

BEYOND THERAPY:
NEURAL TISSUE AUGMENTATION
The Science, The Policy, and The Future

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I once read that if the folds in the cerebral cortex were smoothed out it would cover a card table. That seemed quite unbelievable but it did make me wonder just how big the cortex would be if you ironed it out. I thought it might just about cover a family-sized pizza: not bad, but no card-table. I was astonished to realize that nobody seems to know the answer. A quick search yielded the following estimates for the smoothed out dimensions of the cerebral cortex of the human brain.

An article in *Bioscience* in November 1987 by Julie Ann Miller claimed the cortex was a "quarter-meter square." That is napkin-sized, about ten inches by ten inches. *Scientific American* magazine in September 1992 upped the ante considerably with an estimated of 1 1/2 square meters; that's a square of brain forty inches on each side, getting close to the card-table estimate. A psychologist at the University of Toronto figured it would cover the floor of his living room (I haven't seen his living room), but the prize winning estimate so far is from the British magazine *New Scientist's* poster of the brain published in 1993 which claimed that the cerebral cortex, if flattened out, would cover a tennis court. How can there be such disagreement? How can so many experts not know how big the cortex is? I don't know, but I'm on the hunt for an expert who will say the cortex, when fully spread out, will cover a football field. A Canadian football field.

- Jay W. Ingram

I not only use all the brains that I have, but all that I can borrow.

- Woodrow Wilson

Introduction

One of the most interesting and controversial possibilities of this new age of artificially induced neurogenesis and neural grafting is the prospect of Neural Tissue Augmentation, or NTA. NTA differs from cell replacement therapies used with Parkinson's and other disorders because the individual who receives the new brain cells is entirely healthy. Rather than using neurogenesis for curative or therapeutic purposes, NTA is utilized for the enhancement of performance and the modification of specific functions of the brain. Naturally, this is and will continue to be a highly controversial practice, so it is only prudent at this early stage to begin to seriously address the development process and the potential aftermath. It is hardly an overstatement to say that NTA will have far reaching impacts on the social order and even on the definition of being 'human'. This paper seeks to explore a series of fundamental questions beginning with the scientific basis for NTA and ending with an overview of predictions and important societal challenges that may arise.

Overview.

The first section examines the recent developments in the area of neurogenesis, or the growth of new neurons. Long thought not to occur in the primate and human central nervous systems (except in the olfactory bulb), the latest research has demonstrated its presence in the human hippocampus and the primate cortex. We will conduct an overview of these and other studies and relate them to their potential for NTA.

The next section provides an argument and a model for why grafted neural tissue should be able to functionally integrate into areas of the human cortex. Using examples from both normal brain function and recent studies of neural grafts in patients with neurodegenerative diseases, we will explore the promise of adding new neurons to a host brain.

The section following examines the relationship between cortical tissue volume and behavioral performance, suggesting that in some areas increased volume may boost

performance of certain brain functions. This provides much of the rationale behind the belief that NTA may serve as a cognitive enhancement.

The last section in the science portion looks at early targets of NTA, distinguishing between promising areas in the cortex and other areas in the brain that are better off left alone. The use of ‘experienced’ tissue is also briefly examined.

The policy portion begins with a discussion of issues in the development and standardization of NTA, and offers some preliminary predictions about how it may be implemented. The controversy around the use of embryonic and fetal tissue in neural grafting techniques and research is overviewed, followed by a section on neurogenesis and the potential for early implementation of NTA among the elderly.

Next we examine possibilities in the regulation of NTA and public opinion, and briefly look some aspects in the development of psychosurgery and cosmetic surgery and their correlates to issues around NTA implementation.

The last sections examine the potential societal impacts of cognitive enhancement technologies in the education, corporate, government, military and civil sectors.

Recent advances in stem cell research, neural grafting, and neurogenesis in particular are at the heart of the growing optimism around Neural Tissue Augmentation (NTA). New studies are being released on almost a monthly basis it seems, and they are expanding our understanding of how new neurons grow, what chemical signals control their growth, and to what extent they will integrate functionally into a brain. As we gain more insight into the chemical controls that release the potential of stem cells, not only will cell replacement therapies become a standard treatment for millions of people, NTA will also become a reality which policy makers, patients, and philosophers everywhere will have to face. The first step, however, is to understand why stem cells hold so much promise for the future of brain science.

Stem cells are undifferentiated cells that, under appropriate conditions, can give rise to more specialized cells with a variety of specific functions in the body. One of the early kinds of stem cells to be discovered was the Haematopoietic Stem Cell (HSC), the precursor to cells in the circulatory system, including white and red blood cells. Incredibly, a single HSC from a mouse can regenerate the complete circulatory system of the animal. (Osawa, et al., 1996) Stem cells are not, however, necessarily restricted to the development of one or a few particular types of tissues. They can broadly be divided into totipotent, pluripotent and multipotent classes, signifying the potential of the cell for differentiation. Like the fertilized egg, totipotent cells are able to develop into all the tissues that eventually make up the animal. Pluripotent stem cells, while able to generate most of the tissues of the body, are not able to produce certain tissues like the placenta necessary to the life of a developing fetus, and are therefore not considered to have total potential. (NIH, *Stem Cells...*) The multipotent stem cells, like the HSC described above, are able to produce an even more restricted set of cells for a particular system, like those that make up skin tissues, or cells and tissue in the circulatory system. This distinction is important, as multipotent stem cells are more readily accessible for cell replacement therapies, but do not have the flexibility of pluripotent cells. One of the central challenges in stem cell research today is to discover methods of

turning certain multipotent cells into pluripotent cells, especially those that, like CNS stem cells, are not easily available.

Stem cells do not only exist in the developing organism. Many of the tissues in an adult also have stem cells, regenerating blood cells, muscle cells and even central nervous system (CNS) cells. While there is much that could be written about this currently very popular topic, we will restrict our overview to examining the difference between embryonic and adult stem cells, and then from this background address some of the most exciting new discoveries in the growth of new neurons, or neurogenesis.

Embryonic Stem Cells.

Pluripotent stem cells derived from the embryo are appropriately known as embryonic stem (ES) cells, and, producing some degree of controversy, are generally taken from the extra embryos generated in fertility clinics or from the fetal tissue of terminated pregnancies. (McKay, 2000) They can be extracted and grown in the lab, creating a variety of different possible cell types. While it is illegal to grow a complete human from ES cells, the potential medical benefits of growing tissues are tremendous, and include the production of new neurons and other CNS cells. One important difference between ES cells and adult or somatic stem cells is the ability of ES cells to be “immortalized”, or differentiated indefinitely in a culture. Long-term differentiation potential is a key ingredient for cell replacement therapies, where significant numbers of cells are required to meet clinical needs. Immortalization is currently not possible with somatic stem cells, limiting their realistic use for the widespread production of certain medical treatments. It is now possible, however, to use Somatic Cell Nuclear Transfer (SCNT) to produce totipotent and subsequently pluripotent cells from an egg and a somatic cell, bypassing the need for using fertilization-derived embryos. In this procedure the nucleus of an egg is removed, and the somatic cell is fused with it to produce a totipotent cell. Once the totipotent cell develops into a blastocyte, pluripotent cells can then be removed for use in cultures.

Adult or Somatic Stem Cells.

Somatic stem cells are present in many tissues in the adult body. They are responsible for the regeneration of blood cells, muscle tissue and even CNS cells. While naturally multipotent, these stem cells can under the right cues and conditions develop into other cell types, much like pluripotent cells. This has not yet been accomplished in humans, but mouse CNS stem cells have been differentiated into muscle, blood, heart, liver and intestinal tissues. (Bjornson, 1997) Somatic stem cells and their potential are important due to the currently controversial source of ES cells and other stem cells necessary for research and cell replacement therapies. Cell replacement therapies like those used in brain disorders like Parkinson's have necessitated stem cells from a fetal brain or from removing a portion of the brain from epileptics. (NIH, *Stem Cells...*) These sources have the disadvantage of being either controversial or extremely limited in number. Scientists are now able to use mouse CNS stem cells to differentiate into dopamine producing neurons for use with humans, but these stem cells quickly lose their ability to renew cells, effectively limiting their widespread clinical use. (Studer, 1998) If human somatic cells could be differentiated into a variety of tissues like pluripotent cells, then significant clinical obstacles would be overcome, as more easily obtainable somatic cell types could be differentiated into CNS cells. While human CNS stem cells have been found in the olfactory bulb and, more recently, in the hippocampus, they are not accessible in enough quantity to allow for cell replacement therapies from these sources. The discovery of CNS stem cells, however, and the fact that the brain accepts new neurons has very exciting implications for the future of CNS repair and augmentation, especially as we learn more about the chemical cues that make human multipotent SC's act like ES cells.

Neurogenesis in the Adult Human.

Neurogenesis has been observed and researched extensively in non-primate mammals, especially the canary, zebra finches, and the rat. (Nottebohm, 1999) It had been thought, however, that neurogenesis was not present in the primate CNS. A series of recent studies have overturned this long-held notion that the human CNS, with the exception of the olfactory bulb, does not generate new neurons. In the November 1998 issue of *Nature Medicine*, Fred Gage of the Salk Institute for Biological Studies in La Jolla, CA and Peter Eriksson of the Sahlgrenska University

Hospital in Goteborg, Sweden published a study entitled, “Neurogenesis in the Adult Human Hippocampus”. This bombshell showed that in a normal human hippocampus, 500 to 1000 new brain cells were grown *every day*. (Eriksson, et al., 1998) The researchers injected human subjects with BrdU, which is incorporated into DNA during cell division and passed on to daughter cells. (Eriksson, et al., 1998) Because the BrdU is only incorporated into dividing cells, any cells that contain the chemical must have been formed after the injection. The researchers then used immunofluorescent labeling to mark the BrdU and neuronal proteins like Neuron Specific Enolase (NSE) to verify that the cells were indeed neurons. (Eriksson, et al., 1998)

Due to the location of the neurogenesis, it is assumed that the new neurons play a role in creating and storing memories and other learning associated tasks. Gage conducted studies with mice where different sets of mice were given more or less stimulating environments. The mice with more stimulating environments were found to have grown more neurons in the hippocampal region, supporting the hypothesis that new neurons are tied to learning tasks. (Gage, et al., 1999)

In an even more recent and equally exciting development, Elizabeth Gould and Charles Gross of Princeton’s Department of Psychology have found that substantial neurogenesis occurs in the adult monkey cortex. Due to significant similarities between primate and human brains, this study strongly suggests that the same may be true of humans. Gould and Gross replicated much of the technique used in the Gage and Eriksson experiment, using BrdU to label new brain cells in the Rhesus monkey neocortex. (Gould, et al., 1999) They then used fluorescent retrograde labeling to follow the axons of the new neurons, and found that they originated in the subventricular zone (SVZ), a finding in concert with other research on CNS stem cells. New neurons were found in the prefrontal region, the inferior temporal region, and the posterior parietal region. (Gould, et al., 1999) All these areas are responsible for higher level cognitive processing. Significantly, no new neurons were found in the striate cortex, a lower level processing area for vision. (Gould, et al., 1999)

The existence of potentially widespread neurogenesis in the human brain has a number of implications for neural tissue augmentation (NTA). The most obvious insight is that the brain produces new neurons during normal function and integrates them into its existing morphology, something formerly thought not to happen. Many of the difficulties of neural grafting or transplants are immediately avoided if targeted and controlled growth can be regulated from within a brain. The chemical cues that guide differentiation and growth are the subject of numerous studies around the world, and it will be a matter of time before scientists are able to manipulate the genetic expression of cells and their chemical signals to stimulate neurogenesis and NTA in regions of the brain that are not the normal targets of new neuron growth. The signals could also be used to expand growth in currently targeted areas, or in areas where disease, trauma, or age have impaired functioning.

The second major implication of widespread neurogenesis is that the brain is able to functionally integrate new neurons into certain existing morphological units. Few would dispute that we are unable and will remain unable in the near future to ‘program’ the brain, and so this self-organizing characteristic is vital to the prospect and progress of NTA. NTA will most likely be pioneered with the use of targeted neural grafts, following on the heels of successful CNS cell replacement therapies for neurodegenerative diseases. In a recent victory indicative of what is to come, scientists at Harvard University’s McLean Hospital successfully transplanted neural tissue into the brains of patients with Huntington’s disease (HD), a fatal and incurable neurodegenerative disorder that primarily affects the striatum of the basal ganglia. Thomas B. Freeman, Francesca Cicchetti, and colleagues grafted fetal striatum tissue into the basal ganglia of patients. Not only did the new neurons survive, six of the patients exhibited a 20% improvement over the course of a year, when a 15-20% decline is usually observed. (Freeman, et al., 2000) The tissue of the graft was successfully integrated into the striatum of the patients, and no evidence was found that the HD penetrated the new tissue. (Freeman, et al., 2000) Prior to these studies it was assumed by many that the grafts would soon exhibit the degeneracy of the surrounding tissue in the form of aggregations of mutated huntingtin proteins. The new tissue lacked the genes that coded for this mutated

protein, and were therefore seemingly able to replace the HD infected striatum cells. (Freeman, et al., 2000) In a patient who died of a heart attack 18 months after the treatment, the neural graft also exhibited no immune rejection from the host brain, helping to answer additional doubts about the transplantation process. (Freeman, et al., 2000) Shortly after the release of the American study, the study was confirmed by researchers in France, who found that after two years, three out of five HD patients implanted with neural grafts showed significant improvement. (Bachoud-Levi, et al., 2000)

As one of the researchers from McLean commented, the use of fetal cells is both controversial and unrealistic for widespread clinical purposes. The future of the cell therapies depends on the use of stem cell lines that can produce the needed tissue without having to utilize fetal or other problematic sources in great quantity. It is likely that these techniques will be feasible in the near future, opening the door to extensive use of CNS cell therapies, and therefore also laying the foundation for neural tissue augmentation in healthy brains. NTA may even prove easier than working with a brain region that is undergoing degenerative disease, as the possibility of the disease spreading to surrounding areas or invading the grafts is not present.

In addition to neural grafts, the possibilities of triggering and chemically controlling neurogenesis in order to produce NTA are becoming increasingly promising. Neurogenesis derived NTA would avoid the problems of rejection, perhaps better ensure functional integration, and be less traumatic to the brain than invasive surgery, possibly opening up the likelihood for NTA in brain regions where grafting is not the ideal option. In the end, the ‘internal’ approach is likely to be preferred for these reasons. One of the studies that has helped suggest the potential of neurogenesis-derived NTA is the work of Jeffery Macklis and colleagues at Harvard Medical School. Macklis induced apoptosis, or cell death, in a population of neurons in layer IV of the anterior cortex of rats, an area that is not the normal target of neurogenesis in a mammalian brain. Using BrdU as a marker, the researchers observed significant neurogenesis in the damaged area, though there was no evidence that any integration or functional recovery occurred. Retrograde

labeling was also used to verify that the neurons successfully created long distance corticothalamic connections. (Macklis, et al., 2000) While the means to achieving the neurogenesis are clearly not viable for human or medical use, the study raises hopes that the chemical cues for neurogenesis may be uncovered, allowing for use of drug or other non-destructive catalysts. Clearly this general approach will figure largely into the future development of NTA.

Yet another recent discovery that may hold promise for NTA manipulates the levels of certain growth factors during development. Vaccarino and colleagues have found that fibroblast growth factor 2 (FGF2) is expressed during early neurogenesis in mammalian embryos. A microinjection of FGF2 was delivered into the ventricles of a rat embryo during early development, ultimately increasing the volume of the adult cerebral cortex by 18% and the total number of cortical neurons by 87%. An injection of the same growth factor slightly later in development was found to increase the number of glia. Using BrdU as a marker for cell division, the researchers found that FGF2 seemed to increase the proportion of dividing cells. (Vaccarino, et al., 1999) The author is not aware of any studies that have tested the intelligence of the rats. If applicable to primates and humans, this technique may resolve a number of technical obstacles relating to the invasive nature of surgery, the degree of integration possible in mature individuals, and the sheer breadth of NTA possible across the cortex. It also has benefits in that the procedure does not seem to adversely effect the 'lower' brain, where alteration of function is perhaps not as beneficial as in cortical areas due to the homeostatic nature of some of the regions. However, ethical issues arise due to the lack of the possible consent of the child, foreshadowing an inevitably sticky public policy question that may stall the use of this technique well beyond the use of other techniques in adults. That said, politics and public policy will be likely obstacles to the advancement of many areas of NTA, and it is difficult to predict what the direction of public opinion may be in the coming decades. These and other policy questions will be addressed in the latter half of this paper.

The Functional Integration of New Neurons

Dr. William Landau of Washington University in St. Louis was quoted in 1992 as saying:

The likelihood that [neural] tissue will make a functional connection with the way other cells work is improbable. The circuitry of the brain is complex. It's not like putting a piece of liver into another liver. There are different types of tissue in the brain. I can't conceive of how infantile brain cells stuck in an adult brain will make proper connections. (Fumento, 1992)

Studies like those cited above, however, have shown the progress in the field, and seem to strongly suggest that new neural tissue can be integrated successfully into the functioning of a developing or mature mammalian brain, through use of either grafts or neurogenesis. From this point it is theoretically a small leap to NTA, though of course NTA may present a host of unique variables that will effect the outcome of the pioneer efforts. It would seem reasonable to assume the subjects' brains in the above studies were able to 'reprogram' the new neural tissue to function with the existing anatomy. Despite the studies the issue still remains in some contention.

The question arises as to whether this is something that may be restricted to the situation of replacing degenerated areas, or perhaps only areas in certain parts of the brain, or whether this 'reprogramming' and integration is a case of a more widespread characteristic of neural processes. Regarding the latter possibility, there are models of brain function that suggest that functional integration of new neural tissue may be an unsurprising event. We will now use one of those models to examine the question of why and how this integration may be taking place, and why we should expect that it might occur in NTA in addition to its demonstration in curative therapies.

One of the most comprehensive of these models derives from the work of Nobel Laureate Gerald M. Edelman and the Neurosciences Institute, and has been called Neuronal Group Selection theory, or NGS theory. At the heart of the theory is

the hypothesis that the brain operates as a selectional process, using homeostatic guides and other value systems to select upon a diversity of behaviors and internal experiences or states represented in functional neuronal groups. The value systems are embodied in what has been called the diffusely projecting modulatory system and other structures like the hypothalamus and pituitary gland that help serve homeostatic functions. (Bear, 1996) The modulatory system is composed of brain areas like the locus coeruleus and the dopaminergic systems that project diffusely to many areas of the brain, and release neurotransmitters that, among other functions, modulate the strengthening or weakening of the synaptic connection patterns associated with the adaptive value of a particular behavior or internal state. (Bear, 1996) These areas are thought to play a key role in the reinforcement of pleasurable behaviors that fulfill an organism's needs and in the aversion associated with painful, unpleasant, or maladaptive behaviors, along with other structures like the amygdala. (Hamann, 1999; Bear, 1996) The strengthening and weakening of synaptic connection patterns has also been demonstrated to be dependent on neural activity and the coincidence or degree of synchronization of that activity. A significant and growing body of research has supported this model of Long-Term Potentiation (LTP) and Long-Term Depression (LTD). The basic observation of the LTP/LTD model is that the strength of a synaptic connection, and the strength of a pattern of synaptic connections, is dependent on the activity of the synapse or synapses, with more excitation leading to stronger connections. Synchronized inputs will also strengthen connections, while de-correlated activity may weaken overall connectivity. (Bear, 1996) There is also evidence that a small amount of activity leads to a greater weakening in synaptic connectivity than no activity at all. (Rittenhouse, et al., 1999) LTP and LTD tend to lead to the creation of functional neuronal groups, where a population of neurons becomes strongly connected through the coincident activation associated with a unitary aspect of behavior or experience. (Edelman and Tononi, 2000) The differential amplification of adaptive neuronal groups occurs through the strengthening of synaptic connection patterns, both in activity dependent and in neuromodulator-induced strengthening. (Edelman and Tononi, 2000)

In summary, one of the basic tenets of NGS model is that functional wiring of much of the brain occurs in the absence of explicit programming. Instead, adaptive neuronal groups and coordinated functionality between those groups are ‘differentially amplified’ and retained through the selective strengthening by the value system and LTP/LTD of the connectivity within and between the active neuronal groups during behaviors. Adaptive behaviors and neuronal groups are therefore in large part selected, not programmed, which means the brain has the capacity to wire itself without instruction. This self-wiring characteristic is the basis for the functional integration of new neural tissue into existing brain morphology. We will now examine this self-wiring process in more detail as we seek to understand why this functional integration should occur.

Developmental Selection.

Formation of neuroanatomy is constrained and guided broadly by genetic expression and chemoaffinity, but at the finer levels of synaptic connection there is tremendous diversity that is not programmed or directed by genetics. On the contrary, the state of diversity is the foundation for activity-dependent neuronal selection, where neurons that fire together tend to wire together, leading to the formation of specialized, functional neuronal groupings as observed in sensory and motor maps. (Edelman, 1989) An example of the selectional process is the topobiological organization of sensory maps, where nearby locations of sensory input on the finger, for instance, are also nearby in the neural pathways that carry their input and in the structures that process the input. (Edelman and Tononi, 2000) The activity dependent wiring present in many developmental processes has been shown through the injection of tetrodotoxin (TTX) which eliminates action potentials. After the action potentials were eliminated in an area of the brain, aspects of normal developmental wiring like the segregation of inputs ceased to occur. (Bear, 1996) In the fetus, where much of this early stage may take place, external stimuli are replaced by internally generated “waves” of activity, as observed in the research of Carla Shatz at Stanford. In the retina of a mammal, Shatz and her colleagues recorded asynchronous waves of activity that traveled across ganglion cells in the retina, stimulating ganglion cells adjacent to each other while being de-correlated with the other eye. The adjacent activation

pattern strengthened ascending pathways such that higher level representations of the visual field preserved the topographic layout of the retina. The de-correlated activity between the eyes in Shatz's studies selectively strengthened synchronized inputs while weakening the desynchronized inputs from opposite eyes, producing segregation of inputs. (Bear, 1996) This process has also been described as Hebbian modifications. A similar stimulation-dependent process has been shown by Hubel and Wiesel to take place during the development of the ocular dominance columns in cats during the critical period. (Hubel and Wiesel, 1970) Still further evidence has been observed in the development of binocular receptive fields, where temporally correlated input from vision is necessary for the fields to emerge. The synchronized sampling of a single object of vision provides the correlated inputs that will strengthen those synaptic connection patterns that represent a shared area of the field of vision. When monocular deprivation occurs, two predictable events result. The ocular dominance columns for the open eye are represented in more tissue than those for the closed eye, and the binocular receptive fields fail to functionally develop. (Hubel and Wiesel, 1965)

The basis for all these developmental processes is vitally different from the 'programmed' wiring that may put into place the more generalized morphology of the brain. Whereas development through genetic expression is an information-driven process, in that 'instructions' for patterns of cell extension, migration, and death are 'read' and executed, the process of developmental selection requires no such pre-determined information or instructions. Behavior and the value system's modulatory influence select upon the extreme and messy diversity of synaptic connection patterns in the immature brain. Many functional neural groups and pathways arise as they are selected upon, as in the case of the segregation of inputs cited above, and are therefore dependent on the organism's experience, environment, unique history, and value system inputs to produce their adaptive characteristics. This self-organizing capacity of the brain that can occur in the absence of prior knowledge of the minutiae of its own organization and the environment bodes well for the future potential of integrating new neural tissue into a developing brain, or even, as we shall see, into a mature brain.

Experiential Selection in a Mature Brain.

Neuronal Group Selection Theory posits that selectional processes occur not only in the developing brain, but also play a major role in the normal functioning of the mature brain. The underlying mechanism of activity-dependent and neuromodulator-dependent synaptic strengthening and weakening remains the same into maturity, though the constraints on plasticity are significantly increased. Hubel and Wiesel and many others have shown the presence of a very well defined critical period for most developmental processes. Despite this period, substantial re-mapping and rearrangement of the boundaries of functional neural groups or pathways occurs in the cortex of mature mammals. The stability of cortical maps may in fact reflect a dynamic balance in competition between neural groups and inputs rather than a structure defined and left in place through genetics or development. As we might expect if this were true, reorganization of cortical receptive fields and modular units occurs when there is a significant alteration in inputs or activity associated with an area of cortex. When a sensory input source is damaged, or the target of a projection is lost, apoptosis or synaptic weakening will often result in surrounding neural tissue that innervated those areas. (Sanes, 2000) Formerly weak connection patterns from adjacent receptive fields will then become strengthened, eventually exhibiting a stronger representation in that area of cortex. Merzenich and Kaas have observed this process following the severing of the median nerve of the right hand of monkeys. The nerve normally innervates the palm or glabrous side of the hand. Shortly after the surgery, the cortex that is usually responsive to that nerve became unreceptive to cutaneous stimulation in most of the monkeys, and almost immediately became responsive to the dorsal surface of the hand. (Merzenich and Kaas, 1982) Over the next weeks, these areas of cortex became further enlarged to represent more of the dorsal surface, while adjacent cortical areas expanded their receptive fields into the now defunct glabrous cortical field. (Merzenich and Kaas, 1982) Evidence for receptive field rearrangement has even been observed in the peripheral nerve areas following damage to sensory inputs. (Darian-Smith, 2000) Studies have also shown that stroke victims have the ability to more than double the size of the map of a degenerated cortical area following training. (Liepert, 2000) These and other studies have demonstrated that even in a mature

brain there is the capacity for functional self-organization and re-wiring in the absence of explicit instruction. This capacity seems to extend not only to the amplification of neuronal groups relative to competing units in the same tissue area, but also to tissue areas developing entirely new functionality, as seen in the Merzenich and Kaas studies. The parallels to NTA are strong, as new neural tissues would also face the obstacle of relatively wholesale functional re-wiring and integration in the absence of programming from either genetic or external human sources. From these studies we can be cautiously optimistic about the likelihood that new tissue can be functionally integrated into the existing morphology of a healthy brain.

Evolutionary Overview.

The evolutionary record indicates that humans and chimpanzees began to diverge around 5 million years ago, with human brains eventually growing to be about five times larger than our nearest existing primate cousins, a dramatic increase in tissue volume seen mostly in the cortex. Contemporary humans have a cranial capacity averaging 1300 cm³, with a range of 1000 cm³ to nearly 2000 cm³. (Kolb and Wishaw, 1990) While the organization of neurons is surely more important than the size alone, it is instructive to note the growth in cranial size from the australopithecine brain which averaged 500 cm³ to the Homo Erectus which averaged just over 1000 cm³. (Kolb and Wishaw, 1990) A number of studies have shown that this increase in size is not due to an increase in body size. (Jerison, 1975; McHenry, 1982) Jerison developed the Encephalization Quotient (EQ) to relate brain size to expected brain size based on body mass, with 1 being the average for mammals. Chimpanzees have a 2.48, dolphins a 6, and humans a 6.30. Stephan has found that most of the increase in high EQ animals is found in the neocortex. (Stephen, et al., 1970) He created the Progression Index (PI) to compare the actual neocortex to expected neocortex of a mammal. The PI shows the human neocortex around 3.2 times greater than that expected for non-primates and around three times greater than for a chimpanzee of the same size. (Stephen, et al., 1970) Within the neocortex, Passingham found that the greatest increase is in the associational areas, not the motor or sensory regions, which are actually slightly smaller than expected. (Passingham, 1982)

It is not unreasonable to hypothesize that many of the advanced functions of the human brain required an amplification of previously specialized regions, together allowing for the complexities of tool use, symbolic associations, and thought that have characterized our species. This observation is not restricted to our species, as the most intelligent and social of the mammals have seen similar increases in EQ, including, of course, chimpanzees, but also dolphins. While sheer size is no doubt crucial to the complexity of functions in more advanced brains, clearly the particular organization of the brain is paramount as well. In the next section, we

will examine the body of evidence linking neural tissue volume to performance in brain functions, in addition to proposing a theory as to why regional tissue volume is such an important constraint on performance.

A Theory of Neural Tissue Volume and Performance.

The relationship between performance and neural tissue volume is easily observed on a number of levels, but is perhaps most apparent in the primary sensory and motor cortexes. Degree of motor control and two point discrimination are performance measures that clearly exhibit a greater representation in the cortex based on degree of control and acuity rather than muscle size or skin surface area. This relationship is observed in the somatic and motor maps that have been assembled by Penfield, Woolsey, and others, where ‘important’ body parts enjoy increased cortical representation relative to their size and inputs, and concomitantly display increased control or discrimination. It would also appear, as discussed in the prior section, that modular units or neuronal groups show competitive characteristics. In the case of cortical sensory maps for example, a digit will have a primary cortical receptive field with strong synaptic connections due to long-term temporally correlated inputs. The boundaries of the receptive field will be limited by competing functional groups that also have strengthened synaptic connections because of their highly correlated input patterns. The boundaries are not likely to merge on this level due to the de-correlation of inputs, (but if two digits are taped together, we would likely see a fusing of the fields). (Sanes, 2000) The question naturally arises: for what are the functional groups ‘competing’, and how does the constraining factor relate tissue volume to performance?

A given area of cortical tissue contains a variety of representations of aspects of behavior or experience that are embedded in the synaptic connection patterns of neuronal groups, which in turn differ in their internal connection strengths and in the strength of their association with other cortical areas. Because multiple patterns of synaptic activation exist in a single area of cortex, multiple representations or cortical states exist in the same area as well, and may co-exist by cycling through the possible patterns of activation.

The existence of cycling cortical states has been observed with the Optical Imaging technology developed by Amiram Grinvald at the Weizmann Institute of Science in Israel. (Tsodyks, et al., 1999) Neurons in Area 17/18 of the visual cortex of the cat are selective for oriented lines. Voltage sensitive dyes that were applied to a small patch of this cortical area revealed that a pattern of neural activity was consistently evoked by a vertical grating stimulus, revealing a functional map of activation (on the order of 2mm). Interestingly, this same functional map appeared in a cyclical fashion even absent the appropriate stimuli, strongly suggesting that the tissue area cycles through multiple but stable cortical states, or, if cycling is absent, that a set repertoire of stable cortical states exists in a given tissue area. (Tsodyks, et al., 1999) The stimulus-invoked activation of a particular functional map or cortical state therefore occurs when non-local neural activity (originally from external stimuli or other internal sources) evokes the particular cortical state due to historically strengthened associations (see LTP/LTD model and modulatory model). This suggests that the brain interprets and processes behavior and experience not so much through the generation of new circuits and neuronal groups, but through the activation of *pre-existing* components of behavior and experience as embodied in the tremendous diversity of cortical states in different tissue areas. (Edelman and Tononi, 2000) These pre-existing components, perhaps wired in neuronal groups, form a repertoire or ‘vocabulary’ for behavior and experience, whose ‘grammar’ is provided by historically and adaptively strengthened connection patterns between functionally associated neuronal groups (see *reentry* defined below). It is this greater or lesser diversity of cortical states or ‘vocabulary’ that is directly constrained by the tissue volume dedicated to a particular brain task. For these reasons, we can hypothesize that the relationship between the population of cortical states and neural tissue volume forms much of the basis for the link between tissue volume and the performance of a given brain function, as the performance of that brain function may depend in large part on the ‘vocabulary’ available for recruitment.[†]

[†] This may suggest that neurogenesis is the site of creation for entirely new components of behavior or experience, or entirely new associations between existing neuronal groups. This hypothesis is resonant with studies that have found primate neurogenesis in the hippocampus and in the higher associational

If much of cortical tissue does contain pre-wired neuronal groups, then questions arise as to why there is not expression of those states when they are activated in a cycle or during the spontaneous reverberation necessary to keep them stable. NGS theory proposes the existence of a ‘dynamic core’, or a unitary but constantly changing pattern of strongly connected neuronal groups that are active at any one time. (Edelman and Tononi, 2000) The neuronal groups active in the dynamic core at any point in time are incorporated due to the historically strengthened connectivity with other contemporaneously active groups, and are therefore ‘bound together’ because of a functional association in the organism’s past. ‘Reentry’, defined as the bi-directional statistical dependence of activity in one neural area based on the activity in another strongly connected area, binds together the various components of behavior and experience as embodied in the active neuronal groups or cortical states. (Edelman, 1989) Functional and coordinated behavior naturally arises due to the activity-dependent and neuromodulator-dependent processes that helped produce the strengthened patterns of connectivity, which were originally, in most cases, coincident in time and progressively active in sequence. The adaptive nature of behaviors depends on the past modulation from the value systems. Therefore, cortical states that become spontaneously active will not become expressed or made aware of until they are ‘bound’ into the dynamic core, creating functional reentry with other nervous system areas. Isolated areas of activation therefore remain just that, isolated. However, the presence of a larger ‘vocabulary’ of behavioral and sensory components that can be integrated into the active dynamic core will enhance performance of complex brain tasks by allowing for increased diversity and resolution within behavioral representations when integration does occur. It is tissue volume, therefore, that constrains the potential ‘vocabulary’ of behavior, and in turn constrains the performance of certain complex brain tasks. We next examine what some of those tasks may be and what the possible effects of NTA may be on those functions.

cortex, but not the primary sensory or motor areas. Gould and colleagues have also found that neurogenesis rates are higher in rats with rich learning environments than those with stimulus-poor ones. (Gould, et al., 1999) The neurogenesis may supply a diversity of connectivity onto which selectional processes more closely akin to those seen in development may occur, leading to the formation of new neuronal groups and pathways rather than merely adjusting the relative strengths of connections within the existing neuroarchitecture.

Early Targets for NTA

The possibilities inherent in NTA are numerous, but difficult to predict at such an early stage in the development of the techniques. However, some predictions can be made based on the successful CNS cell replacement therapies that we have seen so far, on other research related to brain function, and on models like the NGS theory. We will limit these predictions to statements that can be supported by at least some level of accepted research, and leave complete speculation about other matters aside, though of course much of this section will be speculative in nature. Some of the questions that we will endeavor to answer are: What areas of the brain are best suited to early NTA attempts? What types of effects might we see? Is it possible to use ‘experienced’ neural tissue? We will not try to address the ethical concerns inherent in these procedures at this time. The policy section will attempt to deal with those and other questions in the framework of current local and international law and the core policy issues that face the future of NTA.

The Pioneer Efforts.

If the basic neural processes that underlie normal brain function are the means to the successful integration of new neural tissue to an existing brain, then those areas in which dynamic re-wiring and re-organization have been observed are perhaps the most promising for initial NTA efforts. It is also perhaps the case that those brain areas that have heavily relied on explicit genetic instruction for their functional ‘programming’ and/or display a relatively static wiring scheme will not be optimal for NTA and graft integration. Those brain areas that exhibit a higher potential for self-organization through selectional mechanisms may be better suited, and therefore will likely be the first targets of NTA attempts. In addition to concerns about functional integration, genetic determinism in a brain region may also be an indication of the narrowness and specificity of the region’s function and the importance of that function for the organism. The breathing centers in the brain stem are one such example, and are probably better left alone. NTA may initially lend itself towards the enhancement of higher cognitive functions and general aspects of mental performance associated with cortical areas rather than alterations in ‘lower’ and more basic brain regions. These higher cortical areas both display

the dynamism necessary for successful integration and the relationship between tissue volume and performance that makes NTA an effective procedure. It is in these areas that evolution has made the most effort to maximize tissue surface area due to the volume-performance relationship, and where, on the somatic level, dynamic, competitive characteristics between neuronal populations are most clearly observed, as evidenced by the research examined in earlier sections. These regions of promise include the primary, secondary, and other supplemental sensory and motor cortical areas and the regions within the associative cortex. More specifically, regions displaying somatotopic organization and competitive characteristics like in sensory and motor maps, and the highly distributed associative areas may be the most promising. The table below lists potential targets in more detail:

Primary Motor Cortex	Primary Somatic Sensory Cortex	
Visual Cortex	Parietal-Occipital-Temporal Assoc. Cortex	
Auditory Cortex	Pre-frontal Assoc. Cortex	Limbic Assoc. Cortex

The effects likely to be seen by adding neural tissue to the above areas can be deduced from their primary function and from an examination of their competitive characteristics. It is well documented that fine motor learning in a digit, for instance, will rearrange the boundaries of the motor cortex controlling that digit at the expense of near-by regions. This competitive characteristic would seem to suggest that if there was a greater amount of neural tissue than normal in a section of the motor cortex, an enhancement would be observed in the capacity for fine motor skills, in the speed with which learning occurs, and/or the ability to simultaneously develop a larger number of specialized motor skills. Similarly, resolution and sensitivity may be enhanced in sensory cortical areas like the S1, A1, and the visual cortex, as the capacity for more neural processing can be brought to bear on perceptual tasks. In the associational cortical regions, NTA may produce a number of more generalized effects, like enhanced memory, creativity and ‘intelligence’, while targeted NTA could boost the effectiveness of certain functional units within the cortex, such as Wernicke’s area. While the potential

effects of NTA in associational areas are perhaps not as clear cut as potential effects in the sensory and motor maps, NGS theory may suggest that increasing neural tissue will allow for a greater repertoire of cortical states and patterns of reentry, thus, for example, boosting not only memory capacity but also the associational aspects of memory retrieval.

The hippocampal area is an extremely promising region for neurogenesis based NTA, and may be the first area where NTA is likely to be implemented in the general public. This possibility is explored in more detail under the Public Policy section.

One of the interesting possibilities of adding grafting neural tissue to an existing brain is the use of ‘experienced’ tissue. This is tissue that has already been functional at some stage, and may be able to lend some of that functionality to the host’s brain. Unfortunately this does not seem a likely possibility due to the extremely distributed nature of neural function. Cortical tissue areas are functional given their particular connectivity with other areas and the particular and unique history of the brain. This characteristic would seem to rule out the possibility of using ‘experienced’ tissue unless the tissue was highly modular in function.

NTA and Public Policy

The following sections provide a framework in which to examine policy issues that may arise in the development of NTA techniques, and to make predictions about possible societal impacts. There is a danger that a rapid embrace of NTA technology will bring with it a host of serious problems that should be addressed prior to the ‘rush’ for cognitive enhancements. Here we look at what some of those problems may be and, when possible, suggest preventative remedies.

Issues in the Development and Standardization of NTA

Phase One: Laying the Foundation for NTA.

Neural Tissue Augmentation is an issue to which many people react quite strongly, and it is unlikely that even in the event that we were given successful techniques tomorrow there could be a rapid public acceptance of the practice. A quick reflection on the host of public policy dilemmas that are raised by its existence suggests that this resistance and the concomitant slow acceptance process is probably a good thing. An argument can be made that the gradual acceptance of NTA will be based on a foundation of effective and widespread CNS cell replacement strategies for neurodegenerative and other brain disorders. Logically, the curative aspects of adding neural tissue will precede the phase that brings it beyond therapy to the realm of neural enhancement. Many of the public policy questions that are pertinent to the first phase in NTA—that of developing successful CNS cell replacement therapies—therefore revolve around the issues we are already facing nationally and internationally in regard to the sources and uses of stem cells. Currently, most of the controversy that has arisen is linked to abortion issues and the use of embryonic or fetal tissue, despite the presence of a number of other equally if not more compelling ethical and policy questions. While we will not examine all the debates around stem cells and cell replacement therapies, there are a few that will directly impact the future development of NTA. We will examine these issues as they relate to neural grafting, neurogenesis, and developmental approaches.

Neural Grafting.

The most heated and widespread public debate currently centers around tissue sources for neural grafts. As mentioned earlier, much of the transplantation tissue for the treatment of Parkinson's, Huntington's and other neurodegenerative disorders is originally derived from human embryos or fetuses. This tissue has been shown to be the least likely to be rejected by the host's immune system and the most likely to integrate functionally and/or produce therapeutic effects. (Piccini, et al., 1999; Freeman, et al., 2000) However, the embryonic source of the tissue has brought condemnation by the Catholic Church and pro-life groups, leading to bans on government-supported embryonic stem cell research in some countries, and even a complete ban in others. The United States passed a ban on federally-funded pluripotent stem cell research in March of 1988 under pressure from then-President Ronald Reagan, despite a recommendation for the opposite from the Human Fetal Tissue Transplantation Research Panel. Congress challenged the ban in 1992, then reinstated it in 1996, targeting any research in which human "embryos are destroyed, discarded, or knowingly subjected to risk of injury or death." The 1996 ban was only lifted in August of 2000 under the Clinton administration. President-elect George W. Bush has indicated that he is opposed to lifting the ban, and will likely make swift efforts to reinstate it once taking office, possibly through executive order.

The Human Fetal Tissue Transplantation Research Panel originally made the recommendation to allow government-supported pluripotent stem cell research so long as the use of the tissue was supported by the mother and the decision to abort was divorced from its eventual use. These measures and others were an effort to mollify a White House in opposition, and, while unsuccessful at the time, presaged many of the issues and provisions in the most recent guidelines for pluripotent stem cell research, which makes a careful effort to placate all parties. The current NIH guidelines cover the usage of stem cells from human fetuses and extra *in vitro* fertilized human embryos from fertility clinics. Federally funded research can only occur in the derivation of stem cells from human fetuses and subsequent use of

those cells, and in the use of stem cells derived from human embryos. However, privately funded researchers must supply the stem cells from embryos, eliminating any government funding of the actual destruction or harm of a human embryo. No funding therefore goes to the process of deriving stem cells from embryos. Research which derives an embryo from pluripotent stem cells or which derives stem cells from Somatic Cell Nuclear Transfer are banned from federal funding. (NIH, 2000) The conditions are a victory for patients' advocates and researchers, but have unsurprisingly brought criticisms from abortion opponents, who view the embryo clause as fancy legal footwork amounting to federal financing of embryo destruction.

Many of the clauses in the guidelines address the basic policy issues that face the use of embryonic and fetal tissue. The guidelines specifically forbid stem cell or fetal tissue donors from profiting, and go to great pains to separate the decision for abortion or fertility treatment from the potential use of the resulting tissues. Embryos in excess of clinical need must be frozen to ensure a space of time between the decision for treatment and the decision to donate tissues for research purposes. This is to discourage the production of fetal or embryonic tissue for the sake of a loved one who may suffer from a neurodegenerative disorder. The guidelines also explicitly lay out the requirements for informed consent of the donors.

The adoption of the NIH guidelines is indicative of a changing policy trend not only nationally, but also in countries that have traditionally been even more firmly opposed to the use of embryonic and fetal tissue than the US. While France currently has a complete ban on the derivation of stem cells from human embryos, Prime Minister Lionel Jospin's government drafted a bill In November of 2000 that, if it passes, will remove this ban and set up an 18 member panel to examine all related research proposals. Predictably there has been strong opposition from pro-life groups, but the bill is expected to eventually pass. The United Kingdom also until very recently had a ban on deriving stem cells from human embryos from its 1990 Human Fertilization and Embryology Act, though it was legal to import them. In a vote of conscience, the British Parliament decided to lift the ban under strong

pressure from the scientific community and with the positive endorsement of Prime Minister Tony Blair. The trend seems without doubt to be strongly moving in the direction of allowing greater freedom in the use of embryonic and fetal tissue, which bodes well for the future development of cell therapies that may pave the road for NTA.

The reasons for the changing attitudes towards stem cell research come from many sources, but the rising profile of neurodegenerative disorders like Parkinsonism and Alzheimer's are clearly at the heart of the movement. The movement is only likely to grow, at least in America, where the elderly population is projected to increase from 12.2% in 1996 to 20% in the next three decades. By 2030, one in five Americans will be over 65, with the greatest increase occurring in the bracket over 80. (Blank, 1999) As many of these neurodegenerative diseases are and will continue to impact the elderly more than any other population, the legendary political clout of this group will serve to further expand the scope of promising research. CNS cell therapies have shown tremendous promise in these and other related diseases, and yet the use of fetal brain tissue is unrealistic for widespread clinical purposes. The development of immortalized stem cell lines that can produce the tissue in large quantities is central to clinical applications, and scientists and patient advocacy organizations have been making this argument very effectively to elected officials. As the research progresses and clinical treatments become more widespread, a change in the public perception of the derivation of stem cell, its benefits to society, and the effects of CNS cell therapies will inevitably occur in line with the standardization of the practice. It is this change in public perception that will perhaps open the door further to NTA, though it is the belief of the author that neural grafts will not be the first form of NTA in humans. For reasons described next, neurogenesis may be the pioneer technique in the journey to mental enhancement through NTA.

Neurogenesis.

Recent research has uncovered the presence of substantial neurogenesis in the human hippocampus and olfactory bulb, and in the cortex of non-human primates. Scientists are expanding this area every month with breakthroughs, and

have focused on the possible applications of controlling neurogenesis to help fight diseases like Parkinson's and Huntington's. So far, neurogenesis has only been observed to occur naturally in a restricted area of the human brain, and has been artificially stimulated to occur in rats through the destruction of neurons. (Macklis, et al., 2000; Gage, et al., 1998) These studies have raised the hopes that the chemical mechanisms that stimulate and control neurogenesis will be uncovered in the near future, allowing for targeted neuron replacement without the use of transplanted tissue. This option is far less controversial, if at all, as it does not involve the use of human embryonic or fetal tissue. Ultimately, this technique may be the preferred method as it is potentially non-invasive and a 'self-repair' mechanism. Strong arguments can be made that governments concerned with the use of human embryonic tissue for CNS therapies should actively support research in neurogenesis-based approaches as a specific alternative. This would be supported on the one hand by patient advocacy groups, by-passing the pro-life debate altogether, and on the other hand invest in what in the long-term is possibly the more viable strategy for fighting neurodegenerative diseases and even senility. (Cameron, et al., 1999)

The battle against age-related mental performance decline or senile dementia may be the key to the first steps into neural tissue augmentation. The role of hippocampal degeneration in age-related memory decline remains controversial, with much of the most recent research indicating that though a likely factor it is perhaps not the primary cause. (Wickelgren, 1996) Even if that turns out to be true, there is a large body of research linking human hippocampal activity and growth and increased learning, and, in at least one study, increased mammalian hippocampal neurogenesis and memory related activities. (Gould, et al., 1999; McGuire, et al., 2000) There have also been a number of studies that have observed human hippocampal shrinkage following elevated cortisol levels with a concomitant decrease in memory performance. (Cameron and McKay, 1999; Lupien, et al., 1998) While hippocampal shrinkage or neurogenesis reduction may not be the primary cause of senile dementia, boosting neurogenesis levels in the hippocampus through drug delivery may be one the most effective means of compensating in the biological substrate. Stimulating learning and social activity

on the part of the elderly person will continue to play an important role in combating normal age-related mental performance decline in addition to any neurological interventions. The rapidly rising population of elderly in America and their families will provide an ever-increasing demand for therapies like this one, potentially driving them to widespread use. The existence of a nootropic that will boost memory without adverse side effects through the stimulation of the brain's own 'NTA mechanisms' will create a substantial market among the ranks of the healthy, as evidenced by the current demand for such 'smart drugs' even when of highly questionable effectiveness. (Blank, 1999) In this manner, the quest to fight age-related memory decline may serve as the foundation for the first forms of NTA to come into prevalent use.

Embryonic and Developmental Approaches.

One of the possibilities for NTA involves its implementation in the developing brain, where plasticity is significantly increased and global changes can perhaps be more easily effected using drugs or genetic manipulations. The use of fibroblast growth factor 2 (FGF2) to selectively expand the cortex of developing mice suggests chemical approaches that may be successful. Regardless of the scientific possibilities, however, the use of children is the most fraught with ethical problems, in particular the issue of informed consent, which is of course not possible. Until the field of NTA is highly developed and standardized, it seems extremely unlikely that any experimentation will occur with developing brains.

Phase Two: Pioneer Efforts.

The logical step that will follow memory-boosting through manipulating hippocampal neurogenesis rates will be to apply the same drug therapies to other natural sites of CNS neuron growth in the mature brain. If Gould's study of cortical neurogenesis in primates ends up applying to humans, it is quite possible that memory-boosting will be followed by cortical enhancements, effecting associational, linguistic, emotional, conceptual, and memory-related functions of the brain. If neurogenesis is used to create new associations or concepts, or new pathways linking prior areas, then increased levels of this activity could produce the kind of ferocious learning that occurs in children. These possibilities of course are

at this point entirely speculative, so we will not develop them too much further. One of the last obvious avenues of NTA is targeted neural grafts to areas that are not normal sites of neurogenesis. This will necessarily be quite invasive and may be perceived as more ‘artificial’ and questionable in legitimacy for enhancement purposes by the public. It may be the case that by the time public opinion has shifted enough to allow for these kinds of therapies, the use of induced neurogenesis will be refined enough that growth can be fostered in areas across the cortex.

Regulating NTA.

Different techniques to achieve NTA will likely be treated very differently by the public and by regulators. Three categories come to mind that compose different scenarios for regulation of aspects of NTA:

1. Like the current situation with ‘smart drugs’, the less invasive techniques may win popular support because they seem less threatening and lack the obvious physical alteration of the brain that would occur with neural grafting. It may also appear to be more ‘natural’ because the drugs will be targeting already existing mechanisms in the brain. There is the question, however, regarding whether smart drug are currently tolerated largely because their effectiveness is quite limited. Time will tell if the public or regulating bodies react differently to substances that have more profound effects, and possibly trigger associations with illegal psychoactive drugs. These NTA techniques would be unregulated and their practice would be largely controlled in the market with regulations only as the quality of the procedures.
2. The second category is that of illegal psychotropic substances, where public opinion and governments have deemed many of these drugs to be harmful to society to the point where their distributors and users are imprisoned. If the public feels so threatened by certain potentials of NTA, such as the development of a ‘sub-species’ of super-humans within the species for instance, or if governments deem the potential for social stratification and discrimination too great a price to pay, the use of certain

- NTA techniques may be banned. This will predictably drive the practice to the black market, as it will likely be almost impossible to end the demand for NTA, much as is the case with banned psychotropic substances.
3. The third category is one that will perhaps not arise till far into the development of NTA, and that is the active encouragement or even requirement of certain procedures by the government. Once certain practices become extremely standardized, governments may choose to require certain techniques during or prior to the development of young people. This effort may stem from conclusive evidence of solely beneficial effects and/or from the desire to minimize the effects of stratification that will inevitably occur through the selective use of the techniques in the population.

The eventual policies that govern NTA will likely be an amalgam of the three possibilities above, and will of course change with time and the development of the techniques. Many of the issues that policy makers will face in deciding these regulation questions will remain the same, however, and it would be wise for discussion to occur early in the process before aspects of the practice are implemented ahead of the schedule of regulators.

One of issues that will face early research into CNS therapies using neurogenesis (as well as neural grafts) is the problem of informed consent when the very organ with which a patient consents is damaged. While this will not be an issue with NTA in adults, the issue is of central importance in curative applications, especially during the initial phases of experimenting with human subjects and induced neurogenesis. One scenario that illustrates this problem is the use of the technique with a patient with serious enough mental deficits from Alzheimer's that the viability of 'consent' is brought into question. If the therapy that was meant to alleviate the symptoms of the disease goes wrong, in the form of uncontrolled growth or a tumor for instance, and ends up further damaging the brain or even killing the patient, the practice as a whole may be brought under significant fire. Procedural safeguards are vital to ensure the protection of patients who are incapable of rational consent or who may be under pressure due

to institutionalization. The possibilities of institutionalized patients ‘consenting’ under duress for procedures that may have an experimental rather than therapeutic focus are very real, and certainly have precedent in the use of electroshock therapy and lobotomies. (Blank, 1999) Electroconvulsive Treatment (ECT) has suffered serious damage in public opinion due to its widespread, misguided and often abusive use from the 1940’s to the 1960’s. ECT has been shown to be therapeutic in certain serious disorders, and is used today with far stricter guidelines and with anesthesia. Because of its past history, however, many US states have placed restrictions on its usage, leading some observers to charge that patients in dire need of the therapy are denied access due to Hollywoodized misconceptions. (Peterson, 1994)

The widespread practice of frontal lobotomies in the middle of the 20th century had a devastating effect in the practice of psychosurgery for decades after it was finally replaced by drug therapies. (Blank, 1999) There are perhaps a number of possible parallels between NTA and lobotomies in the area of public reaction and opinion. Lobotomies became popular as a quick fix for behavioral problems, rapidly expanding the practice without serious controls or public debate about the treatment, its implementation, and the likely effects it would have in the future. Though NTA is very different from the practice of lobotomies, it is possible that the more invasive varieties may inherit some the public’s and the research establishment’s distrust from the failed policies and tragedy surrounding frontal lobotomies. Hopefully this will have a beneficial effect in slowing down the rate of research and experimentation and increasing levels of public debate about the possible long-term effects of NTA. On the other hand, psychosurgery is making a comeback in the form of very well controlled and targeted lesions to help certain disorders like severe obsessive-compulsive disorder. It remains to be seen how the field and the public relates to these new and more careful techniques, and whether their use may help alter the landscape for NTA as well.

Another related example that can serve as a lesson for the development of NTA is the history cosmetic surgery. The practice began in earnest during and after World War I in order to help badly burned or scarred soldiers return to a

somewhat normal life. (Haiken, 1997) What began as a primarily curative practice quickly moved to the stage of ‘beyond therapy’, where treatments were made available for women who wanted to ‘perfect’ their beauty. Early attempts included the injection of paraffin wax into the body to fill out soft tissue areas, which shortly after its discovery was fairly widely used. Needless to say, the long-term effects proved to be quite damaging, and the early practitioners fell victim to what could be seen as a pattern of quickly embracing and implementing ‘miracle’ procedures due to popular demand, but not conducting inadequate testing. Not only did people become seriously ill from these procedures, the field itself suffered a significant and deserved black eye. (Haiken, 1997)

The historical examples of the frontal lobotomy and cosmetic surgery suggest a possible danger in the development of cognitive enhancement techniques. There will undoubtedly be significant public demand once the procedures have been shown to work, much like the demand now for ‘smart drugs’ and other quasi-effective techniques. Tremendous professional discipline must be undertaken to reign in the rush to market that may occur, in order to allow for a prolonged period of testing and public policy discussion. Ideally, a specific body should be formed to provide oversight to this potentially burgeoning area, a body that does not currently exist in the United States. The same attention that FDA gives to pharmaceuticals should be provided to these and other cognitive enhancement techniques.

Stratification and Discrimination

If the promise of NTA and other cognitive enhancement techniques becomes realized in the next decades, and it is legalized, there will inevitably be serious and far-reaching implications for societal equity and stratification. NTA raises many of the same issues of genetic modification, where questions must be asked long before the practice becomes prevalent. The foremost questions are who will have access? How will those who don't have access be treated differently than those who do by private and public entities? Will a new form of social stratification arise based on the differing biology within the human species, a difference that is pronounced enough to substantially effect performance in learning and on the job, and thus perhaps a difference that is impossible to ignore by educational institutions and employers? We will address each of these issues in turn as we attempt to answer these questions.

Like most technology-intensive procedures, NTA may be accessible first and most widely to those who can afford it. This will have the unfortunate effect of exacerbating the disparities that already exist in education and job opportunities. One could imagine a scenario where memory enhancements are the first and most widely used form of NTA, common perhaps among elite students and those seeking a corporate edge. Government regulators will be forced by interest groups to address concerns over discrimination in hiring, in access to services, equal application of the law, and stratification effects that may occur. Members of the governing and corporate elite have often been given the benefits of a history of assets and access that enables them to take advantage of higher education. The educational status and connections that go along with this process become the primary means of access to the jobs in the public and private sector that form the elite of a society. Legitimacy is by and large granted to this process, despite its essential historical bias for previously favored groups, for a number of reasons, in many countries perhaps chief among them the educational status the individual worked for and earned. If and when NTA becomes a prevalent practice, particularly among 'those who can afford it', a sticky situation develops where educational institutions and employers may begin to prefer 'enhanced'

people over normal people, catapulting NTA users into an elite position, perhaps even an elite among the elites. It is not unreasonable to ask whether the advantage conferred to them through their biological alterations may be viewed differently than the advantages normally conferred through wealth or social status. Not only could the new enhanced elites be viewed as illegitimate—a consequence of surgery and not a work ethic—there may be a genuine fear that a fundamentally different *type* of person will be ruling over the ‘normal’ people. Clearly the potential for discrimination goes both ways in this regard. Either way, NTA could bring about elements of a ‘class’ tension unlike any that we have experienced before. It is the fear of or the consequence of that tension that could be part of the effort to ban the enhancement techniques altogether, a position almost certainly to be represented in the spectrum of competing interest groups.

There also exists, of course, the possibility that NTA will become so prevalent and accessible due to the advancement of technology and popular demand that it will be infused in various degrees throughout much of society in the developed world. If this were the case it may be that NTA becomes another legitimate factor in hiring and educational access just like other unequally distributed advantages that occur in today’s society. Regardless, if NTA is legalized, efforts will likely be made to reduce the effects of discrimination and stratification, much like financial aid and affirmative action currently do in regard to monetary and racial matters. The exact form of this compensation could come in a myriad of different kinds of policy that will depend on the particular way in which NTA develops and is implemented, and so we will not try to address all these variations in this paper. Suffice it to say that these ameliorative attempts may be key to the early acceptance of NTA when the practice remains restricted for the general population. Almost certain to be passed in countries like the United States are explicit provisions that the rights and protections afforded to any citizen will be afforded in an equal manner to both the cognitively enhanced and the non-enhanced, with the possible exception of provisions relating to discrimination in educational access and hiring, where preferential treatment may not be banned given higher performance on standardized assessment measures. Regardless of

the eventual dynamics of these policies, it is bound to be a highly contentious area of legislation and legal rulings.

Societal Sector Impacts

There are a number of characteristics that may arise in the application of NTA strategies in the population. These will have a substantial impact in all sectors of society, from educational institutions to corporations to the organs of governance. Primary among these effects will be stratification, probably beginning with the educational process and leading to prevalence in other sectors. Contemporary society certainly has a number of indicators as to the likelihood of a given individual entering into a privileged institution of higher learning or the ranks of the governing or managing class. NTA and other enhancements will inevitably become one of these indicators in the next decades, though of a different nature in its explicitly biological origin.

Another effect that we are likely to see with prevalent NTA and enhancement techniques is a self-reinforcing competitive dynamic that will propel the field not only in technological advancement but also in demand in the population. Once NTA is utilized, it immediately will create a competitive dynamic in its sector, pushing other individuals to meet or exceed the cognitive enhancements of their competitors, whether it is in education or the business world. The effect may truly be one of a slippery slope, and if regulators confront this issue it will likely have an impact on early policies governing the use of enhancement technologies. After a certain point, however, it will be very difficult to contain the practice in the context of a market system. The following sections explores issues raised by widespread NTA and other enhancements in the education, corporate, government, military and civil sectors.

Education.

Similar to the role the educational process plays today in American society, the educational process will continue to provide a gateway to elite jobs and positions

of influence. The current unequal distribution of assets has led to certain groups traditionally having a higher representation in the most privileged institutions of higher learning, though this is being ameliorated to some extent by financial aid and affirmative action policies. Access to certain institutions of higher learning has become a good indicator of the future patterns of wealth and influence distribution, and this situation may not change in the coming decades. What may definitely change are the indicators of access to the institutions themselves, as NTA and other cognitive enhancements enter into the scene.

There will likely be an early effort to categorize certain of these enhancements as ‘academic steroids’, not to be used and generally frowned upon. Of course, as a cognitive enhancement may be relatively permanent, this is not a position that is tenable for long, especially as the practice becomes more widespread. Realistically, some types of enhancements may never be tolerated, but there is sure to be a class of accepted ones, and these will confer an advantage to those who possess them. The sheer diversity and gradations that will exist of different types of enhancements will make it difficult if not impossible for educational institutions to divide applicants into groups that have similar levels of enhancement. In time, institutions will likely be forced to, or will prefer to, use a standardized assessment measure for all applicants regardless of biology, though of course there may be affirmative action programs like those that exist today. The use of standardized assessment will de facto make cognitive enhancements necessary for access to the most elite universities and schools, and therefore will become a major indicator of access to positions of influence.

In the educational sector we can begin to see the competitive process that will develop, not only between students but also among faculty, if for no other reason than to keep up with their students. This competitive process will drive the technological enhancement demand, much like the demand for external ‘enhancement’ technologies that exist today, like computers, which quickly became standard for many students, and certainly for those who could afford them. This element in the educational sector may portend a rapid standardization and acceptance of enhancement techniques, as a generation of students may be

the future crafters of public opinion and comfort level with these technologies. The eventual movement of elite students to elite jobs will further create a dynamic where those in positions of influence are themselves recipients of cognitive enhancements and therefore will likely have a bias in its favor. These two elements together may create a societal acceptance of the practice with a speed that would seem unthinkable to many today.

Corporate Sector.

The competitive nature of the market system may create strong incentives for corporations to push for the acceptance of cognitive enhancement strategies like NTA, and to push for weak restrictions on hiring practices. In the areas of finance, technology, biotechnology and many other contexts the presence of cognitive enhancements may confer great advantage to both the employee and the employer. This dynamic may in fact alter the labor relations between companies and their most highly skilled labor, as companies begin to invest in the enhancement of key personnel in R&D and other areas. The expense involved in such mutually beneficial procedures will develop a relationship reminiscent of that which existed in Japanese companies in the 70's and 80's, where employee loyalty over the long-term is valued and expected, and, perhaps, even 'required' in certain contractual arrangements. These arrangements may be very attractive to researchers in universities who do not have the resources for the kind of enhancements that corporations could provide, and that would possibly assist them immeasurably in their work. The competitive element arises again, and we might even see this to the extent that some of the best and most cutting edge work will begin to take place in locations that can afford such relationships. The willingness of governments to enter into such agreements remains to be seen, though it is quite possible that corporations will display a greater willingness. It is unlikely that governments will 'invest' to the same degree in personnel without creating strong incentives for loyalty, or such researchers could potentially become lost quickly to competing employers.

The change in labor relations will also exacerbate the disparity that already exists between skilled and unskilled labor. ‘Flexibility’ may remain for the latter, along with other indicators of impoverished working conditions.

Governance.

The possibility of NTA and cognitive enhancements raises a plethora of issues in governance, regulation, and politics. We will examine a subset of these issues, including what political dynamics are likely to develop, what are some key issues in regulation, and what are the possibilities for a more enlightened government.

If, as this paper is predicting, NTA will move from CNS cell replacement therapies, to use among the elderly, to use among students, then we can expect that there will be substantial pressures from within and without of governance structures to legalize and de-regulate aspects of cognitive enhancement. The elderly will certainly constitute a powerful and growing voting bloc for the legalization of techniques to boost age-related brain and mind deterioration, in particular memory functions. The gray area in this approach between curative aspects and enhancement will further lend itself to the pro-NTA position during this crucial early phase. Once enhancement techniques are available on the market, especially for memory enhancement (a seemingly value neutral function), students will become a major source of demand for this technology. Those students who do utilize enhancements can be expected to enter into elite universities, if indeed the enhancements work, and then will begin to form the next generation of societal leaders, some or many of whom will have benefited from this practice. At this point the pro-NTA political pressure will move from an external source among the elderly and patient advocacy groups to a shared reality *within* the power structure. These and other dynamics may well be powerful enough to counter the anti-enhancement groups that will inevitably exist, though it is less clear from what base they will draw. Likely candidates include liberals who are concerned with stratification effects, religious conservatives who identify the practice of NTA and enhancement as somehow in conflict with God’s will or the scripture, and perhaps even a populist movement that opposes it based on selective access and stratification effects. The latter

possibility is especially interesting because it could foreshadow a tension between those in government and management and the greater population.

Regardless of the overall legal state of NTA, the government will of necessity use certain regulatory practices. There may be an early conflict between granting the right of people to reach their fullest potential, whether through character development and normal learning alone or in conjunction with augmentative technologies. The highly personal nature of NTA and other enhancement technologies and their basically positive orientation may make it difficult for the government to create an outright ban. Some have made similar arguments for the legalization of certain psychotropic substances, but it is perhaps the case that the measurable increase in performance associated with successful NTA puts such techniques in an entirely different sphere than psychotropic drug use, which has a weak or non-existent claim to such societally-valued, measurable enhancements. A ban would also be problematic on the side of enforcement, as the demand for such techniques is likely to be tremendous, and the effects are not as clearly societally damaging as those associated with certain drug use. A black market would almost certainly flourish, bringing with it the competitive element as the effects of the enhancement trickle into societal sectors.

The government should provide strict regulations for the development and testing of enhancement techniques, and establish a body for that express purpose. The degree of control that the FDA has over pharmaceuticals is an appropriate standard to use given the potentially long-term and devastating effects of bogus augmentative technologies.

In the distant future, if and when NTA and other cognitive enhancements become standardized, the government will be in a position to require certain procedures at either the genetic level or in the developing child. While such an idea might seem unthinkable to many now, prevalent and successful use of enhancement technologies will almost certainly lead down that path due to concerns for equal opportunity and, possibly, sheer ability to negotiate what will be a world increasingly adapted for 'the enhanced'. The move from regulation over

development and a market-based approach to distribution to required or strongly encouraged enhancement technologies immediately brings serious questions regarding the autonomy of the individual and the degree to which a government may engineer its people. For as long a period as possible, therefore, it may wise to forego any positive requirements for enhancement, especially in regard to children and genetic changes.

One of the most intriguing possibilities of enhancement technologies is not just the alteration of cognitive and intellectual functions, but the augmentation of the ‘spiritual’ and/or objectively rational aspect of human function. Taken to extreme levels, augmented individuals may be more biologically fit to govern due to increased objectivity and compassion, however they may be measured, or they may be preferred by the populace due to the perception of such characteristics. This raises interesting questions about the how the dynamics of democracy may change if this were to come to pass, and if a true ‘philosopher-king’ could and would be believed in and supported by the people, notwithstanding whether it is a superior form of government.

Military Applications.

The US Department of Defense (DoD) has traditionally been a major funder and developer of cutting edge technologies that may have military applications. Millions of dollars of DoD money has been poured into artificial intelligence research, and if these augmentative technologies show promise, it is quite possible that monies will also flow to support this effort. Exactly what role the military will play in the development of enhancement technologies is difficult to predict, but it is clear that they would benefit highly from its uses in both strategy and combat situations, as in the example of brain-machine interface technologies for piloting planes. Competition if nothing else will force the US and other militaries to explore the possibilities of cognitive enhancements.

Civil Society.

The effects of NTA and cognitive enhancement in everyday life are many, and it would be impossible to try to predict them all given the tremendous number of

variables involved. Some of the changes will be observed in the stratification of society, the possible impact this will have in social communication, and even the patterns of reproduction and mate pairing. A number of more whimsical questions also will present themselves, such as what will the dynamics in a family be if different members have different levels of cognitive enhancement. Will some children be favored over others? These are all interesting and real possibilities if NTA becomes a widespread reality. Given the advance of technology and the likely demand, widespread access is an eventuality that is almost bound to happen in time. Though we may not be able to predict the exact effects it may have across society, we can be relatively certain that it will transform the human social order in a manner perhaps not seen since the industrial revolution. Developing technologies are suggesting that NTA will be a reality, and so it is in the best interest of the people and their politicians to begin addressing it as soon as possible, as we hope for as painless as possible a transition into this new world.

Conclusion

Neural tissue augmentation is a single component in technological revolution that will occur in the next decades as computing power explodes, and as new paradigms promise to deliver capabilities that currently seem like science fiction. One of the most powerful of these paradigms is evolutionary computing. This selectional paradigm will develop software and embodied forms of intelligence that use evolutionary processes to design not only their outward morphology, but also internal systems to govern their behavior, much like we govern ours. Part of this effort, in tandem with NTA strategies, will be the development of a neural-digital interface, so that augmentation will not be limited to nervous tissue. The creation of a selectional machine that can interface with the brain like neural tissue and yet can access digitally stored information and routines will usher in a time of unparalleled transformation, not only of society, but of what it is to be human. It can be said without too much overstatement that this technological leap will introduce changes to our humanity on an order that have not been seen for million of years.

And yet the development of technologies that capture our imagination and our deepest hopes threaten to be embraced by us before we have afforded ourselves the time and deliberation to examine the consequences, and to probe the nature of *our* progress in relation to the progress of our technology. However, given the path of history that we have tread, we may very well not come upon the hindsight and intelligence to understand what we have done until far along our journey. Only then may we have sufficiently developed our intelligence, and not through experience alone.