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# The Neuroethics and Feasibility of Genetic Engineering on the Nervous System

*Our project deals with an idea which may seem, on the face of it, frightening to some; the insertion of modified brain cells, microglia, to try and alleviate Alzheimer's disease (AD). Although more similar to a macrophage than a neuron, engineering microglial cells represents both a neuroscientific and a neuroethical challenge, not least because it seems like the stuff of zombie B-movies. In the interests of assessing the feasibility of the project in social terms, we are producing this report dealing with the potential use, and ethics of the use, of genetic engineering (GE) on the nervous system, as well as expounding a little on some of the scientific concepts behind various approaches. We felt that the ethics of the issues raised are best analysed in light of the science behind the various neuroscientific applications of GE, and so we present them together.*

## Medicine and Synthetic Biology

Synthetic biology is a broad and expanding discipline in which biological systems are modified on the genetic level to engineer new structures and functions of benefit to human kind, be that in the realms of industry, or art, or medicine, etc. Genetic engineering (GE) purports to improve our understanding of the mechanism of pathologies, create better diagnostic tools and even open up whole new ranges of methods with which to tackle human diseases, from cancer to neurodegenerative conditions. The later may be achieved via the cheap, efficient production of drugs, particularly gene products which can be administered therapeutically, or even through the insertion of genetically modified organisms (GMOs) or genetically modified host cells (GMCs) into the body, where they can produce proteins in situ and employ complex systems to tackle disease-state targets accurately and effectively. The ability to insert a synthetic genome in a chassis to the site of pathology in the human body could allow for specific drug delivery, synthesis and activation, and following a bottom-up approach help usher in an era of highly personalised medicine.

However, from its conception, the idea of engineering bacteria, let alone human cells, has met with opposition from people of many different beliefs and backgrounds for a variety of reasons, though even those who stalwartly defend GMOs in other arenas may be cautious with about their use in humans, in vivo. Opponents' arguments vary from religious to safety concerns, especially over the malevolent potential of this Promethean technology and the possibility of unintended negative fallout, despite the fact that the use of biotechnology is already common place in medicine. In fiction, for example, GE is often portrayed as a part of some dystopia. The use of GE in medicine is entangled with engrained social values and politics, and therefore necessitates the participation of the extended patient community as well as academic experts and medical practioners in the field. Generally, scientists from all fields view GE more favourably than laymen, and tend to view the issues at hand in a more

teleological fashion as opposed to the deontological outlook more prominent in the public, who express with greater frequency moral, spiritual and cultural unease **(Small 2009)**.

It is important to clarify that we are talking here about intervening with GE technology at the post-natal stage, and that this discussion is not at all about 'designer babies' for any purpose. Specifically, we are interested in assessing the ethics of GMO/GMC insertion and neuro-genetic engineering (NGE). One of the first things we must accept, then, when considering GMO and GMC solutions, is that they will tend to suffer from the same social pitfalls that plague conventional medicine, in that they take responsibility away from the patient. These therapies would promise minimal lifestyle changes in favour of a non-preventative treatment that cures the ailment so those lifestyle choices can endure. Of course, in the case of cancer or AD, for example, there's little (though not nothing) a patient can do to completely avoid its contraction and progression in terms of life style changes. Diseases such as these offer the most germane targets generally, given their public profile. Infamous conditions will tend to be able to demand more controversial treatment, and sway public opinion, purely due to their social profile, perhaps as a case of GE being seen as the lesser evil.

We could talk at great length about the use of GE across the human body, but in the interests of time it is best that we focus upon the insertion of GMOs for medicinal purposes, as this is less explored than general GE concerns in medicine and is directly relevant to our project. The idea of consuming GE 'bugs' is unsettling for many, as it poses risks to the integrity of human genetic systems as well as the possibility that a putative cure could become a new and formidable pathogen of science fictional proportions.

One of the most obvious uses of invasive GMOs in medicine is in cancer treatment. The activity and action of many a drug is constrained by metabolic limitations and drug delivery often suffers from lack of selectivity, which in cancer can lead to the death of non-cancerous cells. The use of bacteria to target cancer cells, given their anaerobic properties and ability to migrate through the body, is already an active area of research **(Che-Hsin Lee 2011)**. Anaerobic bacteria grow and multiply in the vicinity of cancer cells, because they provide a low oxygen environment. Cell death may be induced by bacterial accumulation **(Che-Hsin Lee 2011)**, but the 'hunter-seeker' ability of bacterial tumour killers could be greatly improved by synthetic biology techniques, which could increase their selectivity and cancer lethal potency. This could be achieved by making them express the correct binding proteins to latch onto certain cancerous cell types and to produce effective killing agents at the tumour site after a detection mechanism triggers their release. Because bacteria can proliferate around a tumour, their attack can be sustained and remain persistent for much longer periods of time than pharmaceuticals.

Such an application of inserted GE cells differs greatly from our project's proposal to insert re-engineered microglial cells into the brain because it can be used in 'ethically neutral' tissue. That is to say, for example, that there is no intrinsic problem with manipulating the breasts to fight breast cancer, hence surgical interventions are common. However, even with this far more basic building block on the way to what our project posits has a serious ethical concerns. One of the first that springs to mind is safety. Most such GE constructs will have an engineered 'kill-switch' that induces the death of the cell in response to a certain signal or condition, for example temperature, a particular drug, radiation, etc. This

can stop the genetically modified (GM) bacteria in a patient's body from going out of control. Yet there is always a risk, however slight, that random mutations in bacterial DNA will overcome the kill-switch by chance, or that the switch will be ineffective for other reasons. There is also an issue of transfection; if the new genes inserted into the bacteria could transfer from bacterium to host and alter human genetic content, it may cause genetic disease – though since this could generally only effect somatic cells and not enter the germline, it is not heritable and in most cases would only persist as long as those affected cells survive. However, the distinction may not always be clear for the general public, for which the idea of gene transferral seems frightening.

The ethics here, then, may be more to do with fear than anything else. It is important to keep the public, primarily potential recipients of GM cell insertion treatments, informed on biology, including genetics and synthetic biology. Education is often seen as key to advancing patient-doctor interaction, but synthetic biology is all but completely overlooked in hospital education initiatives. This is because, while the field promises much, it has produced very little that can be brought into medicine. However, because it may one day deliver big time on its promises, we need to have a population capable of at least vaguely understanding technology that otherwise would seem more frightening.

One commonly touted argument against GE is that it is unnatural, and therefore a morally wrong practice to undertake. Those that adhere to this view would understandably be extremely concerned about being the host to millions of GM vassals, even if these cells are trying to dissolve tumours. Here, we have two underlying assumptions, one philosophical one ethical; genetic engineering is unnatural, what is biologically unnatural compromises the 'sanctity of life' and is therefore morally wrong.

If we take 'nature' to comprise, as John Stuart Mill defines it, 'a collective name for everything that is' **(Mill 1904)**, GM cannot be unnatural, or 'everything which is of itself, without voluntary human intervention', in which case GM is no more unnatural than human thought **(Vogel 1996)**. Scientifically, one could argue that genetic engineering is not, per se, unnatural, because evolution involves the rearrangement of gene motifs into shifting patchworks of genetic information that alter the phenotype of an organism simply through genes being differently positions or spliced and appended to generate new protein forms. Some cell types can undergo extensive genome reconfiguration within a few generations **(Shapiro 1992)**. In other words, biochemical systems within cells naturally perform genetic engineering in order to evolve. Without this understanding, conventional evolutionary theory struggles to explain molecular genetics.

Yet, people do make distinctions between things that are not really synthetic and what they perceive as a more 'natural' version. For example, organic farm produce is often considered more 'natural', and contraceptive pills are considered 'unnatural'. These brandings colour and reflect the moral stances people have on these issues. But is 'natural' simply an aesthetic and somewhat romantic tag? Not necessarily, biological nature is often felt to define the boundaries of human action, and in the case of other creatures comprise and arena of autonomy in which they can act and that must not be interfered with or otherwise adjusted by GM, as nature must 'live and grow by itself' **(Verhoog et al 2003)**.

In the case of inserting GMCs/GMOs, we are impinging on this autonomy as well as expanding human action into 'nature'. However, if feels very unscientific to treat nature as a distinct 'otherness' opaque to human understanding. Its 'opaqueness' is simply a product of the difference of opinion between those that are willing to analyse nature and those that are not. In the case of inserting GMOs/GMCs, the human is not genetically modified, only the therapeutic cellular agents. However, the consequences of any technology is a derivative of its intrinsic nature and the context of its use, this context being the human body. GMC/GMO insertion is particularly open to being deemed unnatural, because the synthetic cell will commonly contain genes not native to its own species and the insertion and growth encouragement the host cells receive could be 'unnatural', even without the GM, by because its receptor environment could be out of its indigenous range. Brian Goodwin proposed instead a conception of organisms as dynamic wholes, in which genes impact a cell's development via the proteins they produce, and so do not on their own determine particular features of the organism **(Goodwin 1994)** but utterly depend on protein-protein interaction. Therefore, the consequence of transferring information from one organism to another, both in terms of inserting genes into GMCs/GMOS and inserting these cells themselves into human patients, is inherently unpredictable, because predicting protein-protein interactions is an un-mastered science. Perhaps this uncertainty is what people instinctively mean when they brand GM 'unnatural'.

GMOs/GMCs are also 'unnatural' because they contain gene combinations that are so unlikely to arise in nature that they are effectively impossible outside the laboratory. They may also contain genes from other species that originate from entirely different domains and kingdoms of life. There are protestations that this technology can create 'unnatural' and undo 'natural' species, so that released GM cells, be they in the body or the wider natural environment, may damage delicate ecosystems and biodiversity (on an organismal or cellular level). However, 'species' are dynamic, genetic-boundary-less populations that constantly undergo genetic change **(Straughan 1999)**, unintelligibly dividing into different species to varying degrees of genetic, ecological and geographic separation. Therefore, while GE technology may not need to overly concern itself with changing the nature of species, the impact of releasing GM entities is a very real danger. Kill-switches for organisms/cells inserted into the body should ensure that they do not become some sort of dominant life form in the body's microbial ecosystems, but as discussed before, there are no absolute guarantees kill switches will be consistently effective.

The word 'synthetic' is, after all, in the name 'synthetic biology', so if we accept that GE is 'unnatural' at least as regards public perception, the next question is why is being unnatural bad or even amoral? In the context of applying GM to humans or the human environment, it is often said by opponents that GM compromises the 'sanctity of life'. This was originally a concept of the Abrahamic religions that symbolised the unique holiness endowed upon human life because we share something of it with God. Genesis says that God created Adam as He 'breathed into his nostrils the breath of life' **(Genesis 2:7)**. It has since evolved into a non-religion specific idea of human dignity that suggests human life is in some way special as compared to the rest of nature and not to be interfered with, or, alternatively, that human life epitomises the natural vs. synthetic distinction. However, many opponents of GM tend to use the phrase as a 'culture wars slogan' **(Gushee 2006)**. Rationalised and de-relgionised,

it is a moral conviction dictating how human life ought to be perceived and treated, a useful and progressive distinction in law for example, but perhaps a less useful one in science where the bioethical issues are more complex and viewing humans as immutable biological entities is not particularly helpful. At any rate, in the GE debate, the 'sanctity of life' is more of a fence sitter than anything as one might equally, rationally argue that not pursuing GE technologies compromises the sanctity of life as we fail to exploit an avenue to save lives, even if doing so may change it in somewhat disconcerting ways.

Another ethical worry with inserting GMOs/GMCs is that of ownership and patency. Could genetic circuit constructs, the sequences of genes added to otherwise 'natural' cells, be patented? Can genes of any organism be owned, whether entirely or as a certain component in a circuit? Should they? These are perhaps more practical and germane questions for synthetic biology. Being able to patent gene systems could boost failing industry interest in medical conditions, such as AD, for which pharmaceuticals have made little headway. There are many fears over the power of pharmaceutical and biotech companies, especially in terms of access to research and results, and any monopolisation on synthetic biological treatments that use inserted GM cells could come to exemplify C.S Lewis' statement 'What we call man's power over nature turns out to be a power exercised by some men over other men with nature as its instrument' **(Lewis 1947)**.

In summary, seeing GE as morally acceptable depends upon not seeing nature as a model to which we must conform. In terms at least of inserting GMCs and GMOs, the technology is not itself ethically neutral and this prematurely colours views on its applications. Because we are talking about medicine, when making decisions on bioethicality we must weigh this technology's future potential to save lives against its potential to undermine some innate human dignity. Pitted against one another, I would hope that society would place its support behind furthering synthetic biology in medicine because it could one day be such an asset, and not limit medical progress to the confines of some especially amorphous philosophy of life, no matter how exalted and pertinent that philosophy is in the rest of modern human culture.

**Medical Neuro-Genetic Engineering**

The brain is the command centre. It is the seat of power presiding over functions both cognitive and autonomic and it is the site of some of the most subtle, and many of the most crippling, medical conditions, congenital or contracted. Since it is the part of us that most makes oneself one's self, attitudes towards infringing on its natural sovereignty with GE can be expected to vary to a greater degree compared to even GMOs. It is possible that the insertion of new genetic information into brain regions, using chassis from microglia, to bacteria, to viruses, to just gene products created elsewhere in the body, to grafts of new GM neurons and stem cells, will form the basis of viable medical treatments in the near future. Our iGEM project attempts to demonstrate this. In the discussion of various uses for neuro-genetic engineering (NGE) it is generally assumed that the ease of taking the proposed treatment is proportional to severity of the condition being discussed. For example, an Alzheimer's patient may

consider brain surgery to implant chassis with genetic circuits designed to mitigate their affliction, but someone who is sleep deprived would probably not consider micro-neurosurgery, though they may well consider a tablet with a retrovirus which, through one method or another, performed NGE in their brain to cure their insomnia.

Neuro-genetic treatment's first port of call may well be to alter neurotransmitter expression levels and sensitivity in discrete brain areas, or the whole brain, because many brain conditions manifest through their disruption. GE would be advantageous over drugs that stimulate the production of, or inhibit, the same transmitters, because it could be more finely tuned, making it more patient specific, possibly with better side effect profiles because the mode of action is more direct.

Depression is a good example. The monoamine hypothesis holds that depression results from the depletion of monoamides, such as dopamine, serotonin, noradrenalin, etc., which can be bolstered by tricyclic drugs and selective-serotonin-reuptake inhibitors (SSRIs). Depression is not generally regarded as so simple nowadays; in reality it is more an umbrella term for many pleomorphic diseases **(Holzheimer and Mayberg 2011)**. It is a multidimensional ailment for which a complex composite GE treatment system may be very useful. It is thought that increasing monoamides may not combat depression directly, but indirectly, through the promotion of secondary neuroplasticity **(Krishan and Nestler 2008)**. Neuroplasticity underlies our ability to learn and remember, so these faculties may experience side effects in NGE treatment which enacts longer lasting changes than the drugs. Making neuroplastic changes with medical treatments already occurs via pharmaceuticals, so more directly promoting connection changes with NGE should not pose a significant ethical concern in this area, beyond those already associated with anti-depressants even if changes in connectivity alter behaviour and cognitive abilities. If, however, NGE proves to be more pervasive and persistent in this respect, we may want to abandon it is an option because the social aim, at least, with depression treatment is to salvage a person's personality from the confines of depression, and if we change it too drastically in the process the treatment can be seen to have failed. However removing depression is itself a drastic personality alteration, but because it is 'pathologised' (and rightly so) it synthetically mediated removal is not considered an ethical issue in of itself.

Some of the current general concerns with anti-depressant drug treatments would apply to NGE, but are somewhat amplified by NGE's potential to be longer lasting and more direct. For example, anti-depressants' use with children is often criticised as a way to easily deal with a troubled child without proper analysis as to whether their depression is clinical i.e. using it as therapy for troubled times, not to combat medical depression. There is some evidence to suggest that administering SSRIs to children leads to an increased risk of suicidal thinking **(Shearer and Bermingham 2008)**, demonstrating the dangers of making changes in the brain even with drugs, which whose effects are more temporary than the envisioned action of NGE.

The synapse is an extremely complicated neurological formation and is key to understanding and controlling neuronal systems. It is the suspected site of dysfunction for depression and other neuropsychiatric diseases, but the high specificity and targeting required of drugs to control minute and subtle details of synaptic function is too high for modern methods to deal with. A NGE approach that

changes the genetic information in the neuron itself, perhaps influencing the local mRNA or inserting new mRNA at the synapse, would allow us to make more finely tuned changes.

Such delicate and personalised management could also go a long way towards helping manage other illnesses, such as schizophrenia, bi-polar disorder and autism spectrum disorders (ASDs). These are pervasive neurodevelopmental disorders with high genetic loads (~80%), and so if NGE was implemented early to change faulty genetic information, it is possible that such an intervention could promote healthy brain development and prevent developmental brain issues occurring.

ASDs have been described as an epidemic, and although this is largely attributable to increased public awareness and diagnosis, the rising age of fathers in the Western world, with their low quality mutation prone sperm, may be effecting a real increase. Despite being a developmental disease, it has been shown that it is possible to alter the ASD disease phenotype, including Fragile X and Rett's syndrome, in animal models using genetic techniques. Rett's syndrome is an X-linked condition. Full homosygosity and hemizygosity is usually fatal, though girls heterozygous for an MECP2 mutation can exhibit the disease phenotype due to lyonisation, leading to autistic, cognitive and motor defects. This can be modelled in mice by inserting confounding DNA code in the MECP2 gene to produce an analogous phenotype, which, with drug mediated removal of the insertion, can restore the fit phenotype **(Guy et al. 2007)**. In humans, of course, this would not work because the MECP2 gene is mutated, not artificially confounded by an insertion, but in principle it could be spliced out and replaced with a working gene, or a genetic circuit could be inserted to produce the functional version. It would seem that ASDs comprise one family of phenotypes, which can be induced by a number of gene mutations, though a single de novo mutation can be responsible for ASD aetiology, as suggested by the 80-90% concordance in monozygotic twins. It is possible that other ASDs are caused by similar single mutations, as in Rett's, with the similarity in phenotypes arising because these mutations all cause synaptic dysfunction which hampers experience dependent plasticity and synaptic modulation after initial synaptogenesis **(Zoghbi 2003)**. Such could explain why ASD children develop normally for ~6-18 months.

What would 'fixing' these genes mean? In the case of a condition like Rett's syndrome, it could mean life and a far greater increase in the quality of one's life. But in the case of adult with milder ASDs, the sudden ability to 'correct' neuronal function in their brain and remove even some autistic symptoms could have a fairly drastic change to their personality, something they may be very unwilling to undergo, which is why such GE interventions, if developed, should perhaps not be advertised as a 'cure'. In fact, the autistic rights movement believes that those on the spectrum are more disadvantaged by society than by their condition, and it is a fairly common feeling amongst the ASD community that prenatal testing for autism is a form of eugenic elimination in an effort to make individuals conform to neuro-typicality. Many autistics would consider their autism of part of who they are, not an appendage to their personality but ingrained in it, and its curing less a modular removal of something unwanted, than a cleansing for a new personality. There is also the colder question of what society itself would lose by curing all ASDs. Professor Baron-Cohen notes that 'we do not inadvertently repeat the history of eugenics or inadvertently 'cure' not just autism but the associated talents that are not in need of treatment'. The ability to see the world differently as a result of a mild pathology can be useful. Savant

skills and the focused genius of some autistics may well have helped human society to develop to where it is today, perhaps stereotypically, though not exclusively, through scientific/technological innovation.

Clearly, some ASDs such as Fragile X and Rett's are so severe, affecting both peripheral and central nervous system and having larger anatomical and cognitive effects, that they are clearly in need of treatment, something NGE may be able to offer to even older sufferers. But at which point in the spectrum do we cut it off and decide that NGE is no longer appropriate? At which point does human neuro-variation end and neuro-pathology begin? The same problem arises with other conditions, such as obsessive compulsive disorder, hyperactivity disorders, etc. This kind of distinction could be made and a cut off region identified, but it is never going to satisfy all parties, and a whole area of NGE 'cut-off' justification ethics would have to spring up for spectrum diseases.

But how does NGE really differ from, say, psychological and pharmacological treatment? The distinction is instinctive, perhaps because GE involves directly tampering with genetic composition and gene expression. However, our environment affects our gene expression patterns and cellular structure just as surely. For example psychological interventions in children have been shown to ease ASD symptoms by encouraging the use of, and thereby strengthening, underused prefrontal networks **(Just et al. 2012)** for processing higher level social situations, while pharmacological treatments stimulate epigenetic changes. The raw changes induced by NGE treatments could be largely the same, stimulating increased connectivity and the expression of the correct proteins directly in a more complete and pervasive way. This raises the point that NGE is more a means than an end, a way of ensuring changes we are already seeking to make with other types of treatment.

Bi-polar disorder is an episodic disturbance of mood into elation or depression, and much current treatment is psycho-educational, to help patients regulate the mood swings. As such, as opposed to the personality removal concerns with ASDs, NGE treatment may focus more on giving patients more autonomy over swings, or removing extremes, though how this could be achieved is unclear. Perhaps the inositol phosphate metabolism could be targeted, as the current gold standard treatment is lithium, an ion which stabilises mood by increasing the availability of important signalling molecules from this system at synapses. Such would not be seen to compromise a person's selfhood in the same manner as NGE ASD treatments as patients already live much of their lives in a stable mental state.

Schizophrenia is a heterogeneous syndrome characterised by hallucinations, delusions, disorganized thought, catatonia, alogia, avolition and anhedonia. Daniel Weinberger postulated that imbalance between two dopaminergic systems due to connectivity issues may cause the syndrome while others believe that spurious glutamatergic activity could disrupt synapse strength. Mutations in synaptic genes and genes like DISC1 **(Blackwood et al. 2001)** have also been associated with schizophrenia. A NGE solution may promote the correct connections and replace incorrect with correct genes, or produce working gene products from a plasmid. Such would be much easier in pre-prodromal patients, to transfect all the correct cells and encourage all the right connections. However, there is an ethical issue in that many patients will never develop full psychoses but early intervention could drastically help those that would have. Therefore, NGE treatments take a risk; they would, if effective,

help those that would go on to develop schizophrenia in their early adulthood, but may change the brains of patients that would never have developed the syndrome, to unknown effect.

In AD, neuro-degeneration results in the loss of many cholinergic neurons, and the corresponding drop in acetylcholine levels in affected networks. A NGE system that boosts acetylcholine could stall memory loss in the early stages of the disease. In AD, a protein called β-amyloid is incorrectly created in the brain cells, and nucleates and aggregate with other abnormal protein, such as some isoforms of ApoE **(Strittmatter 1993)**, into dense plaques that distort cells in the vicinity and disrupt synapses. They are thought to engender the creation of neurofibrillary tangles in surrounding neurons. These abnormal tangles are made up of poorly soluble hyperphosphorylated isoforms of tau, a microtubule-binding protein that normally is soluble. As the cytoskeleton is vital for cell structure and transport, these abnormalities impair synaptic function and trophic support, meaning that the neuron will eventually die and leave behind the neurofibrillary tangles. The entire process may be initiated by an imbalance in BDNF and pro-NGF signalling, as older brains produce more pro-NGF due to oxidative stress. This can initiate inappropriate cell cycle re-entry, and increase AD gene dosage. With time, the plaques and tangles grow and spread, leading to neuronal death. It is theoretically possible to insert a chassis, such as a microglial cell, with a genetic circuit that tackles multiple parts of this problem, for example producing BDNF to balance signalling and a protease to disperse the plaques. It is also possible to conceive of similar systems to deal with other plaque based diseases, such as Lewy bodies in Parkinson's disease. This is a good example of one advantage of NGE over conventional medication: one treatment can tackle many related issues through the production of multiple gene products.

The ethical implications with diseases such as AD are a little different to those of neuropsychiatric conditions. In the case of AD, we are dealing mostly with older patients, who may not greatly benefit from an (assumedly) expensive NGE procedure, or may not have the presence of mind to fully appreciate treatments that they agree to or refuse. An uninformed decision is, really, no decision at all. If the procedure must be surgical in order to insert the new genetic information, there are auxiliary medical issues to consider, with its feasibility in old age being a concern. Moreover, GMC insertion would understandably likely be seen as a last resort and used only in patients that clearly suffer from dementia. For this reason it may be quite ineffectual at stopping a disease whose progression is already profound. Therein lies another issue, because AD can only be confirmed beyond doubt post-mortem when the histopathological signs can be observed, and a NGE treatment which tackles one dementia is unlikely to have much of an effect on another form. In any event, it may not ensure enough years of quality life and have a god enough cost-benefit ratio to be seen as a viable treatment by public health bodies, such as the NHS, though it may find its market in private medicine.

The question of whether or not to treat attention deficit hyperactivity disorder (ADHD) also courts the same sorts of questions. Its pathological status is somewhat questionable, and it is clear that NGE changes that are 'too strong' or are higher up the 'scale' will be more neuro-enhancements than medical treatments. Especially in the US, stimulant drugs, such as Ritalin, and non-stimulant drugs such as atomoxetine, are already commonly used in many communities and often supported by doctors and teachers – however, diagnosis of ADHD is mainly discerned using questionnaire responses and the disorder is so relatively mild in terms of impact on peoples' quality of life, that NGE seems like a

somewhat drastic response, though this would depend upon its ease of implementation in the future. This would be more a question of therapy, than of medicine.

As this example of ADHD has demonstrated, the line between illness and health is not a clear one, and brain conditions are infamously misdiagnosed. With no real biomarkers for many mental problems, such as schizophrenia, the use of NGE to treat the illness hinges entirely upon behavioural analysis, which is more subjective, more prone to human error. Because permanent NGE could represent a drastic change, the call for its use must be solid, or we risk building a separate problem atop one that was never really there.

There has also been enough advancement in the neurochemistry of the autonomic functions the nervous system handles, to make NGE there a tantalising possibility. Sleep disorders could be cured using NGE without the need to continually take drugs. For example, narcolepsy is kept at bay with the drug modafinil, which has a variety of effects on a range of neurotransmitter systems, for instance by increasing synaptic dopamine concentrations, an effect certainly possible using NGE technology. Funding for such NGE research may well come from military bodies, because a drug that could negate sleep entirely would be of great strategic value. This is a good theoretical example of medical GE breakthroughs running into the future enhancement market, and highlights the difficulty in separating the ethical issues of medicine from commerce and politics.

Similarly, body weight could be controlled by altering the levels of appetite hormones such as leptin, ghrelin and melanocortin, encouraging the obese to eat less, but could also be used as an enhancement to help the healthy loose more weight. So doing may even compromise health, a fact which, though against the spirit of the technology, would nevertheless be an ethical counterweight to its positive medicinal applications. There are, however, very few medications currently available for weight loss so NGE, again assuming easy implementation, could be very attractive. This is the same sort of slide that brought Viagra into sale as a sexual enhancer (and indirectly responsible for that slough of annoying e-mails in your spam box) from its use to combat male erectile dysfuntion. If society decides against widespread NGE enhancements, we would have to demand and tightly enforce the ring fencing of NGE technology.

NGE technology could also reduce or eradicate pain perception in certain areas, which would be a great relief to those suffering from chronic pain. Whilst ultimately pain is of great evolutionary advantage, its eradication in a wide range of circumstances and bodily locales has long been the goal of researchers, clinicians and sufferers alike, and where pharmaceuticals have failed to find a complete pain blocker, NGE might. The genetic deletion of sodium channels Nav1.7 and NaV1.8 results in a phenotype in mice where thermal, mechanical, visceral and inflammatory pain thresholds are significantly heightened, while neuropathic pain is unaltered **(Drenth and Waxman 2007)**. Though pain thresholds could only be estimated by behavioural changes in the mice, the study indicates that an antinociceptive NGE treatment could practically eliminate most forms of pain by targeting these genes. In humans, a nonsense mutation in SCN9A results in loss of Nav1.7's function, and while other perceptions remain intact the mutant suffers from channelopathy-associated insensitivity to pain (CIP), body-wide, including some forms of neuropathic pain. And NGE treatment which silenced these genes in

regions of neuropathic pain may be able to ease patient's suffering, and in the case of CIP, and NGE treatment could introduce a working version of the gene (CIP greatly reduces life expectancy).

In this case, there would be serious concerns about the leakage of this technology, because while the social use of NGE to lose weight or sleep well, complete pain eradication has more potential military use, a classic component of a 'super soldier'. Otherwise, the case with the peripheral nervous system is a little clearer cut. Because the brain is not directly involved it is like having GE treatment in any other part of the body – it is not doing to undermine personhood. Although, having said that, pain processing does occur in the CNS, at the level of the spinal cord and in the brain, where pain is actually registered and from which peripheral nerves receive descending inputs that modulate their activity. Therefore, it is not inconceivable that pain NGE technology may encroach upon the brain, bringing with it the ethical uncertainty of what this may do to the mind of a patient.

**Therapeutic Neuro-Genetic Engineering**

For a long time now, genetic research has been conducted on criminality, addiction, aggression, altruism, impulsivity, sexuality, parenting prowess, etc., all areas which have met with at least some, often questionable, success in animal models that could be generalised to humans, if not some success for gene identification in humans as well. With the ability to change gene expression in the brain, using bacterial, viral or mammalian vectors for new genetic information, we open the door on rehabilitative and therapeutic treatments, which could 'fix' anti-social attributes not classically seen as medical concerns, and not progressing one's abilities in a way that could be considered a neuro-enhancement. This is a sort of middle ground between the issues discussed in the last and next sections, and as such is greyer even than those.

The use of this biotechnology, then, could stretch from the ward to the shrink's sofa, and even the court room, as perhaps a part of a sentence signalled by the judge's gavel. It may become psychologists' prescription for difficult, heavily biologically engrained cases and corrective neuro-genetic procedures could also possibly become part of court ordered rehabilitative intervention in the future. The possibility seems all the more likely when one considers the plummeting cost of genetic procedures and the increasing strain on government's budgets, burdened by the costs of keeping prisons and rehab centres running. Compliance with medication is already commonly court demanded for offenders posing a threat to themselves or others. In the future, they would be forced to comply with NGE treatments. Of course, this may seem more dramatic given how our current social landscape reacts to GE generally, but this may not be so in the future, just as there is no great opposition to many court ordered drugs in the modern day.

However, less subtle interventions still strike many as to heavy handed. For example, several US states employ laws that permit or demand sex offenders to take as manufactured hormone, medroxy-progesterone acetate. This reduces sex drive and relapse. It is in this instance that we most see the

divide between criminal and commercial psychological use, because one may safely wager that opposition to commercial availability to such a drug would be stronger than use on criminals. Historically, criminals and 'criminal classes' have been served a less complete portion of human rights than law abiding citizens, and even today in British society opinions as to what is permissible to more extreme offenders can stretch towards the suggestion of the death sentence – so, what is forcing them to comply with NGE, in the face of death, even if many people in our society cannot stomach the idea of it for themselves?

Hence, perhaps, the use of this hormone in American courts, but not American pharmacies. It is possible to predict, from simple inspection of human behaviour, that passing NGE corrective treatments for paedophiles, for example, will be easier than introducing the simplest of neuro-enhancements. But, once that threshold is breached, what is to stop genetic sexuality meddling being used to make homosexual into heterosexuals, or vica versa? Homosexuality may have genetic, and is popularly thought to have significant epigenetic, groundings. It is no longer considered an affliction in progressive societies, but as an alternative, and socially acceptable sexuality, whereas paedophilia is not, because it is considered a heinous form of abuse. This is where we might first see elements of cosmetic psychology coming into play, once enabled in terms of NGE, which would highlight the conflict of morality on an individual versus societal scale. For whatever reason, a person may wish to convert to heterosexuality from homosexuality, or vica versa, and for whatever reason this may represent a great increase in quality of life for them. One then may plainly argue that it is an appropriate course of action for this individual. However, at the societal level such choices seem more disturbing, because the social profile of the treatment user will have completely changed in a way that will force many associated persons to treat them differently. For example potential partners would likely be wary of people who had undergone such NGE. In the case of paedophilia, NGE sexuality correction may appear socially just.

Court ordered NGE treatment would be aimed at bettering society, potentially in opposition to bettering the stance of the individual. This need not, and almost definitely would not, be a case of subjugating individuals, offenders or otherwise, to conform to government wishes – we may be in the realm of, but we are not talking about, science fiction after all – however there is a genuine question of using NGE therapy to tangible benefit, as with current medications **(Farah 2002)**. For example, violent offenders are often made to attend anger management classes, to both their personal benefit and the benefit of their community, which has to deal with less hot-blood. GE may have the same effect, in less time and perhaps more surely, though intuitively we feel uneasy about this **(Farah 2002)**. Perhaps the reason for this is that the neurological use of GE precludes the ability to accept or resist the progression of the change, at least in an instantaneous or direct fashion. There is something about the locked in course, and the possibly permanent nature of NGE therapy, which raises warning flags. It is the inability to opt-out effectively after a treatment, which is most worrying.

**Enhancement Neuro-Genetic Engineering:**

Cosmetic surgery was the quackery of the day in nineteenth century America, a practice born of vanity that tampers with the God given. It is, after all, seemingly contrary to the Hippocratic oath as it inflicts harm and no physical relief **(Elliot 2007)**. Now, it is now a mainstream medicine, and even the vainest transformations can be accepted by doctors, clergy and feminists. The view had shifted from 'enhancement' to 'therapy', becoming, in historian Elizabeth Haiken's word, 'psychiatry with a scalpel', and these conversions are common in medicine where the boundaries between pathology and consumer pressure are indistinct. In the same manner, it is not inconceivable that enhancement NGE technology will come into play as 'psychiatry with transfection' in the near future, with a path smoothened in the same way as that for cosmetic surgery by the technology's use in medicine and in the interests, perhaps, of 'neruo-equality'.

Neurons and glia are, of course, essential ingredients in what may make you, 'you', in that it is in their networks that we harbour our intelligence, memory, voluntary motion, ability to learn etc., a fact appreciable without having to appeal to genetic determinism. Indeed, much of neural interaction, from efficacy to network expansiveness come down to developmental and on-going environmental events more so than genetic scripting. Brain enhancement through synthetic biological methods need not be germline alterations of a consortium of genes in the sense that they have to subscribe to the 'designer baby' approach so critiqued in popular culture, but could conceivably be a result of transfecting adult neurons/glia with plasmids, inserting new cells with engineered abilities or otherwise altering synapse strength and the number of inter-neuron/network connections. This is, post embryonic, an invasive type of treatment. Indeed, using microglia to halt the progression of AD, and therefore cognitive loss, by dissolving senile plaques is only one philosophical step (albeit very many scientific steps) from a genetic system for cognitive gain.

Neuro-enhancement would clearly encompass intelligence, but intelligence comprises many different domains all of which have an uncertain genetic basis. Assuming that it is feasible, we can envision a world in which NGE can boost intelligence, combat the neuro-genetic load, induce eidetic memories, help with recall, abolish the need for sleep, endow autistic savant abilities without social skill detriment, etc.

These enhancements cause a variety of neuroethical issues, for example, concerns over social justice. Competition against those that can afford, as opposed to those who cannot, NGE neuro-enhancement is certainly unjust, though perhaps not that different in principle from the poor un-educated vs. the rich private schooled of our nation. However, such employment of NGE may widen that social divide. At the same time, these changes may boost the intellectual power of society generally, and help spur innovative growth and positive social change. Few would argue against a generally more intelligent society, many argue against boosts to certain social strata or populations, however, highlighting the need for mass availability. Of course, mass availability would just raise us to the status quo in terms of relative intelligence, and so perhaps would create a society dependent on, though not necessarily reaping the benefits of, neuro-enhancements. Liberal eugenics is the idea that genetic enhancement could be made available in a biotechnology market place driven by the same consumer laws as any other, but it is a concept which makes a lot of us uneasy, even if we cannot pinpoint why.

Perhaps this is because genetic enhancement technology may render indulgers a product not of their actions, but of their choices.

Moreover, as Farah notes, there may well be 'hidden costs' in such enhancement, for example the up-regulation of a specific protein may decrease sleep requirements but decrease attention span, or have subtler influences on satiety, irritability, etc., and so may change the dynamics of our society in other, more varied ways. Also, because genes associated with intelligence tend to be multifunctional (pleiotropic), it may not be possible to increase and decrease intelligence in a modular manner to apply enhancements to discrete faculties. Altering the expression of many would also change other physiological parameters, for better or for worse. In fact, it has been suggested that intelligence does not have any real underlying genes, but that intelligence manifests as an emergent property **(Mitchell 2013)**, given sound development from a robust genome and relying on how the brain integrates its components/inputs, though these may be made to diminish/augment **(Crabtree III 2013)** due to NGE.

Another clear problem already touched on is that of personal identity, if we take personal identity to mean the identity that a person generates over time **(Audi 2002)**. Synthetic neuro-genetic alterations would effect change over a smaller time-frame in a manner quite unlike the slow progression of natural cognitive development. Its impact on personality and identity could therefore be quite dramatic in that such change may lack continuity with one's previous state of being. Of course, other events can alter identity quickly, for example many forms of trauma, stress and distress, a sudden, precipitous change in circumstance or environment. There is, however, something more intrinsic about tampering with brain cells with NGE, at least in a philosophically aesthetic sense, even if biologically, for example, trauma type events also come with profound neurological change.

Moving along similar lines, it is also plain to see that NGE offers substantial gain to individuals without pain. Its use could lead to an increase in one's abilities without the concomitant struggle to acquire these improvements, beyond access to the required money. Many would be uncomfortable with a situation in which a diligent, hardworking job applicant with a glowing C.V and a first in, say, a neuroscience Bsc, is piped at the post by his slacker colleague, whose slightly better C.V and his slightly better first is the product of NGE, something he was able to access because he is from a well off background. There is nothing really new here, however, because some people will always have unfair advantages over others, given the environment of their upbringing, the random opportunities they stumble upon and their individual genetic make-ups. New experiences continue to define us. They can better us or worsen us in a fashion partly at the vagarious whims of fate and partly as a consequence of our actions. We are not continually re-defined by new genetic information, because we do not generally receive system scale genetic changes during our lives, and if we do by some early and widespread mutation, it is not directed. Therefore, really, NGE can be seen to level the genetic playing field in a similar manner to how people already change themselves by exposing themselves to different environments, challenges, etc. It might not be earned in the faculty it improves, but we do not earn our 'starting' genetic make-ups either.

Some, such as Gerald Crabtree, have suggested that in fact human intelligence is in decline, and so NGE interventions of this kind may be more a solution to a very real problem, than a direct

enhancement of abilities. Crabtree makes the argument that prevailing human advancement is a product of societal changes in the face of, and facilitating, raw intellectual degradation. Mean human intelligence may be being eroded by the genetic load incurred through unfavourable mutation and recombination events across the multitude of genes that underlie intellect **(Crabtree I 2013)(Crabtree II 2013)**, in much the same way as the evolutionary degradation of our olfaction **(Gilad 2003)**. Extrapolating from data on the sex-linked X-chromosome **(Crabtree I 2013)**, Crabtree estimates that there are 2,000-5,000 human intellectual deficiency (ID) genes that interact synergistically as opposed to being summative. Therefore, single mutations can damage our holistic intellectual stability. Although intense Palaeolithic selection pressures perhaps served to filter out even minor intellectual defects **(Crabtree II 2013)**, allowing our powerful intelligence to evolve, in modern society slight deficiencies do not necessarily reduce fecundity, especially when masked by nurturing systems, such as education **(Crabtree II 2013)**. Though these claims have been much disputed, if it is the case, NGE may be one of the only ways to help clear out the mutational load.

When it comes to genetic engineering in the brain, one immediately leaps to thinking about intellectual enhancement technologies. However, one relatively overlooked, and at the moment seemingly even more farfetched, idea is that of genospiritual engineering in order to 'choose one's degree of religiosity or spiritual sensitivity' **(Charlton 2008)** by altering genes associated with inducing trance, delirium and dreams. Scientifically, the concept seems rather fanciful, because of the complexity of inter-gene relations, pleiotropy and the vast environmental impact on the manifestation of these attributes, though inducing or making more inducible at will trance-like states, euphoria, satisfaction, etc., as created by misbalances of neurotransmitters in the brain is certainly a possibility. Charlton suggests that such technology may have commercial appeal, as well as societal in allaying spiritual unease and perhaps promoting altruism (e.g. by expanding the range of 'greenbeard' markers **(West and Gardner 2010)** to which altruists respond), which has been shown to have a genetic basis.

Charlton speaks of engineering shamanistic, animistic and revelatory experiences in a fashion that would appeal to those seeking 'a more powerful experience', likely in a trade-off with determination, productivity and status mentalities. However, the desirability of such engineering is probably more questionable than Charlton assumes. It would be opposed both by theists concerned with the artifice and un-spontaneity of engineered religiosity, and atheists who would regard it a nonsensical proliferator of unsound spirituality. Ultimately, this type of NGE would be more comparable to the use of hallucinogens than an enhancement or medical treatment, and suffers risk the same pitfalls of psychedelic drugs no matter how on demand the NGE modifications switch on and off. Genospirituality suffers from a plethora of ethical concerns, more so even than most other areas onto which NGE may one day impinge, because one's 'spiritual' self is wildly seen as innate and integral to an identity which may be substantially altered by such a use of GE, whatever the reality may be.

Ultimately, the danger of NGE enhancement may be much more subtle. Greater genetic choice and malleability may encourage the fortunate to see their talents as earned, rather than what nature has granted them, something for which they should be grateful and respectful. It may undermine our sensitivities towards the less and more fortunate **(Elliott 2007)**. The genetic lottery of life is not always fair, but it is that unfairness that encourages and nurtures empathy from solidarity in society. At the

same time, whilst many might disparage enhancement technology, NGE or otherwise, by making a case against perfection it would seem that the consumer market for these products lie mostly with those on the wrong side of the bell curve. NGE enhancement would be marketed at those uncomfortable about their height, weight, confidence, sexual adequacy, etc. If these people suffer in an emotional sense because of their perceived inadequacy, then is it not the duty of the scientist and the physician to design and deliver technologies to help?

**The Core of the Neuroethical Debate:**

Neuroethics is, as defined by Gazzaninga, 'the examination of how we want to deal with the social issues of disease, normality, mortality, lifestyle and the philosophy of living informed by our understanding of underlying brain mechanisms', **(Gazzaninga 2005)**.

When it comes to considering any medical practice that is going to affect the brain, especially NGE, there are many ethical issues to consider. For example, with uncertainties surrounding NGE to do with un-desired consequences on the brain, it may be difficult to ever reach a position where all parties in a procedure can give fully informed consent. This may be due to an underlying misunderstanding, ignorance or confusion about what synthetic biology is amongst doctors delivering a treatment and patients receiving it, as well as varying opinions amongst the general public as to what constitutes a person, and what exactly is, if there is indeed, 'selfhood'.

NGE would, in many of its applications, have both short-term and long-term effects on a person's character. This does not represent a physiological concern, and may even be the by-product of returning the brain to a healthy physiological state. Whether or not this changes the intrinsic nature of a person will likely be the driving question that divides proponents and opponents of NGE generally. The philosophy of self is a large field, and this is not the place to examine in detail its theses and anti-theses in an NGE context, though a brief examination is required.

The modern conception of the self has its roots in the philosophies of Rene Descartes and David Hume. Hume observes and error on Descartes' part; his famous realisation 'I think therefore I am' (*cogito ergo sum*) does not necessarily entail a metaphysical substance, the 'self', only the momentary selves developed by thought. Descartes' view was informed by his dualism, a philosophy completely at odds with modern neuroscience **(Damasio 2005)**. Hume's empiricist view demanded that all knowledge of the world and ideas derived from that knowledge (or lack of it) are the result of sense impressions; thus nothing can be known of a 'self', ergo there is no self. Hume concluded that we are a conglomerate of remembered experiences that perhaps allude to a fictional selfhood that is effectively, utterly mutable. Immanuel Kant proposed instead that the self is not fictional, though neither is it truly detectable, it is the focal point of our subjective emotions, experiences and cognition – and so again, must be mutable.

Many modern philosophers, with a more neuroscientific context in mind, see the 'self' as accompanying experience as a somewhat superficial 'awareness tone' that lacks 'ontic depth' **(Strawson 2009)**. The focal point of the self shifts between experiences, potentially occupying multiple sensations at once, seemingly located at, say, the neocortical reaches in an A-level student puzzling over calculus, and the hunger centre of the hypothalamus as that same student longs for a sandwich whilst in the exam hall. In the modern view of the brain as reducible, a sense of agency is likely an emergent property of activity across the nervous system, rather than being centralised or localised to a specific area. We perhaps constantly experience, or experience upon reflection, an autobiographical self that is made from memory and encodes (in a non-neuroscientific sense), for example, our personality **(Damasio 2000)**. Our own self-identity and that of others is narrated to us through language, through linguistic tags that we associate with stored concepts, and it is at this level in our brain that perhaps we interact with an idea of ourselves and others, and this is where we perceive change. Some see a rendition of the 'self' even in the motor-mapping system of the ancient midbrain **(Panksepp 1998)**. However, without appealing to (other) metaphysical agencies, such as an insoluble soul, the notion of selfhood is vague to say the least.

What does this mean for NGE? If we see the self as, as many theists do, a metaphysical derivative of an immutable soul, NGE is not really a threat to one's 'inner' identity, only outward manifestations of that identity. Therefore, seemingly counter intuitively, basic theistic philosophy should have less to fear from NGE than other philosophies of self. Following Hume's brand of empiricism, NGE could change the nature of information received by the brain and in so doing reformulate a new self – but the information is unlikely to change so drastically as to lead to a complete overhaul of self, and one's autobiographical self will remain unchanged (unless the NGE's purpose is to alter memory or memory access), though the nature of subsequent memory recording could change. Hume's selfhood is ultimately fictional, and so NGE cannot really threaten it. If it helps AD patients hold on to their memories, NGE may even enhance their perception of self. Following the ideas of Strawson, Damasio, Panksepp and others, NGE could have a minimal or a dramatic impact on the transient self that flits across the brain, depending on the purpose of the NGE in question. The self may change because the neurological nodes between which the self flits change due to NGE, and so the nature of information or information processing changes. If the NGE increases attention, for example, we may be aware of things for longer and with greater intensity, and such a small thing as this could eventually have on impact on our personality and our transient experiences. If the NGE simply tried to stall disease progress its effect would be more to maintain oneself. Essentially, this discussion becomes too fragmented over the exact application of NGE and so it is more usefully related in specific circumstances.

The basic idea of selfhood and the fear of change is not just constrained to the individual level. If the use of NGE in medicine, therapy and enhancement technology were to become widely used in the future, we may find ourselves increasingly confronted with the question of what we consider neuro-typical and how far should and individual be from its guide posts to warrant medical NGE treatment, and how far away can we let people get following NGE therapy and enhancement. Especially in the latter two applications, we may well find the guide posts defining what is normal shifting in sync with social

changes brought about in those societies willing to make NGE therapy and enhancement widely available.

There is, even now, a growing concern in the medical community that appropriate human emotion is being 'pathologised' **(Parker 2007)**. Unpleasant affective states are a fact of human life and important not just in a cultural sense but also in terms of personal development, a basic example being heightening our ability to empathise. Thresholds for diagnosis of depression, for example, have slipped down in the last few years. Misdiagnosis with an NGE treatment could have negative physiological, as well as psychological effects, the latter not just for the patient, but also for the family. As a result, a new problem may be created and the other, underlying issue, medical or otherwise, never sorted out.

If medical NGE treatments become as an effective and long-lasting cure as hoped, we may face and entirely different ethical issue of increased attempts at diagnosis for neurological problems and increased societal pressure on those and the families of those diagnosed, to undergo NGE treatment. Diagnosis and being pushed towards even an effective treatment can, especially with affective disorders, exacerbate the condition and put strain on an individual's personal moral views about synthetic neurobiology without being educational or informative. A good example of an analogous situation is the law suit brought against the U.S. national mental health screening programme, which diagnosed a (supposedly previously perfectly contented) fifteen-year-old with obsessive compulsive disorder (OCD) and anxiety **(Lenzer 2005)**. Her parents claimed that the screening was a breach of parental and privacy rights. Societal paternalism and the way it can countermand moral individuality, privacy and parenting on such a contentious issue as NGE represents an even more ethically hazardous situation, even if the treatment suggested is an effective, complete cure. Diagnosis and subsequent medication, NGE or otherwise, also suggests to the concerned party, explicitly or implicitly, that *they* are the source of a pathology that the medical treatment will fix. If this mentally broadens to NGE therapy and enhancement technology, people who are low achievers at school, hopeless at art, socially awkward, etc., may feel that it is due to biochemical factors out of their control and opt for NGE treatment, instead of making the effort to improve in these areas conventionally. This is of special concern with children and young adolescents, who are more vulnerable to suggestion and often more willing to conform to practices they see encouraged around them. They are often also harder to diagnose, be that in a medical sense or in terms of say, intellect. An NGE course of action encouraged by the child or their parents may preclude further natural development in the areas modified as well as the personal development associated with becoming an adult. This means that treatment should be context-rich and well contextually informed, not according to society's generalised perceptions, whichever way they may lean, but the situation of the NGE recipient.

Privacy has always been a premier issue in neuroethics, mostly in regards to brain scanning, but it also could play a major role in NGE neuroethical discussions down the road. This is because if NGE brain enhancement technology becomes a social practice with the same profile as plastic surgery, people may try to model their psyche on others' and we may, though it seems farfetched, see the introduction of patents for specific brain profiles, neuronal networks, brain area development schemes, etc. Perhaps not the sort of thing that seems appealing in the current social landscape, but people already make comments about wanting Stephen Hawking's intelligence, Ronaldo's motor control, David

Mitchell's wit, etc., so if a future society already desensitised to the ethics of neuro-enhancements finds itself able to create these abilities in others through NGE to commercial gain, we arrive at a suggestion that is not impossible, if implausible, and instinctively uncomfortable for the current social mind-set.

NGE technology may result in the degradation of cognitive, intellectual and emotional faculties by acting as a crutch, and may compromise the natural psychology and personal development that we associate with being human. People are born with certain biological tendencies and propensities that can make them vulnerable to certain life events, both positive and negative, but where this vulnerability applies to cognitive, intellectual and emotional challenges people adapt, develop and overcome these obstacles in a manner that develops them as an individual in the social machine. What NGE therapy, enhancement and inappropriate medicine may result in, is a situation where the social machine crafts its own parts instead of being an emergent phenomenon. The removal of mental troubles that are social or mildly medical with ease, assuming NGE offers efficient and complete corrective procedures, could remove the struggle that crafts 'the human spirit', or at least that makes us different from one another. A psychologist may argue that such a future would be characteristic of neuroscience's willingness to intervene at the level of the neuron, and not at the holistic level of the person in question.

**Conclusion:**

Certainly a precautionary, rather than a reactionary approach to NGE would seem best. As is true of the vast majority of ethics, it is difficult to be sure what sort of impact NGE will have on social conscience, but in this case uncertainties are far greater and far more variable seeing as this report has been largely conducted on a field that does not actually exist (though that I for one hope is nascent). I have had to speculate on the science, in order to construct speculative neuroethics on the subject.

What has become clear, however, is that despite misgivings over even GE's place in medicine, NGE is not necessarily as socially uncomfortably as one might expect, and in fact its effects are little different in many cases to those of pharmaceuticals. Synthetic neurobiology is simply and alternative approach with a different set of tools and possibilities; some overlap, others do not, many need to be explored not for the sake of science but for the sake of human life, its preservation and improvement. In the case of using NGE against diseases such as AD, public opinion may well support this extreme form of genetic engineering, though with some types of enhancement and therapy it is a lot less clear and probably will prove to be far more polarising. Ultimately, the latter will only come to fruition if there is a market for it and so public wants and needs and the response of biotech industries will decide its fate outside of the ethicists' debate, as with much modern technology, especially biotechnology. With the line between patient and consumer becoming ever harder to draw, we may see the genetic lottery of life become a genetic supermarket **(Elliott 2007)**.

This does not mean that the debate should not be had, merely that it will become largely reactionary and not precautionary, whereas given modern medical culture the reverse is true in that sphere. The threat of NGE to selfhood is something which depends more on one's personal philosophy than any external, objective truth, though it is certainly neuroscientifically seductive (if not

neuroscientifically correct) to conclude that there is not self, just a jumble of sensations and experiences that NGE changes without there being some core, fundamental alteration. At any rate, we change over the course of our lives, in a physical and therefore neurological sense, and thus psychologically – our personality, our memories, our loves and hates. We cannot even be sure that the atoms in our body are the same as those that made us up seven years ago, and so if we cannot maintain a modicum of physical integrity how can we expect there to be a psychological one that may be undermined by NGE?

There is, lastly, the case of widespread NGE use such that we turn to the search for a perfect human nervous system. The ethics here can be seen as a matter of individual liberty and wellbeing, and the fundaments of the neuroethics may only concern the technologies' regulation and availability. This comes from starting with the question 'what can we do with this technology?' and then seeing all the possible problems that may fold before our new Promethean science, and we are convinced that it is worth a shot. If we start with 'what will this technology do to our nature' then it becomes a question of collective wellbeing, but not one about imposing limitations per se. The trade-off between these two starting points is the same as the trade-off between the individual and the collective **(Elliott 2007)**. For example, if we could cure every blemish the nervous system can currently sport, we could greatly improve the quality of life for some, but what does this say of our society if we begin to view the lack of neural perfection in one arena or another as an epidemic? In order to find a neuroethically comfortable answer along this route, we must come to a medical and philosophical consensus on what concerns and desires are legitimate. The level of mastery sophisticated NGE represents may leave inadequate cultural space of alternative ways to live human life in society. That is not to say we must remain passive in the face of death and disease, but it is to say that we should not be so keen to embark upon the ethic of the sportsman, that of control, perfection, competition and dominancy. We may overlook the value of the 'aesthetics' of life and adopting the ethic of the hitchhiker, who meanders and bumps with the road they are on. In the words of James Edwards, 'It would be a life that conceives itself less as the creation of something hard and enduring and more as the increasingly plastic and receptive medium in which things leave their marks and traces' **(Edwards 2000)** .

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