Prospects and Perils of the New Brain Sciences: a twenty year timescale*

Royal Society Science Policy Lab

20th October 2009

(*This paper is an updated version of a 2006 report for the Navigator Network of the New Zealand Royal Society)

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EXECUTIVE SUMMARY

1. ***Neuroscience is the study of the human brain and nervous system in health and disease. It brings together many disciplines and technologies, from genetics to brain imaging and psychology. It is one of the fastest growing areas of the biosciences, researching the most complex structure in the known universe. Advances in neuroscience have depended, in part on novel technologies and advances in other sciences . This report discusses the current state of neuroscience, and the new knowledges and technologies that are likely to emerge over the coming two decades.***

2. ***Amongst the most powerful of the supporting technologies are:***
    a. ***Advances in direct imaging of the living brain, through functional magnetic resonance imaging, magnetoencephalography and related techniques***
    b. ***Trans-cranial magnetic stimulation (TMS).***
    c. ***'Smart' pharmacological agents and dynamic imaging systems such as single photon confocal microscopy***
    d. ***Mice with specific inserted ('knocked in') or deleted ('knocked out') genes and other 'gene-silencing' procedures, providing animal models for human behavioural and neurological deficits.***
    e. ***Increased knowledge of the human genome***
    f. ***All underpinned by developments in informatics, including data storage and analysis and computer simulation***

3. ***These new technologies are helping generate new scientific insights. These include:***
    a. ***integration of the previous disparate fields of neuroanatomy, systems physiology and psychology in the interpretation of the functional organisation of the brain***
    b. ***better understanding of the molecular processes underlying neuronal communication, brain development, plasticity and ageing.***

   c. ***identification of gene variants associated with a variety of neurological disorders, and their biochemical correlates***

4. ***However, there is still a lack of integration across the various levels of analysis, from the molecular to the systems. In consequence neuroscience, as opposed to particular specialiasms within it, is still data-rich but theory poor.***

5. ***Over the coming decades, a more integrated neuroscience will need to build on evolutionary and developmental perspectives to transcend older dichotomies between, for instance, cognition and affect, nature and nurture, neurological and psychological.***

6. ***Key to this is an understanding of the self-organising plasticity of the brain, its capacity to construct itself in response to experience and environmental contingencies.***

7. ***The basic scientific (and philosophical) problem to be solved is of how a coherent sense of self and of consciousness emerges from brain/body processes. How far can neuroscience contribute to the understanding of the mind without collapsing into naïve reductionism (physicalism)?***

8. ***These advances in neurotechnology and neuroscience raise ethical, legal and social concerns, and require improved modes of public engagement in their upstream management. The next two decades offer the prospect of:***

   a. ***human-machine interfaces, implanted chips and prostheses and methods of focussed transcranial magnetic stimulation***

   b. ***repair of damaged spinal cord and possibly brain lesions via the use of stem cells, though not necessarily embryonic stem cells***

   c. ***increased use of brain imaging techniques both for diagnostic and prognostic purposes and surveillance***

d. increased uses of neurotechnolgies for military purposes including neuroimagig and TMS

e. increased use of 'predictive' genetic testing for neurological and psychiatric disorders

f. new and better targeted psychoactive drugs to treat neurological diseases such as Alzheimer's as well as depression, anxiety and related conditions, based on greater insights into these disorders through advances in neurogenetics and neurochemistry

g. widespread use of 'protective' drugs to prevent neurodegeneration, along the lines of the current use of statins in regulating cholesterol metabolism and thus reducing the risk of atherosclerosis

h. new generations of cognition and performance-enhancing drugs, with concomitant debates about their use and regulation

i. increasingly disputed borderlines between 'normal' and abnormal' behaviour and its treatment

j. greater use of neuroscientific evidence in legal proceedings , with revivals of long-standing debates over 'mad' versus 'bad' and the appropriate responses to each

Acknowledgements

Thanks to Tim Bliss, Radmila Mileusnic, Richard Morris, Barbara Nicholas and Hilary Rose for comments on previous drafts of this report. The responsibility for its content remains mine alone.

Abbreviations and acronyms

ACE	Angiotensin Converting Enzyme
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
BOLD	Blood Oxygen Level Dependent
CREB	Cyclic AMP Response Element Binding Protein
DARPA	Defense Advanced Projects Research Agency
ELSI/A	Ethical, Legal and Social Implications/Aspects
ERP	Evoked Response Potentials
fMRI	Functional Magnetic Resonance Imaging
HGP	Human Genome Project
IVF	In Vitro Fertilisation
MEG	Magnetoencephalography
PET	Positron Emission Tomography
SSRI	Specific Serotonin Reuptake Inhibitor
TMS	Transcranial Magnetic Stimulation

1. INTRODUCTION

The human brain is the most complex structure in the known universe. Its hundred billion neurons (nerve cells) – 100,000 under each square millimetre of the brain's surface - are connected via an almost unimaginable hundred trillion synapses (junctions). Its principal structures and connections are largely assembled into functional modules within the nine months from conception to birth, and refined over the subsequent decade, over which time they continually adapt their configurations and linkages in response to changes in the growing child's biological and social environment. Surrounding these neurons are some tenfold more of a variety of supporting cells known collectively as glia. But this is only a start to the complexity, for the brain cannot be considered in isolation. Brain and body interact not merely via the two-way flow of information through the spinal cord and peripheral nervous system, but are in constant hormonal, physiological and immunological communication, It is important to emphasise this mutual relationship. Not only are levels of circulating hormones in the body in part controlled from within the brain, but many of these hormones themselves enter the brain through the bloodstream and modulate cerebral processes. Furthermore, brains, like all other aspects of human biology, are evolved structures. Thus brains, along with the rest of our nervous, immunological and hormonal systems provide each of us with the inherited and learned resources through which, across the 10,000 or so generations since *Homo sapiens* emerged, people have created a myriad of social groupings, not least today's complex technological societies.

Understanding the brain's mechanisms and dynamics has proved biology's most intractable – and fascinating - problem over the three centuries since the birth of modern science. During this period, its functioning has been approached via a variety of scientific disciplines: anatomy, physiology, biochemistry and genetics, psychology, physics and information sciences. Whilst each of these sciences have developed their own characteristic methodologies, experimental approaches and theoretical frameworks, the past decades have seen attempts to establish, if not a common ontology, at least a common epistemology so as to unify the disparate fields, if by no more than providing an overarching name: ***neuroscience***.

Research into brain and behaviour has become one of the fastest growing areas of modern biology, and as with other such fields, it becomes increasingly difficult to dissociate the research findings from the technologies that enable them and the biotechnologies they generate. Hence neuroscience is one of a new breed spoken of collectively as technosciences. Neuroscience publications have spawned a host of new journals and threaten to engulf even the pages of more general journals such as *Nature* and *Science.* Some 30,000 neuroscientists meet each year at the annual jamboree of the American Neuroscience Association, 6000 at the biennial meetings of the Federation of European Neurosciences. In the US, the NIH entitled the 1990s the Decade of the Brain, whilst the current decade has less formally become known as the Decade of the Mind. The rapid growth has been accompanied by new and increasingly ambitious claims, both for answering deep rooted questions about the biological processes underlying memory, cognition, emotion, even, according to some neuroscientists, consciousness itself, and for providing new hopes for dealing with hitherto intractable diseases and disabilities. This growth has brought in its train, however, new and hitherto undreamed of prospects and perils, which in turn have led to the coining of three further self-explanatory words: neurophilosophy, neurotechnology and neuroethics.[*]

In this report, I offer one neuroscientist's overview of the current state of play in neuroscience, neurotechnology and neuroethics, and attempt to project forward likely developments over the coming two decades. However, it is important to begin with a number of caveats:

First, such predictions have in the past proved remarkably inaccurate, both in over-estimating the speed at which new understandings will emerge (e.g. 'artificial intelligence') or health benefits will accrue (e.g. genetics) but also under-estimating the rapidity of technological development (e.g. informatics).

Second, my viewpoint is personal, framed by my formation as a biochemist who has spent his researching career in one small part of the neuroscience forest, exploring the molecular and cellular mechanisms of memory storage in experimental animals (Rose,

[*] Along with others – neuroeconomics, neuroaesthetics, neuromarketing, neurolinguistics

2003, 2006). Having lived with a social scientist for the past forty years, I am conscious that there is a tendency for natural scientists to speculate about social issues in ignorance of the body of data and evidence offered by the social sciences, and I hope I have not strayed too far into areas outside my competence.

Third, I assume as background a stable social and economic landscape, in which research and development continue much as today, patenting law is unchanged, etc. Probably a dubious assumption, but necessary!

The text below is organised in the following way. After a general overview of the field, I focus on eight specific areas in which advances are being made or claimed. Three concluding sections then reflect on the ethical, social, legal and philosophical implications of these potential advances and summarise my view of the critical themes for the coming decades.

2. The Current State of the Neurosciences

a. The new technologies and their potential.

i. Linking anatomy, physiology and psychology.

The sciences of the brain with the longest history are anatomy, physiology and psychology, disciplines stretching back even prior to the dawn of modern science. Each has been transformed over recent decades. The windows into the living brain offered by the new imaging techniques have transformed anatomy, previously able to study only dead, fixed brain tissue, albeit at the increasing magnifications offered by the electron microscope and its modern avatars These new instruments have begun to achieve an integration at whole brain level of anatomy with physiology, as it becomes possible to visualise regional activity in human brain whilst the subject is engaged in specific tasks. What was once the province of experimental psychologists treating the brain as little more than a black box whose inputs they could control and whose outputs they could measure has now become amenable to analysis by more biologically based sciences.

Computerised tomography and positron emission tomography (PET), the earliest of such imaging methods, have largely been succeeded, for the human brain, by functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). fMRI is based on the assumption that the more active the neurons in a brain region are, the greater the blood supply required to provide them with the necessary energy. The rate of blood flow can be measured by placing a subject in a scanner and applying a strong magnetic field across his or her head. Oxygenated haemoglobin in the blood responds with a specific signal that can be measured (BOLD signal). fMRI integrates this signal over a few cubic millimetres of tissue and a few seconds of time, and the technology is steadily improving in resolution. However if this sounds impressive it is important to note that the current minimum voxel (unit of analysis) for fMRI at around 55 cubic millimetres, contains 5.5 million neurons, 22-55 billion synapses, 22km of dendrites and 220 km of axons (Logothetis, 2008)! (Logothetis suggests the ultimate limit of resolution may be some 300X300 μm^2).

Because fMRI generates so much data activity is routinely averaged over several voxels. The signalling time for neurons to communicate is of the order of milliseconds, not seconds. It follows that within this volume of many million neurons and their interconnections averaged over timespans thousands of times the length of time any one cell may be active, some cells may be excitatory, some inhibitory of others (excitation and inhibition both increase the BOLD signal). However, some neurons which active in a control condition might be inactive in the experimental condition, so the sum total of averaged activity might be zero and the brain region appear to be silent in the experiment. Further, even if an area ‘lights up’ in a particular fMRI experiment it does not mean that that area is ‘the site’ of the attribute being studied in the experiment; it could be a transient region of passage, for instance, through which neurons in one region are ‘passing on’ information to another as many brain areas become dynamically and briefly engaged in a task And finally to this list of caveats, BOLD is only a surrogate measure for neuronal activity, which can only directly be measured electrically.

It is also possible to couple fMRI with PET, making it possible to identify the brain distribution of molecules labelled with short-half life radioactivity. A further refinement, diffusion tensor imaging, makes it possible to map the great axonal (nerve) tracts that carry information between disparate brain regions (Miller, 2006). A further approach to improving understanding of the relationship between fMRI signals and brain function, favoured by some physiologists, would be to combine fMRI with single cell recording by means of implanted electrodes in monkeys or apes. (Ethical objections to the experimental use of primates in this way without obvious therapeutic purpose have been raised, notably by animal rights groups in the UK, which have successfully blocked the establishment of a primate centre in Cambridge and have challenged the building of a neuroscience research centre in Oxford,)

MEG also utilises magnetic phenomena to identify neural activity. Signalling within the brain is largely electrical, and when an electric current flows, there is a minute, but measurable magnetic field orthogonal to it. MEG provides a more direct measurement of brain activity than fMRI's surrogate of blood flow, and can do so millisecond by millisecond rather than over a longer time interval, In this, it resembles the use of the traditional electroencephalograph to measure changes in electrical activity in response to stimuli, called Evoked Response Potentials, ERP. However MEG's spatial resolution is much inferior to fMRI. The current challenge (which is partly that of solving certain complex mathematic problems) is to improve MEG's spatial resolution and then to run the two imaging systems in complementary fashion.

The results of such imaging studies, perhaps because their results can be presented in dramatic computer-enhanced false colour, have captured popular imagination and are routinely used to illustrate newspaper articles about advances in the neurosciences. However, their critics argue that they can mislead, interpreting 'silent' areas of the brain as inactive and implying that the areas that 'light up' represent the loci in the brain of particular properties, from decision making to religious fervour and 'romantic love.'

ii Stimulating the brain. The finding that signals from the brain can be detected magnetically has led to the development of a reciprocal technique: the attempt to modify the behavioural 'outputs' from the brain by focussing intense magnetic fields onto specific brain regions – Transcranial Magnetic Stimulation, TMS. Such methods are in essence a development from the earlier uses of radio receivers or electrodes implanted into particular brain regions (deep brain stimulation; in the UK some 30,000 people currently have such implanted electrodes). Focussed electrical or magnetic stimulation can produce mood changes, for instance to alleviate depressive episodes, but also transient losses of memory or disorientation. The implications and possible uses of such techniques are discussed in sections 3e and f below.

iii Cellular physiology. Dynamic imaging techniques have also become available to physiologists working with non-human subjects. For decades it has been possible to implant fine electrodes into the brain and study the electrical responses of single cells in either anaesthetised or awake (so-called 'behaving') animals. From the 1960s on this enabled visual physiologists to map the organisation of the visual cortex, with its topographically organised columns and blocks of cells responding to specific patterns or movements. In the 1970s researchers studying a particular region of the rodent brain, the hippocampus, found that if a train of electrical impulses was fed into the cells, they responded with a long-term change in the efficacy of their synapses. These properties can be studied both in the awake or anaesthetised animal or in thin slices of brain tissue incubated in vitro, Such in vitro preparations (along with the use of cell cultures) make more precise biochemical and physiological measurements possible.

Because the hippocampus is known to be a brain region associated with learning and memory, this phenomenon, long-term potentiation, was seized on as a physiological model of how the brain responds to and records – thus 'remembers' – new information. Extensive analysis of the cellular, pharmacological and molecular mechanisms of this phenomenon over the subsequent thirty years has provided important insights into the biochemical, structural and physiological processes involved in remodelling brain circuits in response to novel experience, often called 'memory'. More recently these insights

have been enormously enhanced by the availability of new forms of single photon confocal microscopy. Neurons maintained in tissue slices or in cell culture can be loaded with light sensitive dyes that respond to the flow of ions such as calcium into specific regions of the cell in response to electrical or pharmacological signals. Digital recording enables this flow to be tracked over milliseconds, and for the biochemical mechanisms of such cellular responses to be studied even at the scale of a single synapse.

iv *Smart pharmacology.* It is above all in the context of pharmacological research that classical neurophysiology begins to intersect with the new cellular, molecular and even genetic sciences. Transmission of signals within an individual neuron, from its dendrites across its cell body and along its axon, is essentially electrical. By contrast, communication between neurons across synaptic junctions is (with small exceptions) chemical. Neurotransmitters, released from the pre-synaptic side of a junction between two neurons, cross the short extracellular space to the post-synaptic side, where they bind to receptor proteins, in turn altering the electrical signalling properties of the second cell. There is a wide variety of such neurotransmitters, though each specific functional ensemble of neurons specialises in but one or two from the range. Glutamate, acetylcholine, serotonin and gamma-amino-butyric acid (GABA) are amongst the commonest. Whereas it was once thought that each neurotransmitter interacts with but a single type of receptor, it is now clear that there are many different types and sub-types of receptor for each – several dozen for glutamate for example.

To add to the complexity, circulating in the fluid-filled space between the neurons there is a range of other molecules (neuromodulators), including growth factors, steroid and other hormones that can modulate the effect of the neurotransmitters. These varied mechanisms provide each post-synaptic neuron with exquisitely sensitive ways of discriminating and responding to inputs. They have also in recent years provided a new focus of activity for pharmacology. Virtually all psychoactive drugs work by interacting with, enhancing or diminishing the effectiveness of particular neurotransmitters, by altering the efficacy of the enzyme systems that synthesize or degrade them or interacting with receptor proteins or other neuromodulators. Aricept and Rivastigmine, used to treat

cognitive decline in Alzheimer's disease, work to boost the effectiveness of acetylcholine in the hippocampus. Prozac and related drugs are SSRIs (specific serotonin reuptake inhibitors) intended to boost serotonin levels in the treatment of depression. Benzodiazapines interact with the inhibitory neurotransmitter GABA. Genetic and protein sequencing techniques enable the structures of individual receptors to be determined, and thus make it possible for pharmaceutical companies to engage in the rational synthesis of molecules designed to interact precisely with specific receptors ('smart' drugs) rather than the older generations of more general purpose psychochemicals like monoamine oxidase inhibitors or barbiturates.

v Human genetics. The rapid advances in human genetics since the success of the Human Genome Project (HGP) in completing its draft of the human genome have inevitably helped focus attention on genetic variation associated with neurological and psychological disease (although the distinction between the two has been greatly weakened through the integrative programme of the neurosciences). A small number of neurological diseases are directly attributable to mutations in single genes. The best known example is probably Huntington's disease, an autosomal (ie one in which the gene variant does not lie on one of the sex chromosomes, so its effects are not limited to either sex) dominant (ie one copy of the errant gene is sufficient for the disease to manifest itself) condition. The mutation results in irreversible neurological degeneration, generally manifesting itself in a person's middle years. The gene, the variations in its sequence which result in the disease and affect its severity, and its protein product have been identified. In most neurological disorders however the genetic association is much weaker. Alzheimer's disease is an example; some 5% of cases are familial, early onset and associated with a specific gene mutation. In the remainder, although there are a number of predisposing genetic risk factors (notably the gene variant *ApoE4*) these are not strongly predictive.

The situation with conditions like depression and anxiety is even less certain; there are claims that variations in the sequence in certain genes might predispose alternatively to depression or anxiety, depending on the variant. More contentious are the claims, largely

based on more traditional genetic methods such as twin and family studies, that a wide range of human behavioural traits, from intelligence to anti-social behaviour, are under varying degrees of genetic control. These are discussed in more detail in section 3e below.

vi Molecular genetics and molecular biology. A major contribution to basic neuroscience has however come from the rapid development of techniques for adding, subtracting or modifying genes in laboratory animals, notably the mouse. Thus genes coding for specific proteins can be 'knocked out' such that the animal develops from conception in the absence of the enzymes or receptors for which the genes code. This enables animals to be 'constructed' to test hypotheses about the roles of these particular substances in brain development and behaviour. Alternatively gene variants (alleles) associated with particular human disorders can be 'knocked in,' so that 'humanised' mice can be created containing the Huntington's allele, or variants of the several human mutations associated with risk factors for Alzheimer's disease. Indeed mice with almost any specified gene modification requested by the researcher can now be purchased off the shelf from specialist companies, This may soon become possible for other laboratory species, such as chicks, as well.

The early excitement surrounding the use of such animals however was quickly tempered by the recognition that just how the modified creature developed and behaved was not readily predictable. Thus it seems to depend not just on the specific gene targeted but also the particular strain of mouse used and indeed the laboratory context in which it was bred and reared. This presented the researchers with a timely reminder of the intimate interactions of genes and environment during development that should have come as no surprise. The plasticity of the brain during development means that if one particular protein is absent the production of others to at least partially replace it functionally can often be enhanced. Hence the general move amongst developmental biologists away from studying specific genes to epigenetics – the study of gene expression during development as a function of interaction with the environment. Epigenetics thus focuses on the

complex regulatory processes whereby cellular factors at many levels control which DNA sequences are read and interpreted at any moment during development.

Newer molecular tricks avoid permanent knocking out a particular gene in all body and brain tissues from conception onwards, but instead temporarily inactivate it ('silenced') in a particular brain region, such as the hippocampus in the adult animal. Specific gene targeting by this and other methods is a rapidly developing field. Combined with molecular pharmacology and cellular physiology, it offers the prospect of sharper insights into regional localisation, synaptic function and the molecular systems underlying behaviour.

vii Neuroinformatics. The ever-increasing torrent of data flowing from the neuroscience labs, notably but not exclusively from the imagers, has led to increasing concern over how the data can be managed and integrated to enable consensus understandings to emerge. There have been proposals for a 'Human Brain Project' (sometimes called 'the neurome') to match the earlier Human Genome Project, but the goal of any such project is far less clear than the much simpler task (at least in retrospect) of building sequencers and solving the data handling problems required for the international collaboration of the HGP. However a number of attempts in this direction have been proposed, are under active consideration or development, and these are bound to expand in the coming years.

viii Human –computer interfaces. There is nothing new in the idea of prostheses to rectify sensory deficiencies or enhance performance. Spectacles, telescopes and microscopes have been available for centuries. But the rapid development of information technology, the miniaturisation of components and the parallel increase in the detailed mapping of sensory and motor functions to specific brain regions has led to increased speculation about the prospects of internal as well as external prostheses. Once again, the implications of these developments are discussed in section 3g below.

b. **The intellectual landscape.**

It would be encouraging to be able to claim that a combination of the new technologies, the expansion of the neuroscientific workforce and the input of funding from state, charitable and commercial sources had paid off in terms of a radical transformation of our understanding of brain processes and their links to mental activity and behavioural outcomes. However, that transformation still lies ahead of us, part of the necessary theoretical and experimental work of the coming decades. In this section I briefly survey the emerging knowledge claims of the neurosciences, summarising both problems and prospects.

Bridging levels. Progress in relating brain processes to function at all levels, from that of brain systems to the molecular and cellular, has been substantial. The multiple visual systems involved in analysing signals originating in the retina and integrating them to provide coherent percepts have been explored in great detail, as have the motor pathways through which intentional action occurs. Imaging studies, in both 'normal' and functionally-challenged or brain damaged individuals have pointed to the role of the hippocampus in memory. Similarly, the regions of the prefrontal cortex active when a person is making decisions or value judgements have been identified. The molecular and cellular mechanisms involved in the modulation of synaptic connectivity believed to underlie learning simple tasks have been identified in species as varied as sea slugs, chicks and mice.

Integration remains a major problem. Long-standing dichotomies (neurological/psychological; nature/nurture; cognition/emotion) deriving from long-standing philosophical debates within the history of Western thought, still obstruct new thinking. Approaches to the brain still reflect the problematics and methodologies of the parent disciplines that have come together to constitute the neurosciences. A common language masks radically different understandings. For example, a well-received textbook on learning and memory written by a leading molecular neuroscientist shares almost no common point of reference to one with a similar title written by an eminent

neuropsychologist. Bridging the gaps, conceptual and methodological, between molecular, cell and systems level neuroscience is a major task for the years ahead. A hard-line reductionism still characterises the former, implicit for example in the title of the 'Society for Molecular and Cellular Cognition' formed a few years back.

Cognition and emotion. Many psychologists would still resist such a removal of the concept of cognition from the realm of the organism to that of the molecule. Some cognitive neuroscientists have become enthused by the belief that the way forward in the understanding of brain processes is by way of computer simulations and the modern avatars of what was once optimistically called 'artificial intelligence' (Churchland and Sejnowski, 1992). By contrast, and importantly, the older view of the brain as an essentially cognitive machine has been powerfully challenged. A richer understanding, based both on data from pharmacological and imaging studies and evolutionary arguments, has insisted on the importance of affect – emotion - in shaping thought and action (Damasio, 2003). Because emotions are extensively modulated by bodily processes outside the brain, such as levels of circulating hormones and immune status, new double and triple-barrelled research fields – neuroendocrinology and psychoneuroimmunology (Adler, 1991; Booth and Pennebaker, 2000) are becoming of increasing interest in our understandings of both health and disease.

Beyond the homunculus. Earlier, more simplistic thinking about brain processes assumed that the brain was a collection of mini-organs, 'centres' for vision, smell, pain, memory, emotion, etc. All of these were supposed to report 'upwards' to some integrative site, perhaps in the frontal cortex, (a 'homunculus') which in turn functioned as a command centre for appropriate motor and other responses. It is now clear there is no such homunculus. There are regions of the brain responsible for discrete aspects of information processing, language, computation and even value judgements, steadily being revealed by imaging methods. These observations contribute to the long-standing paradox by which function in the brain seems to be simultaneously localised and delocalised. A recent study, for instance, found that different mathematical operations engaged initial activity in different brain regions, before converging on a common

pathway (Nieder, Diester and Tudusciuc, 2006). The visual cortex contains some thirty or more distinct cell ensembles, each responsible for one aspect of feature detection – motion, colour, shape, direction, angle, etc. (Zeki, 1993). Yet for most of the time, as individuals, we retain a coherent unified sense of conscious awareness.

Consciousness and the binding problem. How conscious awareness (Consciousness, that is, in the restricted sense of being the obverse of unconsciousness; awake and attentive rather than asleep (Koch, and Crick, 2004)) is achieved is a major theoretical issue – called the 'binding problem' the subject of much discussion over the past decade (Singer, 1998; Freeman, 1999). It is clear that all the many brain regions involved are linked together spatially by multiple pathways (called re-entrant because they run in both directions between the regions: Edelman, 2004). However, it is also possible that they are linked temporally as well as spatially. Neuronal ensembles (ie functionally related groups of neurons) in separate brain regions, if they are all active at the same time, will generate coherent electrical oscillations whose frequency may also help generate a unified awareness (eg Canolty et al, 2006). It is this awareness that some neuroscientists regard as the substrate of consciousness. How far this rather narrow definition of consciousness will satisfy a less reductive understanding of the term remains to be seen (H Rose, 2004). (My own view is that consciousness, mental activity, the sense of selfhood, etc. transcend brain processes; one needs one's brain to be conscious in the way, analogously, that one needs one's legs to walk. I haven't the space to develop this argument further here).

Developmental neurobiology. One of the least well-understood aspects of neurobiology – as it indeed is of more general areas of biology – is that of development. How, in the period from conception to birth does the brain emerge, do its 100 billion neurons differentiate and migrate to their appropriate regions in the complex array of mini-organs that constitute the developed brain? An indication of the scale of this process is given by the simple calculation that were it to proceed evenly from conception to birth, rather than as it does in actuality, in a coordinated series of growth spurts, new synapses would have to be created at the rate of 30,000 every second under every square centimetre of cortex.

Surprisingly, such development involves a huge overproduction of neurons and their synapses, and as the brain matures a process known as apoptosis – programmed cell death - occurs, through which cells and their connections are pruned in response to environmental contingencies and experience. This phenomenon, sometimes seen as a form of Darwinian competition and sometimes as a Kropotkin-like cooperative process, seems essential for the development of a fully functioning brain (Purves, 1994). It is here that there are great hopes for the contribution of epigenetics, and the elucidation of the host of control factors that regulate gene expression. Several of the guiding factors that help steer growing axons from their neuronal origins to find their target organs, and the gradients of signalling molecules that ensure that this is an ordered process, have recently been discovered.

Autopoiesis and Evo-Devo. How much of this process is specified by the passive unrolling of a genetic 'programme' and how much is an active response of the developing organism to environmental contingencies? Indeed is such a dichotomy even helpful or do we need new ways of thinking about the process (sometimes discussed as autopoiesis or developmental systems theory; Oyama, 2000)? Advances both in genetics (including the use of variously engineered mice) and developmental neurobiology have now begun to cast light on this hitherto mysterious process. Further insights will come from advances in what has come to be known as 'EvoDevo' – the integration of evolutionary, genetic and developmental theory. One of the less expected findings from the HGP and related sequencing projects has been the remarkable similarity in their genes between different species. For instance, humans and chimpanzees share some 98.4% of their genes. Some specific gene differences between the two species have been identified but their significance is not well understood. What distinguishes humans from chimpanzees occurs during development, and the ways in which the expression of these genes - that is, their utilisation by particular cells at particular times in the synthesis of proteins - is regulated. Development is shaped both on environmental contingencies and the actions of a relatively small number of regulatory genes - genes that control the expression of others (Carroll, 2005). It is this that must account for the much greater size of the human brain, especially its prefrontal cortex. The role of these regulatory genes in brain development is

now under intense investigation, This has led in turn to a new emphasis on brain plasticity – that is, its capacity to modify connections and outputs in response to experience. The importance of such a developmental perspective to the understanding of the adult, long understood by child psychiatrists, is increasingly coming to the attention of neuroscientists as well.

Learning and Memory. Plasticity is not confined to the developing brain. Adults too modify their behaviour as a result of experience, and record and recall that experience in the processes called learning and remembering. Learning involves creating new synaptic connections or modifying older ones (Rose, 2003), and perhaps too, the birth of new neurons. A now famous study of London taxi drivers showed that learning their way around the notoriously irregular London streets was associated with increases in regions of their hippocampus (Maguire et al, 2000). However, although the hippocampus may be required for new learning to occur, memories do not 'stay' there but are dynamically and spatially reorganised through many brain regions – another brain paradox that remains to be resolved.

Social neuroscience. The reports that in apes as well as humans there are neurons or brain regions that respond not merely when an individual performs a particular action but also when he or she observes another performing a similar action (so called 'mirror-neurons;' Rizzolatti et al 2007) have drawn neuroscientists' attention to the fact that humans are social animals, Our brains have evolved to enable us to survive in social context not to solve abstract chess problems. This in turn requires that we can recognise others as having intentions, emotions and desires analogous to our own – a so-called 'theory of mind' that may be lacking in brain-damaged or autistic individuals (Happe and Frith. 1999) A whole new field of 'social neuroscience' is being created, studying the brain events involved in recognising and responding to others feelings and emotions (Cacioppo et al, 2006). Most of these studies utilise fMRI, and are based on presenting subjects with 'toy' problems – 'quandaries' involving making moral judgements considered to reflect emotion, empathy, distributive justice and so forth – even 'romantic love' (Zeki 2009). These attributes are then given brain 'locations' via the fMRI measurements – sometimes

disparaged as a sort of 'internal phrenology'. Both the nature of the quandaries and the statistical methods intended to identify brain sites have been sharply criticised. (Appiah, 2009; Rose and Rose, 2009; Vul et al, 2009).

3. Specific Prospects

a. Recovery of function

Damage to the nervous system occurs from many causes – injury, disease, genetic variants – and at many levels, from the peripheral nervous system through the spinal cord to the brain itself. Unlike the situation for peripheral nerves, severed axons in the central nervous system do not regenerate, and by contrast with glia and most other cells in the body, dying neurons are almost never replaced – an exception being those of the olfactory system. Circumventing these problems, and achieving brain repair, has been a major goal of neurology over many decades. Breakthroughs have frequently seemed imminent only for hopes to be dashed. Spinal cord axons do not regenerate, unlike those in the peripheral nervous system, seemingly because the glial cells that surround and nurture them in some way block the process. It has been suggested that the blockade could be overcome by the use of stem cells – cells that have not yet lost the power to differentiate. One promising line of research has been to derive such cells from the injured person's own olfactory system from which it is relatively easy to harvest them. Animal experiments have suggested that injecting such cells into the damaged region can encourage functional regrowth of axons (Li et al 2003). Such approaches are full of promise and may also hold out hopes for treating such autoimmune diseases as multiple sclerosis.

Damage to the brain itself is a different matter. Stroke, accident, or diseases such as Parkinson's result in the loss of neurons in discrete brain regions. Thus in Parkinson's disease, cells in a deep region of the brain - the basal ganglia - that use dopamine as a neurotransmitter die. Hence the use of L-dopa, a precursor for dopamine, as a therapeutic agent in the treatment of the disease. Early experiments, dating from the 1980s, suggested that injecting foetal brain tissue containing stem cells from aborted embryos might be

able to provide a source of replacement neurons that could substitute for those lost. However, this early work could not be replicated. Current attention is focused on the somewhat extravagant hopes that have been raised over the use of embryonic stem cells – that is, cells extracted from the embryo and then cultured. In the early stages these cells are totipotent – that is they can differentiate into any body tissue. Later they become more specialised (pluripotent) and finally differentiate into fully adult neurons or others of the 250 or so different cell types in the body. The hope is that such cells could potentially replace damaged and regenerate dying cell populations, and could be genetically modified to, for example, rectify the mutational errors that are responsible for such devastating conditions as motor neuron, Parkinson's or Huntington's disease (Connor et al, 2001; Wilmut and Highfield, 2006) The ethical issues surrounding the use of such cells have been vigorously debated; in the US the Bush government blocked the use of federal funds for working with them (with certain limited exceptions) whereas individual States, such as California, voted a cornucopia of funding almost in excess of what can sensibly be spent on research. One of the earliest acts of the Obama presidency was to lift the ban and release federal funding. In the UK the government has overridden ethical debate to fund the work, whereas other European countries have been a great deal more cautious. In less well-regulated societies, such cells are already being used to treat humans, and concerns have been raised about stem cell tourism (Aldous, 2008; Lindvall and Hyun, 2009))

However the ethical debate and the researching hype has overshadowed the very real technical difficulties that lie in the path of successful stem cell therapy for the nervous system. Experiments with animals have revealed problems in the collection, growth and harvesting of the cells, their delivery to the appropriate regions of the brain, and then of finding ways to control their proliferation such that they differentiate into the appropriate neurons (eg the dopamine using neurons in the case of Parkinson's), and do not migrate to other brain regions with potentially disastrous consequences. It is fair to say that none of these problems have yet been overcome, and research on humans may be at best premature. Meanwhile less ethically contentious sources of cells such as umbilical cord, or the recently discovered small pool of neuronal stem cells that persist in the adult brain,

may prove utilisable. The discovery that it is possible to transform adult cells into pluripotent ones once more (Takahashi and Yamanaka 2006) should circumvent the ethical debate whilst leaving the technical one unresolved. The hopes centred on the potential of stem cells is going under any circumstances to make their study a major growth area of cellular neuroscience over the next decades.

b. The ageing brain and Alzheimer's Disease.

Life expectancy in the developed industrialised world, is steadily increasing, and with the greying of the population has come a range of new concerns over the decline in cognitive functioning that may accompany ageing. Although neuronal cell number increases somewhat over the first decades of life, from a person's twenties on there is a seemingly inexorable decline as neurons die and are not replaced (although recent research has indicated that some neuronal regeneration does occur, especially in regions associated with learning and memory such as the hippocampus.) The space previously occupied by the now-dead neurons is filled by sprouting connections from the still living ones, and by glial cells. The significance of such a loss of neurons is not always clear. However normal ageing brings with it cognitive changes that are presumably to be associated with loss of neurons and of their plasticity. An illustrative example is that it takes more trials for a person over 50 than one aged 20 to acquire a simple learned reflex such as to blink to a buzzer that signals a puff of air to the eye– although once the reflex has been learned, it is remembered equally well in old as young.

But superimposed upon the normal ageing processes are a number of neurodegenerative diseases that result in steady loss of cognitive function and frank dementia. The best known of these is Alzheimer's Disease (AD) now recognised as the prime cause of age-associated dementia, and believed currently to affect some 20 million people world-wide. The best predictor of AD is age, with the proportion of the population affected rising rapidly over age 85. In AD, characteristic plaques of protein fragments (amyloid) accumulate in the brain whilst the internal structure of neurons disintegrates, and cells die. It is because the cell death is widespread and not localised that stem cell therapy is unlikely to be relevant, despite much hype. A small proportion of early onset AD

(around 5%) is familial, but the great majority of cases are sporadic. A number of genetic and environmental risk factors have been identified (amongst the former, the presence of the *ApoE4* allele, and being female, and amongst the latter, having had a history of head injuries). Although the genetic predictors are weak, they have helped focus on the antecedent biochemical process leading to AD, and notably the role of a specific protein, the amyloid precursor protein, whose breakdown products form the amyloid complex.

The first generations of drugs intended to alleviate the cognitive decline associated with AD are now recognised to be at best marginally palliative. Intense research in both academic and pharmaceutical labs is now underway, based on the more recent genetic and biochemical insights about the processes of amyloid production. The aim is to develop more rational therapies, either by intervening directly in some of the biochemical processes that lead to amyloid production (the amyloid precursor protein, or a group unattractively called the senilins, etc.) or by immunological techniques targeted at the plaques. It seems highly probable that over the next decade more effective drugs will appear on the market (with implications discussed in section d below). However none of those at present near to market will arrest the progressive decline associated with AD. They are aimed at diminishing its symptoms, enabling the patient to function in the community (by for instance enabling them to recall day-to-day necessities (such as where they left car keys or whether they have done the shopping) for longer periods and thus enabling a longer period of independent living. The longer-term goal must be to find ways of preventing the neurodegeneration that is characteristic of AD and similar diseases (eg frontal dementia or Lewy body disease) and to enable ‘normal’ ageing to occur.

c. New psychopharmaceuticals and pharmacogenetics

One of the chief hopes for practical outcomes from the Human Genome Project was that it would aid in the development of techniques for eliminating genetic diseases. Germ line therapy – that is the addition or deletion of genes in egg or sperm, thus resulting in human genetic engineering – has so far been resisted on ethical, quite apart from technical grounds. However, somatic gene therapy, that is, manipulating the genome of an

individual so as to obviate the deleterious effect of a single gene, has been seen as no more than another sophisticated form of molecular medicine. The optimism that it might prove possible to insert genes to correct for single gene disorders, even for the relatively well-understood condition of cystic fibrosis, has proved so far unfounded. Suggestions that such therapies might become available for conditions such as Huntington's have receded. As most common diseases, of brain and nervous system as well as of the body in general, are not single gene disorders but involve many genes acting probabilistically and in concert, somatic gene therapy has come to be seen increasingly as a will-o'-the-wisp.

It was hoped that population studies relating such gene variants or single nucleotide polymorphisms (SNPs) to a variety of common diseases might reveal gene-disease relationships. However this has not proved simple. The SNP studies involving large populations would, it was hoped, identify perhaps three or four genes of major effect for some commonly according diseases. But the results are much more complex. There may be many tens or hundreds of different genes, varying from individual to individual, associated with any particular disease, or each contributing just 1 or 2% to the probability of the person carrying the condition (Goldstein, 2009). This dashes hopes of using the genetic information either to diagnose or to develop new treatments.

One important issue that has arisen as a result of increases in genetic knowledge is that of prospective diagnosis. The cost of sequencing an individual's entire genome is rapidly reducing, and may soon be down to a few thousand pounds and a few weeks work. Where single gene disorders are involved, as in Tay-Sachs or Huntington's disease, it is possible to say with some certainty that the embryo or person carrying the gene will evince the disorder. This presents a pregnant woman carrying an affected embryo with an acute moral dilemma as to how to act on that knowledge. Tay-Sachs manifests itself in childhood, and few with the disease live beyond age 4. But Huntington's symptoms appear only in mid-life. It is perhaps not surprising therefore that despite the fact that genetic tests for the disease have been available for many years, a substantial proportion of those at risk prefer not take the test. Where any genetic marker is only a risk factor, as

with *Apo□4* in AD, and anyhow there are no current preventative treatments, the merits of testing seem minimal.

However, what the new genetic knowledge increasingly provides is something potentially far more tractable. Identifying genes associated, however probabilistically, with neurological disease offers a powerful new approach to understanding the proteins and biochemical mechanisms whose malfunctioning is associated with the condition. For example, identifying the abnormal amino acid sequences in the protein huntingtin in Huntington's Disease may provide a route to the design of drugs that can interact with the relevant biochemical mechanisms –though so far this is a hope rather than a prospect. Previously, drug design was focussed on the end product of the biochemical chain leading to the disorder. For instance in AD, because amongst the first cells to die are those that use acetylcholine as a neurotransmitter and project to the hippocampus, the first generations of drugs were aimed at boosting acetylcholine levels. However following the genetic studies which have illuminated the biochemical pathways leading to amyloid production, drugs can be designed to target these, with the potential of a more effective 'upstream' intervention.

Pharmacogenetics/genomics (the terms have become more or less interchangeable) is another of the much-canvassed prospects arising from the new genetics that could have considerable relevance to psychiatric disorders. One of the abiding problems in psychiatry is the inevitably phenomenological approach to diagnosis, based around successive editions of the Diagnostic and Statistical Manual and its equivalents. Physiological or biochemical markers to aid in diagnoses are largely lacking, and the SNP studies have not proved helpful. Broad-brush labels such as depression or schizophrenia may conceal a variety of different conditions. It is not appropriate here to chart the long and agonised debate on these questions over the past decade (see eg Bentall, 2003, 2009) but to point to the ways in which the new genetics might be applied. The revised DSM, DSMV is currently under preparation, though not without much debate about the role of the US pharmaceutical industry in shaping the diagnostic criteria.

Pharmacogenetics is based around to two related observations. First, not everyone treated with a drug responds to it similarly, and second, some people suffer severe adverse reactions to a drug used safely by others. The classic example is the antihypertensives, of which there are three broad categories, beta-blockers, calcium channel blockers and ACE inhibitors, with very different modes of action. Some people respond much better to one of these classes that others; some suffer sharp adverse reactions, particularly to ACE inhibitors. Could these differences in response reflect underlying genetic variations? If so genetic tests might be devised to identify which of the three classes should be prescribed and which avoided for fear of adverse reactions in individual patients.

Turning now to disorders of brain and mind, schizophrenia affects 0.5-1% of the population world-wide, whilst up to 20% of the population of industrialised countries is considered likely to suffer from depression at some point over their lifetime (women more than twice as likely than men). WHO has described depression as *the* epidemic disease of our century. Despite intense efforts over many decades, and the evidence from twin studies that there is at least a familial element in the disease, no specific single gene or genes has yet been identified as associated with schizophrenia, nor unequivocally with depression. These (insofar as they are indeed discrete disease categories rather than phenomenological descriptions covering a range of biochemically diverse situations) are at the very least multifactorial in causation.

Whatever the precipitating causes of depression, the pharmacological approach has been built around boosting the efficacy of the neurotransmitter serotonin. Earlier generations of drugs worked by inhibiting one of the enzymes (monoamine oxidase) involved in its degradation. The newer group are the specific serotonin reuptake inhibitors such as Prozac and Seroxat. Despite the ambitious earlier claims that such drugs made people ‘better than well,’ the evidence is that they are little more effective than the earlier generation, although they may have fewer adverse effects. Neither class shows a dramatic gain over placebos (Barondes, 2005). Many cases of depression remit after a few months anyhow, although others are profound and seemingly intractable. Furthermore, as the numbers of individuals prescribed the SSRIs has increased steadily, adverse reactions that

were not apparent in the earlier small-scale trials before the drugs were licensed for use have become apparent. Notably, both SSRIs have been associated with increases in violent behaviour or suicide in small but significant numbers of users. In the UK Seroxat has now been banned for use with children and young persons under age 18. This has hastened the search for potential genetic markers that might indicate in advance who would benefit and who might be harmed by the drugs.

Pharmacogenetics has been seen as the great hope for a pharmaceutical industry beset by problems – the expiry of patents on existing drugs, the huge and increasing costs of bringing new drugs to market, and indeed the lack of new products in the pipeline. Whilst the initial prospect of bespoke tailored drugs designed around each individual's unique genome has faltered in the face of economic reality, there are grounds for optimism that some at least of its potential will be realised over the coming decades. The economic and health benefits of at least a broad screening of individuals for relevant genetic markers (if such could be identified) before prescribing in conditions such as depression are likely to be considerable, despite the well known problems of false positives and negatives associated with such screening.

d**. Cognitive enhancers**

One of the – originally unintended – consequences of the development of drugs aimed at boosting attention and memory in AD, or improving emotional tone in depression, has been the prospect of their use by a much broader range of the 'normal' population to enhance performance or increase happiness. Of course the use of psychotropic agents – from mescaline, opium and coca to alcohol and tobacco - has a history stretching back to the dawn of human society, but the newer drugs claim to provide a much more targeted boost – witness the enthusiasm over the claims for Prozac as an all-purpose happiness provider (Kramer, 1994).

Similarly, the use of caffeine, and more recently amphetamine, to enhance attention and alertness and so aid cognitive and creative work are well established. But could a drug be developed that would directly improve learning and memory retention – a 'smart drug' or

'nootroopic?' Such a drug might have a wide potential market, from students studying for exams to the general population of over-50 years olds that some US diagnosticians claim are suffering from mild cognitive impairment. In a competitive society cognitive enhancers can be seen, as one book of advocacy claims, as providing a crucial 'competitive edge,' and claims that many such potential agents can be found in the official or parapharmaceutical formularies can readily be found, although few if any can meet the criteria set by evidence-based medicine (Rose, 2002). According to a survey in *Nature,* many of its readers have at least tried such agents. (Maher, 2008)

Research on the molecular mechanisms involved in memory formation, and on treatment for the cognitive decline in AD, has converged to generate a range of new candidates. Drugs such as aricept and rivastigmine, designed to boost acetylcholine transmission in AD, or memantine, which affects glutamate neurotransmission, have been seen as possible cognitive enhancers, However there are a sufficient number of adverse reactions to these substances that they may not seem attractive in a non-clinical context. But elucidation of the molecular cascade leading to synaptic modulation during memory formation has pointed to molecular alternatives. One possibility would be substances that mimic the normal role of the amyloid precursor protein, or neuromodulators such as Brain Derived Nerve Growth Factor.

In the US two biotech. start-up companies, formed by rival memory researchers, focussed on a substance with the acronym CREB, which is intimately involved in the mechanisms of gene activation required for the protein synthesis that memory formation demands. Another company has focussed on ampakines – a class of molecules that enhance the efficacy of a particular group of glutamate receptors. It is fair to say that none of these are yet judged to have been effective in enhancing human memory in the ways that their advocates had hoped despite the fact that all of these substances (and a number of others touted as candidates) enhance memory retention for standard behavioural tasks in laboratory animals. The future of the start-ups remains uncertain. More importantly, the types of human memory that we may wish to see enhanced may be more subtle than simply decreasing the number of trials required for a mouse to swim a

maze – the standard learning task often used, However, as research in this field is moving rapidly it is highly likely that effective agents will become available over the coming decade, if only as a spin-off from AD research. In this case their more general availability may present interesting ethical, legal and social dilemmas.

Meanwhile, there had been a converse spin-off from this memory research. An older but ignored research finding, that re-evoking memories makes them labile once more to intervention, has taken on a new lease of life. Laboratory animals, trained on a specific task, can be made to forget it if they are presented once more with the task situation and given drugs that block glutamate receptors or CREB. This finding has led to suggestions that such amnestic procedures might be of help in treating people suffering from post-traumatic stress disorder. This may have been an almost science fiction-like proposal a decade ago (as in such movies as *Eternal Sunshine of the Spotless Mind*). Today both academic and biotech labs, especially in the US, and with the active interest of the military, are actively researching the possibility, and as is the case with the cognitive enhancers, a lively ethical debate on their implications has been opened.

e. The neuroscience of social control

My choice of title for this section may seem unduly provocative. It is occasioned by my own concern over the proliferation of disturbing classifications in the Diagnostic and Statistical Manual. An increasing number of disagreeable or undesirable forms of human behaviour, once regarded as eccentricities, indications of poor upbringing or schooling, or even of moral turpitude, are being considered diseases, of neurological and perhaps genetic origin, for which psychopharmacological treatment may be appropriate. Novel categories are appearing. Some such as autism and Asperger's Syndrome may simply previously not have been recognised, or if recognised, not named as such. Diagnoses such as attention deficit hyperactivity disorder (ADHD), conduct disorder, oppositional defiance disorder, disruptive behaviour disorder, panic disorder, appear to be on the increase (along with depression and anxiety). Some have argued that the labelling of a disorder provides both the labelled individual and those around him or her with a script, a way of describing themselves which in the process becomes 'real.' (Hacking, 1998).

ADHD is a diagnosis increasingly commonly being given to children who, in one educator's description 'disturb their parents and teachers because their classroom performance is erratic.. never seems to be in his or her seat…constantly bothering classmates…' (Cooper, 2004). The diagnosis has been common in the US since the 1980s, with a quoted incidence of as many as 8% of US schoolchildren, most commonly boys aged between 8 and 13. UK child psychiatrists now accept an incidence figure of around 1%, compared with less than a tenth of this in the 1980s. Australian figures are said to approach those in the US. The accepted treatment is the amphetamine-like drug Ritalin, which interacts with dopamine receptors and is said to produce a calming effect, enabling the child to focus more in the classroom. Prescriptions for Ritalin have increased a hundredfold in the UK since 1991. As Ritalin can also act as a cognitive enhancer in 'normal' children a lively playground market for the drug has developed, according the US FDA. Whilst for many years Ritalin has had the ADHD market pretty much to itself rival agents (Adderal, Strattera) are also available, though the latter has been linked with severe adverse reactions such as suicide attempts.

Is ADHD a disease, and if so why is it on the increase? Despite some weak claims for a genetic link, there are no biochemical tests that can detect the condition and its diagnosis, in the vast majority of cases, is entirely based on educators' and parents' accounts of the child's behaviour and response to the drug. This drug response was once thought to be anomalous, but is now recognised as no different from that of 'normal' children. What is clear is that we are moving into a world in which psychopharmacological adjustment of an individual's behaviour to fit within prescribed norms is becoming common and can only become increasingly so with advances in the sophistication of the available pharmaceuticals.

As with the cognitive enhancers, one question that needs to be asked is whether it matters? Except insofar as the drugs may have long-term undesirable consequences for the individual (and the long-term effects of routine use of psychoactive drugs on the

developing brain are scarcely surprisingly, little understood), does such pharmacological enhancement differ in principle from the use of spectacles to correct short-sightedness?

A related example is that of addiction, a matter of major political and social concern in many countries, and said to be reaching or even at epidemic proportions (although the concept of addiction especially in the broader way in which it is often now used, is not entirely clear-cut). The question of why people take mind-changing drugs or alcohol could be approached at many levels, political, social, cultural and psychological. One)to my way of thinking excessively reductionist) neuropsychological approach has been to speak of an 'addictive personality,' itself the consequence of having certain predisposing genes. In this way of thinking, which particular addiction – cocaine, opium, alcohol, even shopping - becomes of minor importance. Treating addiction by replacing an addictive drug with one under medical control (methadone is the common example) has a long history, but current neurotechnological thinking is moving towards the possibility of creating vaccines against the drug, thereby blocking its effects, and thus presumably the craving which it induces (Lingford-Hughes and Nutt, 2003). This too is an expanding research field, to the detriment, perhaps, of more social explanations.

f. Brain imaging and prospective diagnoses.

The advent, first of CT, then MRI scanners, served as the basis for a major leap forward in diagnostics, making it possible to detect the sites of the brain lesions arising from disease, stroke or injury (although as is so often the case with modern medicine, treatment lags well behind diagnosis). The use of fMRI in a number of specialist laboratories has also pointed to the involvement of specific brain regions in more subtle functional deficits in memory, reasoning, affect and decision-making. As the use of such imaging techniques becomes more widespread, however, other prospects have come under serious consideration. Could imaging, for instance, make possible prospective diagnosis, not just of disease but of other disturbing features such as 'personality disorder' or psychopathy? There have been claims that there are differences, detectable by imaging, between the brains of convicted violent murderers and those of 'normals.' Under current legislation prospective detention in the absence of criminal action is not

normally permissible, although in the current ‘war on terror’ and much to the concern of civil libertarians, this principle is being eroded both in the US and UK. However, in the aftermath of a number of high profile cases, changes in legislation have been contemplated by successive UK Home Secretaries, and some forensic neuropsychologists have argued for the use of imaging techniques to identify such individuals (Raine and Sanmartin, 2001). This is but one example of the way in which findings and techniques from the neurosciences are beginning to find their way into legal procedures, discussed further in the final sections of this report.

Imaging techniques are also now being considered as a potential improvement on the classical – and not very reliable - lie detectors. In laboratory experiments using fMRI, it is said to be possible to distinguish the brain signals associated with true versus false memories and deliberate versus inadvertent lying. An alternative imaging technique, the measurement of evoked response potential, has been proposed by one company in the US under the name of ‘brain fingerprinting.’ The company website (www.brainwavescience.com) claims both that the technique has been used to as evidence of the innocence of an individual in a court case, and also that it could indicate whether a person was a terrorist or had been at a terrorist training camp.

On a somewhat less disturbing note, imaging techniques are also finding their way into the commercial world. Advertisers and marketing agencies have been investigating the brain signals associated with brand images, so called neuromarketing (or, sometimes, neuroeconomics, the study of the brain regions involved in the making of economically rational choices). Car manufacturers seem particularly keen to exploit the new techniques, and both Ford and DaimlerChrysler have begun to use scanning to check the impact of their products. DaimlerChrysler has even established a lab (MindLab) in Ulm, in Germany to carry forward the work using fMRI, whilst in the US researchers are investigating the neural processes involved in choosing between Coca- and Pepsi-Cola.

g. Prosthetic implants

The most significant advances over the next decades are likely to come from the coupling of information derived from such imaging techniques with the development of prosthetic implants to circumvent sensory or motor deficits. Cochlear implants to treat certain forms of deafness have been readily available since 1984.There are said to be some 37,000 people with such implants currently in the US. Deep brain stimulation by implanted electrodes to alleviate symptoms of Parkinson's disease, essential tremor and possibly depression are already available; 30,000 people have such implants in the UK.

Implanted electrode arrays in the visual cortex, enabling some limited vision to people whose blindness is a consequence of retinal or optic nerve damage, have been seen as a potential output by visual neurophysiologists since the 1980s.Only recently, however, with miniaturisation of components, are they beginning to become seriously practicable. Some successes have been claimed. At the minimum it should be possible to enable those with such forms of blindness to detect light and dark, form and movement. Similarly, electrode arrays in the motor cortex are being devised which will detect 'intentions,' and translate these into the required act, so enable quadriplegic individuals to move and control their limbs or to control a cursor on a computer so as to communicate. To date, such developments have focussed on the obvious input and output systems – sensory and motor. But as imaging studies increasingly identify regions associated with so-called 'higher' functions – cognition, affect, memory, decision-making, one can envisage the development of direct brain-computer interfaces for ever wider aspects of human thought and action. This is the prospect that has encouraged thoughts about 'cyborgs' and a flourishing speculative field named by its enthusiasts as 'transhumanism.' (www.transhumanism.org).

h. New military technologies

It is well known that from the very birth of science, military needs and goals have proved a powerful stimulus for advance. Whilst the most obvious beneficiaries of military largesse have been physics and chemistry, the biologists too, and amongst them neuroscientists, have found themselves the focus, and often the initiators, of military interest. This interest sharpened significantly since, in the aftermath of the attacks on the

World Trade Centre in New York in 2001, several western governments have declared a 'war on terror.' Two further neologisms have appeared –on the one hand bioterrorism, and on the other, biosecurity, and both have opened a cornucopia of research funding, notably in the US.

One long-standing area of military interest has been the use of neuro- and psychochemicals. The fear is the availability of the highly toxic nerve gasses (as in the release of sarin into the Tokyo subway system by the Japanese cult Aum Shinrikyo in 1995), or, of course, infectious organisms or toxins such as anthrax or botulinus. The prospect is the use of drugs to enhance the performance of ones' own troops or disorient the enemy. The interest of the CIA in LSD in the 1960s and 70s has been extensively documented as has been the use of stimulants such as modafanil by US pilots on long bombing missions in the recent Gulf wars. Less well known has been the scale of research in the US, Europe and Russia, on new generations of neuroactive agents, known in the trade as 'calmatives,' to replace earlier generations of 'non-lethal' agents such as the tear gasses,. The intended function of these substances is to produce temporary incapacitation by affecting sensory and or motor systems but without lasting adverse effects. The development of such substances came to public attention in 2002 with the disastrous attempt by Russian special forces to release hostages held in a Moscow theatre. An opiate-like gas, probably fentamine, was pumped into the theatre, and many hostages died as a result. Related agents have been reported to have been used by the Israelis in their recent attacks on Gaza `and Lebanon (Hay et al 2006).

The new neurotechnologies are also reinvigorating the military's long-term interest in surveillance techniques. The patents taken out over recent years in the US on work funded by DARPA – the Defense Advanced Projects Agency –gives some indication of the goals and directions of such research. The general intentions are to be able both to read and interpret internal brain states at a distance, via, for instance, skin implants and transcranial magnetic stimulation, to be able to communicate directly to one's own forces, and to disrupt those of one's opponents. DARPA has let contracts to study the use of such techniques to fight fatigue in pilots, and also to develop systems for 'disorienting

the behaviour patterns of military or diplomatic personnel.' As one example of a wide range of such initiatives, in 2001 the USAF claimed 'it would also appear possible to create high-fidelity speech in the human body, raising the possibility of covert suggestion and psychological direction… If a pulse stream is used, it should be possible to create an internal acoustic field in the 5-154kH range, which is audible. Thus it may be possible to "talk" to selected adversaries in a fashion that would be most disturbing to them.' (McMurtrey, 2003)

In the current political climate, it must be assumed that research on both psychochemical and psychophysical techniques of this sort is likely to be pursued in a number of countries with strong military interests.

4. Ethical, legal and social aspects and initiatives

It is clear that advances in the neurosciences are raising both hopes of new insights into the human brain and by extension the mind, and treatments for devastating and previously intractable conditions. However at the same time they raise concerns over issues of how the new technologies are to be controlled and regulated. Are there some developments that should be legislated against or banned as too dangerous or because they give rise to severe ethical and moral dilemmas?

The immediate precedent against which these issues are discussed is that of the Human Genome Project and related advances in genetic technology. Early in the international collaboration of the HGP some 5% of its budget was allocated for what became known as ELSI /A– Ethical, Legal and Social Implications/Aspects. Issues around human genetic engineering, cloning, the legitimacy of using embryonic stem cells and many others came under discussion. Several research programmes built a bioethicist into the research team, and in many countries national bioethics councils with varying remits and compositions were established. It was natural therefore that as comparable issues began to emerge from the neurosciences and neurotechnologies that these too should come to be considered by the same bodies. However, perhaps anxious to differentiate themselves, the specialists

began to call themselves neuroethicists. There are now, mainly centred in the US, both departments and journals of neuroethics. Stanford University for example, has a research programme and student courses in neuroethics, and the is a recently established Neuroethics Society (Iles and Bird, 2006)

As well as the emergence of such specialisms, there have been a variety of attempts to engage in a wider debate with the lay public about the potential prospects and perils of the new brain sciences. These are variants of the citizen's juries, technology assessment panels and deliberative democracy methodologies that have been explored in recent years. One example was a project emanating from the King Baudoin Foundation in Belgium and part funded by the European Union. Called 'Meeting of Minds,' it enrolled citizen panels in 9 European countries, who met with experts both nationally and in general assemblies over a two year period. The final report and set of recommendations was presented to the European Parliament in February 2006 (www.meetingmindseurope.org.) These called for, amongst other things, Europe-wide ethical guidelines for brain research, increased funding for 'blue skies' neuroscience research, protection of privacy from imaging, and care over defining the borders of normalcy. It is not clear what impact their proposals will have on either the direction or regulation of research and development. However in the coming decades it will be important to learn from their experience and build upon them in devising methods of public engagement in the governance of science.

However and independently of the fora in which they may be discussed, the issues raised are not trivial. They have been most clearly identified by discussions in the US by the President's Committee on Bioethics and meetings convened by the Dana Foundation.. The US debates are coloured by the specificities of the federal research funding system, its lack of a comprehensive national health care system, its deregulated economy, and above all its focus on the individual rather than the community as the site of intervention and responsibility (as some of the participants in the debates have acknowledged) (Dana Foundation, 2002; Ackerman, 2006). Similar discussions have taken place in Britain

under the aegis of the Nuffield Council on Bioethics, and in Germany and France by their respective National Research Councils.

Amongst the issues over which neuroethicists have agonised, some are common to other areas of medical intervention – for instance the question of informed consent for neurosurgical or pharmacological intervention, and of the definition of death. How far should interventive techniques be used to prolong life in a person who is apparently brain-dead, or in a persistent vegetative state? Who should decide? In the US the case of Terry Schiavo became a cause célebre in this connection. Others focus on the borderline between therapeutic intervention and enhancement. Thus if the ADHD diagnosis is accepted, then treating the child with Ritalin is an attempt to restore 'normalcy,' but trading Ritalin in the school playground between 'normal' children to improve exam performance is enhancement (of course they may be many other reasons why such trading, which is said to be frequent in US schools, might occur). Treating AD with cognition enhancers is therapy, extending their use to university students is enhancement. Correcting loss of sight or audition with prosthetic implants is therapeutic, but providing such implants (were it to prove possible) to provide someone with the type of supervision or distance perception envisaged in some of the DARPA contracts would be enhancement (Miller and Wilsdon, 2006).

Some bio- and neuro-ethicists call for regulation. If cognitive enhancers are, as the press has called them, 'steroids for the brain,' then should their use not be controlled, just as steroids are for competitive athletes? But many take the view that as such distinctions are arbitrary, then there should be no limits. What after all is the ethical distinction between enhancing one's child's success at school by extra coaching and by providing a drug? If it is possible to extend life by genetic manipulation or pharmacology, then why not? (At least one bioethicist has expressed the hope that he could be engineered to live to a thousand, just as at least one prominent biologist has claimed to be willing to be cloned.) In this context scientific potential soon moves into the world of science fantasy, and the ethicists join forces with the transhumanists. Thus a classically posed ethical dilemma focusses on the availability of techniques for inserting human genes into mice. As it is

possible to create mice with the gene mutations involved in human brain disease such as AD or Huntington's, or even entire chromosomes to model Down's syndrome, then a thought experiment asks when and whether, if increasing numbers of the genes required for human brain development were so inserted, would the mouse become humanoid? Yet this ignores the fact that there are not really such specific genes; brain development requires a concert of genes within a genome responding to the contingencies of development. Mouse and human share the great majority of their genes in common and it is, as described earlier, above all their regulation and control during development that makes an embryo become a mouse or a person.

More serious dilemmas revolve around the use of brain imaging techniques, both for prediction of future outcomes, whether of specific diseases or undesired behaviours, and for the 'reading' of private thoughts. How far can and should privacy be protected in a situation in which surveillance techniques increasingly help frame our lives? If our conversations and correspondence, our financial affairs and our spending and travel patterns can be monitored, will there not be increasing pressures from the State to look inside our heads as well, and how far can imaging techniques make this possible? And if thoughts can be read, perhaps too they can be changed by TMS? It does not require much extrapolation from the present state of technology and the scope of DARPA contracts to see the need to contemplate this prospect.

Related to these concerns are the questions of legal responsibility. The legal system has long puzzled over whether a person found guilty of a crime was acting with *mens rea*–in sound mind and intentionally–or was suffering from some constraint, internally or externally generated, which diminished responsibility. Thus, in English law children are not supposed to be held responsible for their actions below the age of 10, as they are presumed not to be mature enough to distinguish between right and wrong. But even in adulthood, someone who has killed another should not be convicted of murder "if he was suffering from any abnormality of mind (whether arising from a condition of arrested or retarded development of mind or any inherent causes or induced by disease or injury) as substantially impaired his mental responsibility for his acts or omissions…". (Sedley, 2004) Under such circumstances

it would not be ‘me’ that freely performed the act; I was under instruction from my brain (what has been called neuro-essentialism), which in turn may have been impaired by any juridically accepted reason implied in the quotation above.

The law thus makes a Cartesian distinction between ‘the man’ and ‘the disease’. Based on claims that the presence of an abnormal allele of monoamine oxidase A is associated with aggressive behaviour a genetic defence, or plea in mitigation, for a convicted murderer has been attempted, though I believe, not accepted by a US Court. An analogous case revolved around whether a man who shot a number of co-workers and then committed suicide was not responsible by virtue of the fact that he was taking Prozac, known to be associated sometimes with violent or suicidal behaviour (Cornwell, 1996). But a plea of acting criminally under the influence of alcohol is not acceptable, as the courts regard getting drunk as a voluntary act for which one is responsible.

Yet if responsibility can be impaired by immaturity or injury to the brain, it must follow that ‘normal’ responsibility too is brain- and gene-dependent. A predisposition to drink, or to act impulsively and hence criminally, it has been argued, is heritable. And even were it not, to all our acts, intentional or not, there must correspond a brain state. And prior to that act, there must correspond some genetic or brain trait that determines it. Perhaps some feature of neuroanatomy or quirk of neurotransmitter or neuromodulator levels might occur, as in untreated disturbances of dopamine metabolism in childhood, which are said to predict future criminality

Neuroscientists may regard the common-sense efforts of the courts to distinguish between situations in which a person is ‘free to act’ and therefore culpable, from those in which he or she is constrained and therefore not responsible for his or her actions, as scientifically nonsensical. They create untenable distinctions which scientific advance and criminal defence lawyers will constantly seek to erode. How far legal common sense may take precedence over neuroscience is likely to remain a contested area (Garland and Frankel, 2004).

5. 'Free will' in a Neurocentric Age

These considerations lead finally to a consideration of the even broader ethical and philosophical implications of the advancing neurosciences. If, in the words of many leading neuroscientists 'I am my brain,' and my brain is an assemblage of cells wired upon according to 'genetic instructions,' albeit shaped by experience during development, what happens to 'free will,',? Much play has been made of experiments which appear to show that the brain has already 'decided' on a particular action some few hundred milliseconds prior to the person being consciously aware that he or she has made that decision (Libet, 2004). Although I think such experiments have been very much over-interpreted, they have reinforced the tendency of some neurophilosophers to hark back to a contemporary version of the 19th century zoologist TH Huxley's view of the mind as merely epiphenomenal. Famously, he described the relationship of mind to brain as that of the whistle to the steam train – generating a lot of noise but irrelevant to the main business of the engine in driving the train. 'Mind language' is dismissed in this view as 'folk psychology' to be replaced as the neurosciences advance by a more exact brain (or even computational) language (Churchland, 1995) . This essentially mechanistic view helps create the ideological climate within which much neuroscience research is conducted and theories framed – notably in many of the current discussions about the neurobiology of consciousness.

A complementary view comes from the recognition of humans as evolved organisms. Leaving aside the somewhat dubious claims from some evolutionary psychologists of a human nature 'fixed' in the Pleistocene, it is clear that certain features of human biology shape the nature of the societies we create just as those societies in turn shape the development and further evolution of our brains (for instance, the fact that our offspring are born neotenous and require many years of nurturance before they can achieve independence is a major determinant of human social relations and the social and cultural structures that surround child rearing.) To pursue these matters much further is beyond the remit of this report (Rose and Rose, 2000). What is relevant however is the conclusion drawn by some from these evolutionary perspectives: that it is possible to speak of an 'evolutionary ethics.' (Gazzaniga, 2006; Hauser, 2006) In this view, a

rational ethical code can be devised, one that turns out to be one that comes very close to the free-market individualism derived from what some see as the Judaeo-Christian traditions of western societies. It follows that advances in neuroscience, coupled with those in genetics and evolution, will help shape and improve our understanding and adoption of that code. This is the argument developed by the sociobiologist EO Wilson (1998), but disputed by many anthropologists and sociologists, who point to the wide variations in ethical and moral decisions across societies and generations, and by neuroscientists who, adopting the autopoietic viewpoint discussed above, argue that it is precisely because of the evolved plasticity of the human brain that we can create so wide a variety of societies (Donald, 2001; Buller, 2005, Rose, 2005)

6. Critical themes for the next twenty years

[NOTE:- Projecting the future in a world currently environmentally, economically and socially unstable is hazardous, For the purpose of this report, I have to assume a ceteris paribus viewpoint which in my more gloomy moments I cannot fully justify]

Neuroscience and its derived technologies will continue to be growth points both in terms of scientific understanding and as potential economic drivers over the coming decades, as UK Foresight exercises have indicated (eg Office of Science and Technology, 2005). Critical to these developments will be:-

1. ***greater theoretical integration across the various levels of the neurosciences from the molecular to the systems***
2. ***greater emphasis on the processes of brain and central nervous system development, integrating genetic and epigenetic understandings within developmental systems and 'evo-devo' perspectives***
3. ***recognition of the brain as an open, dynamic system via increased knowledge of psychoneuroimmunology, neuro-endocrinology, and 'social neuroscience.'***
4. ***advances in data sharing, management and analysis via informatics and versions of a 'Human Brain Project'***
5. ***integration of technologies, for instance, fMRI with MEG and single cell recording and enhanced real-time measurements of brain dynamics***

6. ***resolution of problems (not discussed in this report) of the increasing obstacles to innovation presented by current patenting regimes***

Significant technological and medical outcomes include:

1. ***development of human-machine interfaces, implanted chips and prostheses and methods of focussed transcranial brain stimulation***
2. ***repair of damaged spinal cord and possibly brain lesions via the use of stem cells, though not necessarily embryonic stem cells***
3. ***increased use of brain imaging techniques both for diagnostic and prognostic purposes and surveillance, for both civil and military purposes***
4. ***increased use of 'predictive' genetic testing for neurological and psychiatric disorders, raising new ethical and social concerns***
5. ***new and better targeted psychoactive drugs to treat neurological diseases such as Alzheimer's as well as depression, anxiety and related conditions, based on greater insights into these disorders through advances in neurogenetics and neurochemistry***
6. ***widespread use of 'protective' drugs to prevent neurodegeneration, along the lines of the current use of statins in regulating cholesterol metabolism and thus reducing the risk of atherosclerosis***
7. ***new generations of cognition and performance-enhancing drugs, with concomitant debates about their use and regulation***
8. ***increasingly disputed borderlines between 'normal' and abnormal' behaviour and its treatment***
9. ***greater use of neuroscientific evidence in legal proceedings , with revivals of long-standing debates over 'mad' versus 'bad' and the appropriate responses to each.***

7. Bibliography*

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