [90]. It may sound like science fiction, but these experiments demonstrate that the brain is an electro-chemical machine that operates on ordinary physical principles, and can be accessed with the appropriate technology. In 2006, Mikhail Lebedev and Miguel Nicolelis wrote:

> Less than a decade ago, hardly anyone could have predicted that attempts to build direct functional interfaces between brains and artificial devices, such as computers and robotic limbs, would have succeeded so readily, and in the process would have led to the establishment of a new area at the frontier of systems neuroscience ([91], p. 536).

BMIs are classed as invasive or non-invasive. Non-invasive BMIs use electroencephalograms (EEGs) to access "brain waves" from subjects. Brain waves, or more accurately, neuronal oscillations, occur as a result of dynamic mass action of neuronal assemblies in the cortex [92]. They were first recorded in 1924 by Hans Berger [93]. The technique involves placing electrodes on the scalp to acquire oscillations of different frequency bandwidths. The modern application has simplified the system to a headset that users wear over their scalp. The method has been used to help locked-in patients develop ways of communicating [94], paraplegics to drive motorized wheelchairs [95], as well as normal healthy subjects to perform a diverse number of actions ranging from controlling a computer cursor to playing video games [96,97]. EEG techniques can detect modulations of brain activity that correlate with visual stimuli, gaze angle, voluntary intentions and cognitive states. These properties have led to the development of several classes of EEG-based systems, which differ according to the cortical areas recorded, the features of EEG signals extracted, and the sensory modality providing feedback to subjects. However, although the technology has rapidly developed over the last decade, and does not carry the risk of invasive surgery and long-term effects of indwelling electrodes, EEG-based techniques provide communication channels of limited capacity [98]. Even though EEG has relatively good temporal resolution, it suffers from limited spatial resolution owing to the overlapping electrical activity generated by different cortical areas [99]. Furthermore, during the passive conductance of these signals through brain tissue, bone and skin, resolution is lost owing to the low-pass filtering of the EEG signals [100]. EEGs are also susceptible to electromyographic [101], electrooculographic [102] and mechanical artifacts [103].

While EEGs have been reasonably successful for applications that extract information from the brain, over the last decade methods that non-invasively stimulate the brain have also increased in popularity, and have been used to treat certain types of brain disorders [104,105], including some conditions refractive to pharmacological treatment [106]. Two methods that are currently receiving attention are transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS). In tDCS, a weak electric current (e.g., 1–2 mA) is passed through the brain via electrodes. The electrodes create an electric potential across the brain that causes a shift of ions in neural tissue. Due to resistance (e.g., skin and bone), an unknown percentage of the electric potential is diffused. The amount of electric current that passes through the brain depends on the current density at the electrodes (a function of their size and amperes applied to them), their placement, and the thickness of the skin and skull. An almost unlimited number of electrode positions and current configurations can be implemented, although in practice they are limited to a dozen or so types. The distributional shift of electric current during stimulation has been modeled in some of these, but others remain unknown [107]. Moreover, similar to pharmacological intervention, the effects on individual brains are never the same because of unique structural differences in skulls and brains. The literature employs terms such as "anodal stimulation" and "cathodal stimulation" as if these were absolute concepts, when in reality the important variable is the induced shift of ions in relation to the orientation of neurons *in vivo*. Since neurons typically depolarize in the dendrite-soma-axon-terminal direction, if the average ionic flow is in the same direction, the threshold of excitability can be lowered, whereas if the average ionic flow is in the opposite direction, the threshold can be raised [108]. Even though a functional magnetic resonance imaging (fMRI) study revealed that tDCS produces the most activating effect on the underlying cortex [109], a positron emission tomography (PET) study revealed that tDCS stimulation provokes sustained and widespread changes in other regions of the brain as well [110]. EEG studies support these findings, showing that stimulation of a particular area (e.g., frontal cortex) induces changes to oscillatory activity that are synchronous throughout the brain [111,112]. Hence, stimulation of one area will likely have effects on other areas, most probably via networks of interneuronal circuits [113]. This phenomenon is not surprising given the neuroanatomical complexity of the brain, but it raises interesting questions as to: (i) how the effects are transmitted; and (ii) whether the observed clinical effects (e.g., alleviation of pain) are mediated primarily through the area of the cortex being stimulated, or secondarily via activation or inhibition of other cortical or sub-cortical structures [114,115]. Further complicating the picture is that effects can persist up to 12 months [116]. In explaining the mechanisms of this effect, tDCS has been shown to be protein synthesis-dependent and is accompanied by modifications of intracellular cAMP and calcium levels [104], thus flagging the possibility of sharing some features with long-term potentiation and long-term depression [117]. Experiments in humans have found changes in local concentrations of GABA and glutamate, both of which are associated with synaptic mechanisms of learning and memory [117]. Specific claims of long-term efficacy include motor and sensorimotor skills, vision, mathematical cognition, language, memory, attention, decision making and problem solving [104,118–121]—improvements that seem to persist without apparent cognitive side effects [106]. It is these claims, and the low cost and simplicity of the equipment and its operation, as well as its relative safety (generally only a 9V battery is used) that has spurred its proliferation in the DIY cognitive enhancement movement.

TMS on the other hand is expensive, draws a large current to charge capacitors, and is significantly more complex to operate. For the most part, TMS is confined to clinics and institutions. The number of papers published annually over the last decade on TMS has doubled to around 200 and remains high [122] and reflects strong interest in the therapeutic potential of the technology even though the rationale for its use in many conditions is not clear [123], and the mechanisms by which it produces lasting physiological and behavioral effects remains largely unknown [124]. While the precise mechanism of action of TMS in the brain for various conditions has yet to be elucidated, the theory of its operation is relatively straightforward. Essentially, the apparatus delivers magnetic pulses into the brain that induce electric fields by electromagnetic induction. The magnetic field can reach up to about 2 Tesla and typically lasts for about 100 ms [125]. The electric field is induced perpendicularly to the magnetic field in the underlying tissue and can reach strengths sufficient to trigger action potentials in neurons. TMS is delivered in rapid pulse trains, typically from 0.1–20 Hz. Specialized pulse trains also exist, for example "Theta Burst Stimulation" [126]. When used therapeutically, TMS is usually delivered over repeated sessions (rTMS). One of the reasons, perhaps, why very little is known about TMS's mechanisms in the brain, is that it appears in very few animal models. One study, in an attempt to identify the mechanism by which rTMS may alter neuropsychiatric function, found that it may downregulate beta adrenoreceptors [127]. Another study found that rTMS may increase dopamine and serotonin levels in the striatum, frontal cortex, and hippocampus [128]. What is known is that TMS can be used to briefly activate [129] or briefly inhibit [130] brain regions in humans—although most likely, both occur with each mode in differing amounts and with different time courses. This effect can be used to localize brain functions in both space and time [131–133]. Because of its ability to localize strong electric fields TMS can also be used to create a temporary functional "lesion" with which to study cognitive functions, such as vision and language [134,135]. TMS has been used extensively in the treatment of depression. PET and rTMS findings have led to the imbalance hypothesis of Major Depressive Disorder (MDD), which postulates prefrontal asymmetry with relative hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) and relative hyperactivity in the right DLPFC [136–139]. Advocates claim that prefrontal TMS treatment for depression is effective [140–142]. A number of meta-analyses have tentatively supported TMS treatment for depression [143–146] but cite several major hurdles that need to be overcome if it is to be fully endorsed. These include lack of knowledge of mechanisms behind its putative effectiveness, and the thorny question of "sham" controls. Active TMS emits loud noises and causes muscular spasms, pain and numbness in the area of application, whereas sham control only produces noises. Subjects can therefore easily discriminate active from control trials. Bioengineers are currently examining ways to retrofit existing TMS apparatus to simulate its artifacts so as to improve testing validity [147,148]. The sham condition poses the same problems for validating effectiveness in treating other conditions as well, including bipolar disorder [149], schizophrenia [150], obsessive-compulsive disorder [151], post-traumatic stress disorder [152] and stroke [153]. Nevertheless, the enthusiasm for this technology, largely due to its non-invasiveness, intuitive plausibility, and ability to trigger direct effects in the brain, remains high even if the possibility of elucidating its mechanism of action will most likely remain a mystery for some time to come.

If non-invasive BMI has proven to be somewhat ambiguous in its effectiveness, invasive BMI has largely avoided this limitation, at least in its short-term efficacy. Invasive BMI relies on long-term recordings from large populations of neurons (100–400 units) via implantation of electrodes directly

into the peripheral and central nervous system, and evolved from experiments carried out on nonhuman primates in 1995 [154]. In 2006, proof of concept was achieved demonstrating restoration of damaged motor function in a human via a neuromotor prosthesis [155]. Six years later, researchers had subjects perform three-dimensional reach and grasp movements [156]. Although robotic reach and grasp actions were not as fast or accurate as those of an able-bodied person, the results demonstrate that years after injury to the central nervous system, useful multidimensional control of complex devices accessed directly from a small sample of neural signals is feasible. As a result, a large amount of R&D money is now being injected into the field with the hope of providing artificial limbs for paralysis and amputee patients. While these developments are encouraging, the biggest remaining problem is a rapid deterioration in the quality of neural recordings from cortical arrays, ranging from several months to a year. A range of strategies can potentially overcome this problem: (1) make the electrodes less stiff; (2) remove the wires tethering the array to the skull; and (3) use a biomimetic array coating to improve electrodes' biocompatibility and reduce the immune response [157]. It is unclear whether these problems will be surmounted in the near- to mid-term future. As subjects desire more functionality over external devices, more electrodes [158], as well as deeper implantation will become necessary. This will add further challenges to the field. Lebedev and Nicolelis have identified four areas where research and development needs to progress before BMIs for prosthetics control can become routine in humans:

1. Obtaining stable, very long-term recordings (*i.e.*, over years) of large populations of neurons (*i.e.*, hundreds to thousands) from multiple brain areas. This task encourages development of a new generation of biocompatible 3D electrode matrices that yield thousands of channels of recordings while producing little tissue damage at implantation and minimal inflammatory reaction thereafter.

2. Developing computationally efficient algorithms, that can be incorporated into the BMI software, for translating neuronal activity into high-precision command signals capable of controlling an artificial actuator that has multiple degrees of freedom.

3. Learning how to use brain plasticity to incorporate prosthetic devices into the body representation. This will make the prosthetic feel like the subject's own limb.

4. Implementing a new generation of upper-limb prosthetics, capable of accepting brain-derived control signals to perform movements with multiple degrees of freedom ([91], p. 539).

While the field has seen rapid progress, there will almost certainly follow a long protracted period of slow development due to the complexity of these problems and we could reasonably predict that routine deployment of the technology will not become commonplace in the near-term future.

Notwithstanding, a therapeutic form of invasive BMI known as deep brain stimulation (DBS) is now being used experimentally to offer relief to patients with Parkinson's, epilepsy and depression [159]. In these patients, electrodes are placed deep into the brain and a low voltage current with an adjustable frequency is supplied from a battery-driven implant device similar to a cardiac pacemaker. The wires are concealed beneath the scalp. After calibration, the device is "tuned" to the individual needs of the patient, for example to quench muscle tremors, or lift their mood. Even though DBS has proven to be effective for some patients, it still suffers from the same problems as BMIs using electrode arrays. In a recent 36-month follow up of Parkinson's patients that had electrodes placed in the globus pallidus interna (GPi) and subthalamic nucleus (STN), they found that while there was clear motor

improvement, there was also a pattern of slight cognitive decline. This likely reflects the underlying disease progression and highlights the importance of non-motor symptoms in determining quality of life [160]. In addition to this, the immune system attacks the electrodes and encapsulates them in glial scarring which significantly reduces their performance [161]. So while the initial implantation can diminish symptoms, after a few years or even months, the efficacy of DBS begins to wane.

Apart from electrode biocompatibility issues, one of the more technical limitations of DBS is that its electrodes target cells indiscriminately. For a truly targeted therapy, both spatially and temporally, cell types need to be controlled individually and at their native frequencies. Optogenetics is a new technique that promises to offer this level of control [162,163]. For some time scientists have known about specialized phototranducing receptors in prokaryote and eukaryote organisms called opsins [164]. Opsins combine a light-sensitive domain with an ion channel/ion pump in the same protein. One example is channelrhodopsin-2 (ChR2). Opsins can be delivered to target cells by transfection, viral transduction or the creation of transgenic animal lines [165]. When ChR2 is expressed in a neuron and exposed to blue light, its ion channel opens allowing positive ions into the neuron. This immediately depolarizes the neuron and triggers an action potential. To date, entire families of opsins have been characterized and tested, each one possessing different phototransducing properties allowing scientists to control the flow of ions into and out of neurons, as well as the rate of neuronal firing. The real breakthrough came when scientists tested the system in living animals [166,167]. Like DBS, the only way to deliver light deep into the brain of a living animal was to use electrodes, although in this case, optogenetics employs fiberoptics. The diameter of fiberoptics is typically one-third or less than that of its electrode cousin. Nevertheless, long-term indwelling fiberoptics poses the same problems as electrodes, and so while optogenetics promises dramatic progress in the control of individual neurons in the brain, ultimately it will not freely progress until BMI biocompatibility issues are resolved.

Currently, the most routine version of BMI is the cochlea implant [168]. The implant works through an array of up to 22 electrodes wound through the cochlea, which send impulses to the nerves in the scala tympani and then directly to the brain through the auditory nerve. Michael Chorost in his book *Rebuilt* gives us a first-hand account of what it is like to hear again:

> I suddenly hear a sharp, pure beep somewhere in my head. It's a single electrode being fired an inch and a half inside my skull. It surprises me so much that my head jerks back and my whole body seizes up ([169], p. 50).

Shortly afterwards, after the first attempt at tuning the device, he describes the sound of dry leaves on the ground not as a rustle, but as a "tinkle". This is an artifact of the device, in that the full auditory range is limited and therefore makes things sound tinny. Despite this limitation, according to the U.S. Food and Drug Administration (FDA), as of December 2010, approximately 219,000 people worldwide had received cochlea implants. Given these large numbers, the BMI for prosthetics field could conceivably eye a similar commercialization model as the cochlea implant sometime in the mid-term future if it is able to overcome the challenges listed above. In addition to this, the drive towards hybridization will ensure that invasive implant technologies will merge with non-invasive technologies, so that for example the cochlea implant might become hybridized with tDCS to further enhance its sound quality via modulation of the neural response to external stimulation.

As BMIs become more commonplace, it is conceivable that humans will employ it to extend their senses. It is even possible that it might one day lead to *interspecies* communication. In this case we might coin the phrase "communabraining" to capture the futuristic flavor of the experience. What would it feel like? The experience of synesthesia might offer some clues. Synesthesia happens when sense data entering through one sensory modality ends up being experienced in another. For example, hearing a sound and experiencing it as the color green. A sub-field of neuroscience called "sensory substitution" [170] has emerged with the aim of leveraging the phenomena to extend the human senses. In an experiment designed to achieve this, subjects were given a special belt to wear fitted with vibrotactile stimulation that activated in response to which direction they faced according to a magnetic compass. After six weeks, some subjects experienced a profound change in their sensory experience of direction. Spatial contexts were felt as being massively enlarged, and spatial relationships could be memorized effortlessly. The authors concluded that "if you want to know what it is like to be a bat [171] you should whistle for orientation and learn to fly". This experiment, of course, is nothing new; similar experiments were conducted in the late 1960s on blind people who were taught how to "see" using a vibrotactile array pressed to their backs [172]. The modern equivalent of this is the first experimental implantation of bionic eyes into human subjects [173,174]. The fact that researchers have electronically linked the brains of pairs of rats for the first time, enabling them to communicate directly to solve simple behavioral puzzles [175], suggests that the possibility of linking human brains with each other, and with other species, is not that far off.

Nootropics

Humans have sought to alter or enhance their cognitive function, mood and performance with pharmacological agents from time immemorial. The recent upswing in the use of nootropics—drugs devoid of toxicity or secondary effects that enhance neuronal plasticity—is no exception. Because nootropics cover such a wide variety of agents, ranging from synthetic to natural, the exact definition, of course, is much broader. The definition also straddles the clinical and non-medical divide [176]. As a generalization, users of nootropics want a quick way of achieving improvement in their cognitive function, either because heritable factors, injury or age-related cognitive under-performance, or because they want to avoid the "authentic" (hard way) of improving themselves [177–181].

An exhaustive review of all nootropics is not within the scope of this essay, however, a look at some of the more popular agents, their putative mechanisms and effects will provide a snapshot of the current cognitive enhancement landscape. Probably the most well-known nootropic agent is Piracetam, a derivative of the neurotransmitter GABA (γ-aminobutyric acid). In the 1960s GABA was discovered to act as a major inhibitory neurotransmitter in the brain [182]. This naturally stirred GABA-related scientific interest and inspired pharmacological invention in the pharmaceutical industry. Piracetam was one of the first results of that exploratory period. It was originally designed to be a calming drug, particularly a sleep inducer, yet in spite of its kinship with GABA, it did not show any type of interference with that neurotransmitter, nor any sleep-inducing activity [183]. Instead, it was perceived to:

(i) directly activate the integrative activities of the brain, having a positive action on the mind

(ii) act selectively on the telencephalon and not manifest itself on lower brain levels

(iii) exert a restoring influence on agitated higher brain activity ([183], p. 35–36, translated from original [184]).

and led Corneliu Giurgea, who was in charge of its development, to coin the phrase "nootropic" [184,185], which roughly translates as "to bend/turn the mind". Piracetam's mechanism of action is not well understood. It appears to influence neuronal, vascular, and cognitive functions without acting as a sedative or stimulant [186]. Putative mechanisms of action differ depending on the disease process being modeled and include enhanced membrane fluidity [187], increased neurotransmitter release (e.g., dopamine) [188], protective effects on specific receptors (e.g., glutamate) [189], increased blood flow [190], enhanced corticosteroid function [191], and effects on calcium channel function [192], although, this last function is questionable in the light of findings that a persistent calcium inflow may have deleterious impact on neuronal cells [193]. At least two actions related to its cognitive effects are that it modulates the AMPA receptor [194], a receptor for glutamate that mediates fast synaptic transmission in the brain, and improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors, which are implicated in memory processes [195]. Thus, Piracetam's mechanisms of action are complex and enigmatic. Less contentious are Piracetam's side-effects. There are no specific studies examining long-term side-effects in healthy users, however, studies in epileptic and stroke patients found that its side-effects are typically "few, mild, and transient" [196–198]. Given that most people find it provides a subtle but noticeable boost to their concentration and memory, and with tolerable side-effects, piracetam has consistently remained a popular choice among consumers. It will more than likely retain this position well into the future, especially considering that it doesn't require a prescription and is relatively inexpensive (roughly equivalent in unit price to the same number of 500 mg vitamin C tablets).

Another popular class of drugs associated with cognitive enhancement is the amphetamines. Ritalin and Adderall are common examples. While Ritalin (methylphenidate) is typically prescribed for attention deficit hyperactivity disorder (ADHD), it has also seen a dramatic rise in non-medical use in students in the last decade [199,200]. In the USA, studies indicate that up to 16% of students on some college campuses use stimulants [201,202]. The most commonly reported motives for use were to aid concentration, help study, and increase alertness [203]. Interestingly, the number of teenagers recently reported to have used of stimulants for school purposes (*i.e.*, Ritalin and Adderall) has declined from higher usage rates recorded in the 1990s [204]. The reason for this decline is unknown, however, "generational forgetting" has been cited as one reason for the increase in the use of other dugs, such as LSD and ecstasy. Methylphenidate (MPH) is a benzylpiperidine derivative. The effects of benzylpiperidine are largely similar to amphetamines [205,206]. MPH is thought to act as a releasing agent by increasing the release of dopamine (DA) and norepinephrine [207,208], although to a much lesser extent than amphetamine [209]. In a human PET study, therapeutic doses of MPH were found to block more than 50% of dopamine transporters (DAT) and significantly enhance extracellular DA in the basal ganglia [210]. It was postulated that because DA enhances task specific neuronal signaling and decreases noise, it could improve attention and decrease distractibility. In addition, since DA modulates motivation, the increases in DA could also enhance task saliency by facilitating interest in the task, thus improving performance. Despite several countries reporting significant increases in MPH prescriptions in children and young adolescents in the last decade [211–214], the literature recommends modulating doses depending on context and the kinds of outcomes desired [215–218]. MPH also has a side-effect profile when used chronically in larger doses than prescribed [219]. Insomnia, stomachache, headache, and anorexia are common examples [220–222]. MPH in some cases

can become addictive. This potentially makes it a much more dangerous drug than piracetam. Will MPH prescriptions rise in the near future? Taking the United States as an example, where MPH non-medical use has actually *declined* in the last five years in younger people, suggests a ceiling of sorts has been reached, which may reflect a number of things: change in cultural trends, shift to alternative drugs, change in diagnostic patterns among medical practitioners, accuracy-of-use reporting, to name some possibilities. It has been suggested that ADHD is not a purely American phenomenon [223]. A worldwide pooled prevalence of ADHD was found to be 5.29% [224]. Variability was primarily explained by methodological characteristics of studies not geographical location. Based on these statistics, and those of non-medical use at around 10–12% in the USA [204], it appears that MPH use will not grow too much further in the near-term future. Whether shifting lifestyles, particularly those of densely populated urban areas, will catalyze a trend towards greater competition among people and hence an increase in stimulant use, is not known.

A stimulant that reportedly has less side-effects in normal subjects than MPH is modafinil. Modafinil was originally developed as a treatment for narcolepsy, and can be used to reduce performance decrements due to sleep loss with apparently little risk of dependency and side effects [225,226]. Its strongest endorsement comes from the military [227] and astronautics [228]. In the United States military, modafinil has been approved for use on certain Air Force missions [229–231] as an adjunct to fight fatigue. It has been approved for use aboard the International Space Station where it helps with the disruptions in circadian rhythms and the reduced quality of sleep that astronauts experience [228]. Modafinil has been shown to enhance working memory in healthy subjects, especially at tasks that require greater concentration [232]. The effect is most pronounced in subjects that have an initially lower baseline of performance. Modafinil's effects on healthy non-sleep-deprived subjects is in dispute. Some claim the effects are insufficient for it to be considered a cognitive enhancer [233–235]. Researchers agreed that modafinil improves some aspects of working memory, such as digit span, digit manipulation and pattern recognition memory, but the results related to spatial memory, executive function and attention are equivocal [233–236]. In a test on a group of sleep-deprived doctors, modafinil cut the number of errors in a short-term memory task and reduced the time doctors needed to plan a complicated move, but did little else [237]. Perhaps on this basis, modafinil could be considered more as a cognitive restorer than enhancer. The precise mechanism of modafinil's action remains unclear [238,239], although one study has raised the possibility that modafinil affects wakefulness by interacting with catecholamine transporters in brain [240]. Even though it clearly works as a "wakefulness promoting agent", it does not fit a classic amphetamine profile [241]. Recently, modafinil was screened on a large panel of receptors and transporters in an attempt to elucidate its pharmacology [242]. Of the sites tested, it was found to significantly act only on DAT, inhibiting reuptake of dopamine. In parallel, another study discovered that it stimulates the nucleus accumbens, one of the key sites in the brain linked to reward and addiction [243]. The study, however, reported that while the nucleus accumbens was activated during test, none of the effects of modafinil on behavioral measures were significant. It would appear therefore that modafinil is much safer to use than other hard stimulants such as amphetamines and cocaine. One of the more serious side-effects of modafinil is skin rash in susceptible individuals [244].

A number of other drugs could conceivably be categorized as cognitive enhancers if taken from the point of view of reversing a psychobiological deficit. These include the anti-depressants and the

anxiolytics, the latter of which beta-blockers might be considered to improve cognitive enhancement for performance anxiety [245,246]. In the same vein, caffeine and nicotine could be considered enhancers in that they improve mood. Indeed, from the reversal position, cocaine could even be considered a cognitive enhancer in that it "consistently antagonizes the learning deficits, psychomotor performance deficits and driving deficits induced by alcohol" intoxication ([247], p. 773). Finally, hallucinogenics and cannabis can be classified as perspective enhancers. No doubt these psychostimulants will remain in use as long as humans exist. Considering that more than just a few synthetic drugs have found a different purpose from the one that they were originally intended for, we can reasonably expect to find new cognitive enhancers entering the market in the foreseeable future. While the mechanisms of the three drugs described in detail above have yet to be fully elucidated, they all appear to share a dopamine connection, suggesting that cognitive enhancers of the future might follow a similar pattern. It is an interesting speculation that, if as it has been suggested, dopamine played an important role in the evolution of intelligence in our species, manipulation of the dopamine system via cognitive enhancers could perhaps, via epigenetic mechanisms [248,249], over generations, lead to changes in the intelligence and behavior of our species.

Genes, Brain and Behavior

The road to genetically enhancing ourselves has begun. We may not yet be in a position to manipulate the human genome for enhanced brains, but animal work is paving the way. One area that is receiving attention is learning and memory [250–253]. The targeting of learning and memory in genetic enhancement research follows the assumption that learning and memory are pivotal functions of human intelligence. Another area receiving interest is neurological diseases, for example Parkinson's and Alzheimer's, and brain injury [254–257]. Understandably, bioethicists are keeping a watchful eye on animal research. Traditionally, animal research has come under the umbrella of therapeutics. Advances made in animal models prepare the way for clinical trials of human diseases. However, animal research into genetic enhancement has broadened the therapeutic program to include developing genetic modifications that "move beyond a state of mere health" ([258], p. 169). This naturally raises questions about inequality. Clearly not everyone will be able to have access to cognitive enhancement via genetic means. The question may never be answered since inequality has existed as long as humans have. An additional theoretical possibility is the use of animal DNA rather than human DNA in human genetic engineering. The resulting humans would be transgenic. Transgenic animals already exist with human DNA, like transgenic chickens that are able to synthesize human proteins in their eggs [259]. Another possibility is the creation of human-animal chimeras. Examples include a "geep" (combination of sheep and goat) [260], a quail with a zebra finch telencephalon (a non vocal-learning species with a vocal-learning species' brain) [261], and a human-rabbit chimera [262] to produce a better research model for testing drugs or possibly growing "spare parts", such as livers, to transplant into humans. These developments are ongoing and relentless, so we can expect to see—at least in the long-term future—attempts at genetic modifications of the brain. A first step has already been taken. Researchers implanted cells genetically modified to express human nerve growth factor (NGF) into the forebrain of human Alzheimer patients [263]. A brain autopsy from one subject suggested robust growth responses to NGF. While the genetic treatment of Alzheimer's can be

considered ethically benign, the MAO-A gene raises a more controversial possibility. Named after a mutation in the neurotransmitter "metabolizing enzyme monoamine oxidase A", low expression levels of it have been implicated in a syndrome that includes violence and impulsivity in humans [264–266]. Low MAO-A activity is hypothesized to lead to a decreased ability to degrade norepinephrine, the neurotransmitter involved in sympathetic arousal and rage. Importantly, many individuals who have low MAO-A do *not* go on to be violent; maltreatment makes a greater contribution towards predispositions to antisocial behavior than differences in MAO-A activity alone. The behavioral outcome is therefore best explained by a gene *x* environment interaction. The identification of this interaction has recently led to it being submitted as a mitigating factor in a number of criminal trials [267]. Thus, the rise in knowledge of genes that contribute to brain and behavior is beginning to change the way we interpret individual responsibility, and could conceivably alter the way we deal out punishment for heinous crimes in the future [268].

Artificial Intelligence

Around the same time scientists decoded the structure of the DNA molecule [269], the field of artificial intelligence (AI) declared itself born [270]. Since then, both fields have undergone tremendous growth, each with their own ups and downs. However, according to some, the promised genetic revolution has failed to materialize [271]: "The promises of the molecular genetic revolution have not been fulfilled in behavioral domains of most interest to human psychology" ([272], p. 475). In identical terms, the same criticism has been leveled at AI scientists for failing to produce anything remotely associated with human beings: emotion, social intelligence and imagination [273]. In an attempt to refocus, AI has been recast as AGI—"artificial general intelligence", the humanized version scientists have been aiming for all along. But this raises new problems. It forces AGI scientists to confront what a human being really is. Since no one has a definitive answer to that question, it could be argued that AGI will have no choice but to produce something that looks, talks and acts like a human, but whether it is a human in essence, will remain forever unanswerable.

A persistent idea in the philosophy of AI is that intelligent agents are modular. Bottom-up automated routines combine to form top-down intelligent actions. Neural networks exemplify this approach. The proliferation of smart agents—wheeled and bipedal robots that can interact with humans—is the first step in this direction. In defining this approach, it appears that the deepest question—what is "self"—can be by-passed. There is no self. The mind is extended and hybridized. In his original thesis of extended cognition Andy Clark argued that cognitive processes are not bound to the organism, nor are they encapsulated by "skin and skull" [274], a claim that is furthered in his argument that we are always coupled to our technology, whether opaquely or transparently [275,276]. An already always hybridized being, "the body" therefore becomes one among many tools utilized in embodiment—in Michele Merrit's words—it is "the bodily-cognitive comportment to and interaction with the world" ([277], p. 223). AGI has embraced this approach because it obviates the implantation of an intelligent homunculus into a puppet. Robots can be built that start out "mindless" and learn by bumping into reality, rather than be born fully aware and intelligent *de novo*—thereby more precisely mimicking the way humans learn. Rodney Brooks is one of the better known advocates of this approach [278,279]. Exemplifying his robots are insect-like creations that behave very much like their

natural counterparts; they operate without top-down control. What Brook's work seems to be telling us is that humans are made up of hundreds, perhaps thousands of tiny robots, that when working in concert, collectively produce the appearance of intelligent behavior. There seems to be some credence to this argument, as Japanese researchers recently demonstrated "robot mirror self-recognition" with nothing more than a microcomputer, a camera and a robot chassis [280]. The machine clearly has no internal sense of self. It invites us to speculate on the nature of our own internal sense of self.

Kevin Warwick has pushed the self-less machine intelligence idea further by using a disembodied biological neural network to control a mobile architecture [281]. Warwick and his team took brain cells from rats, cultured them, and used them as a guidance control circuit for a simple wheeled robot. Electrical impulses from the robot enter the neurons, and responses from the cells are turned into commands for the device. This is achieved using a Micro Electrode Array (MEA) device, a tiny bed of electrodes upon which neurons are kept alive in a bath of nutrients. Nutrients have to be continually added and wastes removed to keep the neurons healthy. The neurons can form new connections, making the system a true learning machine. This, of course, raises thorny ethical questions. If one day in the future it were possible to transfer an entire brain into a machine where it could be kept alive for long periods of time, what does this say about the status of being human? It is not an old idea. Julien Jean César Legallois first suggested the isolated brain in 1812, the so-called brain in a vat scenario. By discarding our bodies we could potentially perform feats that would be otherwise impossible. For example, live in a vacuum, or work in dangerous places, or live forever. It also raises the question about the status of biological neural networks per se. Does a disembodied group of cultured neurons have social rights? One would argue "yes", if the artifice integrates with society and performs social functions like any other social agent—becomes an extended mind so to speak.

The bottom-up AGI adherents have demonstrated that machine intelligence can be achieved using an ensemble of simple agents. However, cognition is clearly more than that. Boicho Kokinov has recognized this and notes that cognition can be described as involving two fundamental processes, a symbolic one (a priori rule-based reasoning, representation, abstraction) and a connectionist one (perception and learning) ([282], p. 2):

1. The ability to categorize and to describe portions of the continuous world around us as separate entities and relations between them. The symbolic approach is best suitable for modeling this aspect—it describes human knowledge of the world as a system of discrete symbolic structures and human cognitive processes as processes of building and manipulation of such structures

2. The dynamic properties of all cognitive processes which are characterized by continuous and smooth changes of the mental state following both the internal dynamics of the cognitive system itself and the external dynamics of the continuously changing environment

However, unlike the AGI proponents who see cognitive complexity emerging from the interaction of simple agents, Kokinov proposes building a system from the ground up using a "micro-level hybridization approach":

"… the micro-level hybridization approach is a particular type of horizontal integration which follows the general philosophy that it is a matter of principle to use two different and complementary formalisms (a discrete and a continuous one) for describing and explaining human cognition and which integrates symbolic

and connectionist mechanisms in modeling every cognitive process and therefore it is crucial to ground the hybridization on the micro level" ([282], p. 3).

Kokinov is referring to building hybridization into single unit level workings of an artificial neural network so that bottom up causality will naturally lead to hybridization at the global level. To achieve this, a cognitive architecture consisting of a huge number of small elements (called micro-agents) each of them being hybrid (*i.e.*, consisting of a symbolic and a connectionist part) is proposed. The implication of this cognitive model for the human brain is that hybridization events at the single unit level—the level of the neuron and smaller, the molecular level—filter upwards through the neural network to produce everything from symbolic processing to consciousness.

This idea is not so surprising when we consider that hybridization is built into our molecular structure:

> […] all known life achieves universality (at least in a limited sense) by utilizing the digital sequence structure of informational polymers (*i.e.*, DNA). Such universality would be exceedingly difficult to engineer in an analog-only system given the challenges associated with building reaction networks where each (programmed) reaction is chemically orthogonal to all other reactions. Orthogonality is, by comparison, relatively easy to achieve with digitized switches. Control is therefore much easier to achieve in an analog system with digital switches than in a solely analog system. Taking all of these factors into account, it is clear that analog-only systems are not capable of adaptation in the same way as living systems are ([283], p. 3).

The upshot of this argument is that if AGI is going to move forward into the future, it will have to begin with the premise that all biological life is hybrid at the molecular level, therefore, all AGI machines ultimately must be built from the ground up as hybridized agents. Furthermore, once this approach is adopted at the engineering level, it will lead to better BMIs that offer greater flexibility and control, as human-AGI hybridization becomes an inevitable part of our future.

In order for human-AGI hybridization to succeed, much more work still needs be done on understanding how the complex neural network of the human brain produces the experience of mind. In short, what is required is to decode the entire neural "Connectome" [284]. In the same way that scientists decoded the human genome, the connectome would involve a brute force attack on the problem to decode the wiring diagram of the brain down to the level of the single cell. Ralph Merkle of Xerox PARC proposes that it would be first necessary to slice the brain into ultra-thin sections and then analyze each one by means of an electron microscope to reconstruct the paths of the axons and dendrites that each neuron takes [285]. Another proposed method to help elucidate the complex neural wiring of the brain is Diffusion Tensor Imaging (DTI) [286–288]. The technique allows scientists to non-invasively delineate fiber tracts in the brain with moderate resolution. However, the technique relies heavily on mathematical algorithms to predict the passage of fibers and needs to be correlated with post-mortem tracing studies. Moreover, it cannot define the precise origin and termination of axons and dendrites. Therefore, it can only serve as an adjunct to help understand global connections, not precise neuron-to-neuron local connections. Delineating local axon and dendrite paths also requires the use of mathematical algorithms, however, these can be ultimately confirmed using the eye. Notably, in a recent study using data from such sections, computer simulations have revealed with great detail and accuracy how neurons synapse onto each other [289]. They demonstrated for the first time that the distribution of synapses in the mammalian cortex can, to a large extent, be predicted. The study also found that neurons, far from forming logical connections, grow independent of each other as

much as possible and only form synapses onto each other where they bump into each other locally. This explains the high level of redundancy that the brain is known to possess. Density, position and orientation of dendrites can all be changed without affecting the distribution of synaptic connections. Henry Markram, one of the leaders in the field, has already modeled—almost to the molecular level—10,000 neurons and their 10 million synaptic connections *in silico* [290]. While this is but a fraction of the human brain, it represents the first step to model an entire human brain in a computer. By modeling neuronal assemblies at this unprecedented level of detail, scientists hope to develop tools that one day will lead to further discoveries. Moreover, once these tools are developed, they will lead to an entirely independent revolution: manipulation of the brain using nanotechnology.

Nanotechnology

The Alcor Life Extension Foundation offers to freeze your brain for future reanimation.

Cryonics is based on the anticipation that technologically advanced scientific procedures and nanotechnology will one day be available to revive cryopreserved humans and restore them to good health. With nanotechnology, it is anticipated that cell-sized machines will be developed in the future to repair damage or cure ageing and disease at the cellular level, including any potential damage from the cryopreservation process itself ([291], p. 1).

Most scientists consider this to be an implausible proposition. At the very least, it is unlikely that it will come true in the foreseeable future. Perhaps a more plausible proposition is "radiotelepathy". Theoretical physicist Freeman Dyson first proposed the idea in 1997 [292]. Radiotelepathy first appeared, as far as Dyson could tell, in the 1931 science fiction novel *Last and First Men* by W. Olaf Stapledon—published one year before *Brave New World* by Aldus Huxley. In Stapledon's imaginary history, Martians and humans live side by side in a state of intermittent warfare for thousands of years, until both species are almost destroyed. After a long period of recovery, a new human species emerges. Uniquely, this new species incorporates part of the Martian biology into itself in a process strongly reminiscent of the real-life symbiotic assimilation of bacterial mitochondria into human cells [293], something unimaginably in Stapledon's time, but perfectly reasonably if one assumes all biological life is fundamentally hybrid. Prophetic as Stapledon was, he went even further and gave his new species the ability for "wireless" communication, which became possible after incorporating the Martian "subvital units" into their brains. The result was they could communicate telepathically. In Dyson's scheme, radiotelepathy is an outgrowth of a more fundamental technology called "radioneurology". Radioneurology involves deploying large numbers of microscopic radio transmitters in the brain, making it the successor of current brain scanning technologies such as PET and MRI.

A rough estimate on the available bandwidth indicates that a million transmitters could be monitored through each patch of the brain surface with size equal to the radio wavelength. The factor of a million is the ratio between the radio bandwidth, of the order of hundreds of millions of cycles per second, and the bandwidth of a neuron, of the order of hundreds of cycles ([292], p. 134).

Radioneurology is a passive technology for the high-resolution observation of mental processes. However, once the technology is established, Dyson argues it will naturally extend to active intervention, turning it into radiotelepathy. Dyson goes on to speculate about the ethics of the

technology. Apart from guarantees that the transmitters and receivers can be reliably switched off, the question of its deployment in children raises some thorny questions. Children would grow up with it, never questioning its use. "Only after they are grown up can they look back and decide whether they are lucky pioneers of a new world or unlucky victims of their parents' ambition" ([292], p. 137).

Mind Uploading/Downloading, Embodiment/Disembodiment

Hollywood has had a long love affair with the concept of neural implantation and mind uploading. Not the first, but one that highlighted the dangers of implantation is *The Manchurian Candidate* (1962, remake 2004). Based on the 1959 book by Richard Condon [294], it depicts a scenario in which the son of a prominent US political family is brainwashed into being an unwitting assassin for a Communist conspiracy. Obviously influenced by the Cold War, it nevertheless manages to raise the very real dangers of brainwashing, which today is no lesser a problem than it was in those days. This time on uploading, the theme is shadowed again in the 1983 film *Brainstorm* where a team of scientists invent a BMI that records sensations from a person's brain and converts them to tape so that others can experience them. Inevitably the military get their hands on it. In 1995 *Johnny Mnemonic* explored the theme of uploading further where the main character acts as a "mnemonic courier", allowing him to carry sensitive information undetected between parties. Johnny achieves this through a data storage device implanted in his brain. The 1995 film *Strange Days* also explores a similar theme of memory transferal using a Superconducting Quantum Interference Device (SQUID) which records events directly from the wearer's cerebral cortex and, when played back through a MiniDisc-like device, allows a user to experience the host's memory as if was his or her own. Finally, in 1999, *The Matrix* depicted a future world in which humans are tricked into believing the reality they experience is real, when it in fact they are just unconscious bodies stored in vats for the extraction of heat and electricity. While the energy extraction sub-plot is clearly absurd, the front story of humans enslaved in a virtual reality world parallels Plato's *Allegory of the Cave*: the idea that the world we see is a mere shadow of what truly exists. The question "what is real?" has driven human enquiry since antiquity. Tapping into the brain with technology offers the promise that we might one day draw aside the veil that separates us from what lies beyond. Or does it?

The implementation of the scenarios depicted here is generally considered to be implausible by neuroscientists, and for good reasons. The first is that the brain is not a computer. There is a very real difference between the activating/extracting neuronal firing patterns from local connections (which is essentially the limit of BMIs) and accessing the global network of the brain. Neuroscientists do not know where the "cohesive self" resides in the brain, regardless whether they agree or not that it exists. Thus, "plugging in" to the brain and downloading its contents begs the question: where do you plug in to get what? Since the brain has dedicated areas that perform specific functions, for example the motor cortex, it is conceivable that a BMI could extract motor cortex information. But where do we plug in to extract: "I like the color blue"? Or, "Free-will is possible if you believe that neuronal elements can decouple, then re-couple and engage in top-down causation". The brain at any one time is in a state of flux. Its entire history is not written into one moment. Any attempt to extract abstract information out of the brain will have to contend with its entire learning history.

The second reason is that the brain is embedded. Not only in our bodies and in space and time, but it is constantly bathed in neurological chemicals that influence its behavior. If it were possible to extract the contents of the entire brain, or even just a portion of its contents, how will the extracted data behave in its new environment? The new environment might be a computer, a biosynthetic entity, a swarm of distributed memory agents, another brain—to name a few possibilities. The embedded mind thesis implies that the quality of the data will change once it is transplanted into its new environment. If true, how does this impact the veracity of the data once extracted? Moreover, who will own the data? Is it different from the everyday externalizations of our mind, the things we say and what we write?

The question "what is real?" extends down to the practical level of every day life when we ask, "what is the truth?" Humans not only deceive each other, but themselves. Currently we stand at a threshold: "… all present indicators suggest that brain images will be proffered by more lawyers in more cases in more contexts for more purposes in the future" [295]. Brain scanning has the potential to be used at all levels of the legal process: pre trial, where it can give direction to investigatory leads and determine admissibility of evidence; during trial, where it may influence decisions on guilt or innocence; and post-trial, where it could sway sentencing by providing mitigating or aggravating circumstances. However, visionaries of brain scanning see it going much further than that: they want to use it to determine whether a person is telling a lie or not. One group of researchers recently proclaimed that fMRI could replace traditional lie detectors [296]. Given that traditional lie detectors (*i.e.*, those that rely on physiological responses) are not held in very high esteem by most courts of law [297], it seems inevitable that newer technologies such as brain scanning will eventually replace them. In one such scenario, scanning technology is discretely secreted away behind oak paneling in the courtroom. While the defendant is cross-examined by the prosecution, data is fed into private monitors viewed by specialists, including the jury. Modification to the court proceedings occurs in real-time based on what the defendant's brain reveals. As attractive as such a scenario is, in reality there are numerous and almost impossible hurdles to surmount before such a technology will remotely offer anything like surety. Even though human brains are generally identical, small variations in neurocircuitry can lead to an infinite variety of subtle character differences. The problem is further compounded by more practical problems such as the delay in the scanning between commission of crime and arrest. This problem may be solved by having all citizens routinely scanned, something that may one day come about through miniaturization and portability of scanning technology. A deeper problem is the nature of truth in the individual itself. Humans are great compartmentalizers. They are even better self-hypnotists. Criminals can, over a period of time, make themselves believe they are not the same person that committed the crime—believe it so resoundly they may appear to be telling the truth during a scanning test. Brains, after all, can change. Especially memory. Subtle differences such as these between individual brains could lead to results that look suspiciously like lying in normals, even when they are telling the truth. Until such comparative neurofunctional issues are resolved, the use of brain scans to separate liars from truth-tellers will be more of an idea than actual reality.

The question of reality extends deep into our personal selves. Our perception of reality can be altered by hallucinogenic drugs, but also with experiments that manipulate our sense of embodiment. The rubber hand illusion experiment is one such example [298]. In about 60% of cases, subjects come to believe that a rubber hand has become part of their body. Researchers have extended the experience

to the entire body using virtual reality [299,300], where manipulating perspective, movement and touch leads to "a radical illusion of transfer of body ownership". The importance of embodiment studies on research into concepts of self-agency cannot be overstated. The experience of self-agency is the most intimate, yet the most elusive of all experiences of being in the world. Research into concepts of self, far from being an abstract pursuit, have deep implications for human behavior and perception of reality. In one set of experiments, researchers investigated how subliminally primed thoughts of an agent prior to action can affect attributions of authorship to that action. They found that the feeling of authorship decreased when people were subliminally primed with the word "God", a supernatural agent who could perform the target action. However, this was only the case for people who believed in God. For non-believers their feeling of authorship remained intact [301]. In a further study, it was found that for the perception of apparent mental causation to feel real, the thought should be consistent with the action, occur just before the action, and not be accompanied by other potential causes [302]. Thus, people can experience will for an action that was never performed, merely by having prior thoughts consistent with the action. What these experiments demonstrate is that even if it were possible to extract the contents of someone's mind, those contents will suffer the same problems of veracity that are inherent in normal everyday speaking and writing.

Conclusions

In the introduction we posed the question what would happen if we changed the brain, what impact would it have on ordinary life? Small and Greenfield have argued that computers and mobile technologies are already changing the brain. In support of this, they draw on what is now common knowledge: stone tools, fire, hunting, animal domestication, and many other technologies and practices all contributed to altering our bodies and brains. Cooking food appears to have caused a reduction in gastrointestinal tract, tooth size, "masticatory skeleton", and "the muscles and size of the stomach and the intestines" ([87], p. 748). During the major phase of our evolution, brain size also increased. During the late Pleistocene, brain size in the modern human lineage decreased again. Inside the brain, however, something else was happening. The externalization and manipulation of symbols facilitated greater neural integration leading to further increased hybridization behavior. The relentless drive towards hybridization that we are currently experiencing is revealed by the increases in our symbolic and technological life, therefore, we could speculate that the brain will probably undergo further progression towards integration, and perhaps, specialization, where the parceling out of certain functions to external processors via BMIs could make room for other parts of the brain to perform different functions. How would further neural integration impact the brain and our social life? It would appear that, on the one hand, mobile technologies, BMIs and other wireless technologies will bring humans closer together. On the other hand, this greater intimacy will have to be balanced against individuals' needs for privacy. Perhaps notions of privacy will change. It may become acceptable to psychologically merge with other human beings. The advent of scanning technology to penetrate our thoughts might cause some people to shrink away, break away from society. Others may embrace it. At the same time, notions of self will inevitably undergo change. As we develop more BMIs and integrate them into our body schemas, our notions of self might expand to include more of the environment. Our sense of self could conceivably smear across vast areas of space and time. As genetic

enhancement of the brain becomes routine, fewer humans will require therapeutic treatments. Performance will be guaranteed. There might be a shift from nootropics to greater use of recreational drugs.

This is the utopian vision. Alternatively, the human brain may be destined for a downfall. The trend of increased psychiatric disorders in the current age may accelerate in the future. However, this seems unlikely. In 2001 The World Health Organization (WHO) estimated the prevalence of mental disorders/brain conditions worldwide to be approximately 13.67% [303]. Individual lifetime prevalence was estimated at around 1 in 4. These are low figures, even counting the financial burden that these figures entail. Most futurecasters fail to take into account the burgeoning mental health industry. Mental health treatments engage a worldwide army of researchers and health professionals. Mental health problems in society not only saps the economy, but also drives it. Moreover, as more knowledge of the brain's workings is unraveled, better treatments will become available, social understanding of mental disorders will increase, and ultimately, genetics will begin to make an impact through screening and DNA repair. The danger, of course, is loss of biological diversity. However, compared to our closest cousins, the great apes, humans are already remarkably genetically homogeneous [304]. Still, increasing our homogeneity might increase the prevalence of mental disorders. But this will become less likely as genetic screening becomes more accessible. And, *in spite* of screening, the human gene pool, like any system, will retain noise. Therefore, it is not so much a question of whether the human brain will disintegrate due to an increase in mental disorders, but what type of new brain can we expect to find in the future—one that may be ordered in ways unimaginable to us, yet be still sufficiently flexible in adapting to the environment, regardless.

Perhaps the most startling possibility of the future human brain is the potential for neurons to be used as neural networks for the control of machines. It is conceivable that an entire human brain could be grown outside the body. Naturally, because the brain requires sensory and other feedback information to function properly, the growing and learning neural network would have to be housed in an exoskeleton and connected to the outside world through a sophisticated BMI. There appears to be no technological barrier to achieving this scenario except the present day problem of biocompatibility of BMI materials. Once housed, the brain would learn to control its exoskeleton until it reaches a level of maturity acceptable to its human handlers. Would this neuroavatar have a self, and could it be accepted into society? Given all we know about the brain, it seems plausible that it would have a self. So long as it has an autobiographical timeline, a value system, and desires, there is no reason to suppose otherwise. However, could it be trusted? A neuroavatar could conceivably go places where no human could go. It might even be able to do things no human could do, such as perform physical feats beyond human capabilities. This might scare some people and engender mistrust. What this hypothetical scenario illustrates is that humans, in essence, are neuroavatars of their own. The distance between the brain and body can be manipulated showing that we are not as securely housed in our bodies as we might like to think. Speculatively, it may imply a certain level of teleological drive at the neuronal level. The brain's remarkable ability to drive hybridization behavior through the current body design has brought it to the point where it is now able to hybridize itself with other mobile architectures, other body designs. Humans would like to say, "we got us here"; however, just like genes might be the silent players behind appearances in terms of our molecular evolution, it might be possible that neurons have a level of independence that drives their own evolution. Alternatively, it could be argued it is "we" who are making the choice to hybridize ourselves with new technologies.

"We" are affording our brains the opportunity to do so. This argument, however, comes into question when we begin to ask, who are we? Are we masters of our own brains?

Conflict of Interest

The author declares no conflict of interest.

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