Recent Developments in Science and Medicine

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Making decisions before you know about them

Previous experiments have detected brain activity associated with a decision before a subject is conscious of making that decision. For example, in the experiments of Haynes and colleagues (Bernstein Center for Computational Neuroscience, Berlin), volunteers in the brain scanner (functional magnetic resonance imaging - fMRI) were asked to choose to press a button with either their right or left index fingers and remember the letter flashing on a screen at the time of their decision. The conscious decision to push the button was made about a second before the actual act, but brain activity seemed to predict the decision by up to seven seconds. Could consciousness be an afterthrought with no influence on a person's decisions?

Philosophers question the neuroscientists interpretations and the subject of free will is still hotly debated. Kerri Smith's expert review (August 2011 edition of Nature) of the field attracted a great deal of comment from readers. A four-year programme funded by the John Templeton Foundation in West Conshohocken, Pennsylvania will bring neuroscientists and philosophers together in a collaborative effort to identify the processes underlying conscious intention and associated brain activity. The work will attempt to distinguish what are now correlations from what could be causal connections between brain mechanisms and behaviour.

Recently, scientists (Fried, Mukamel and Kreiman, Department of Neurosurgery, University of California, LA) have taken the matter to higher resolution to investigate how self-initiated behaviour is encoded in neural circuits in the brain. They studied individuals with electrodes already implanted in their brains as part of a surgical procedure to treat epilepsy. They recorded the activity of 1019 individual neurons in 12 subjects performing self-initiated finger movements. The results show progressive recruitment of neuronal activity over one and a half seconds before the subject is aware of having made the decision to press a button. So the argument continues as to whether free will exists or whether our every thought and action is predetermined by a network of cause and effect from the past.

It is not clear how one could identify what the neurons are actually doing in their activity before we are conscious of making a decision. They may be gearing up to making the choice - will I or won't I? what if this or that? - all sorts of flip flop plasticity preceding a final decision. Haynes and colleagues could predict a left or right button choice with only 60% accuracy at best. Brain activity prior to cognizance of a decision might be a convincing argument against free will if researchers could more reliably predict what the subject had decided from their prior brain activity.

The free will/determinism controversy has significance in law where the question of how responsible a person is for his or her actions is of prime significance. People are more likely to behave morally when they consider they act out of free will. It has been reported that people behave less morally in a test where they are encouraged to think determinism is true.

I am wondering if this is another case of a need to embrace the paradox. At the level of our individual selves we have free will. But perhaps at some universal level transcending our individual selves all is ordained. Or as the philosophers say - we make rational decisions in a deterministic universe; an interplay between freedom and determinism. It reminds me of our current genome/epigenome understanding of genes and environment. The genome is the deterministic hardware - the given (genes); the epigenome results from our interaction with our environment which programmes our genes on or off in different ways in different cells and determines our health, longevity and life view and how we, as individuals, function and behave.

References

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Kerri Smith (2011). Neuroscience vs philosophy: Taking aim at free will. *Nature* 477, 23-25 (2011).

The burden of disorders of the brain

It appears that more than a third of people in Europe (164.8 million persons) suffer from mental disorders and only a quarter of these receive help. Wittchen and collaborators (Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Germany) report 12-month prevalence and disability burden estimates of a broad range of mental and neurological disorders in the European Union. The burden of mental disorders appears to have increased since 2005 but this is largely due to the inclusion of new disorders and also the inclusion of childhood/adolescence as well as the elderly. The most frequent disorders are anxiety disorders, insomnia, major depression, alcohol and drug dependence, ADHD in the young, and dementia. There is no indication of improved care which is still inadequate and subject to delays. The four most disabling single conditions were depression, dementias, alcohol use disorders, and stroke. The estimated number of people affected by major depression in the 30 countries studied is 30 million — the single greatest burden of all human diseases.

However, should all the disorders included be labeled mental disorders, are they necessarily brain disorders, and should they all be classified as diseases that urgently require treatment? The definition of mental disorder has varied widely in the past – some mental disorders, e.g., hysteria, have disappeared – new disorders constantly appear, e.g., social phobia and post traumatic stress. For some disorders, there are many contributing factors that may place them outside of the definition of brain disease. In other cases, defective brain processes are clearly responsible, as

in Alzheimer's disease. Sometimes mental anguish is temporary – it is not clear in all cases that labeling and clinical treatment with possible over-emphasis on drug treatment are required.

References

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Gene therapy – replacing a defective gene in situ

Gene therapy is the replacement of a defective gene in the patient with a good copy of the gene. The field suffered a major set-back in 1999 when a patient died from gene therapy to treat a liver disease and again a few years later when three children treated for X-chromosome-linked severe combined immune deficiency disease (SCID) died of leukaemia. (Children born with SCID lack a functioning immune system rendering them extremely vulnerable to infections.) Delivery systems have been the main problem in gene therapy and scientists have worked towards safer ways of delivering good copies of the defective gene, in sufficient amounts, and in such a way that they are retained. Recently, encouraging results have been reported by a team at the Institute of Child Health in London using gene therapy to treat a type of SCID caused by a deficiency in the gene, adenosine deaminase (ADA). Gaspar and co-workers report the introduction of good copies of the ADA gene into the patient's own bone marrow cells in culture, followed by transmission of the modified cells back to the patient. They report that 4 out of 6 children treated with gene therapy in this way have had their immune systems restored. (The other two are still being treated with enzyme replacement therapy.) Of the 30 children worldwide who have been treated with gene therapy for SCID due to ADA deficiency, none has developed leukaemia, and 21 have been able to discontinue the enzyme replacement therapy.

Other diseases are being researched for gene therapy. Patients with cystic fibrosis (associated with build up of mucus in the body) use a nasal spray to deliver the good gene directly to the lungs. It is hoped that patients with muscular dystrophy may be treated by finding some way to target the non-mutant gene in a virus package directly into muscle (currently direct injection of the normal gene into muscle is not feasible as it is not possible to do enough injections for this to work).

Another gene therapy approach is to genetically engineer the patient's own cells to specifically fight a disease. For example, Porter and colleagues (Abramson Cancer Center, Univ. Pennsylvania, USA) have succeeded in genetically engineering a patient's T cells to fight his leukaemia cells. Similar chimeric antigen receptor trials are planned against pancreatic cancer, brain glioblastomas, and a rare lung cancer called mesothelioma. Haemopoetic stem cells have also been used to produce immune T cells genetically engineered to attack melanoma in a mouse model. It may also be possible in the future to modify the HIV receptor in immune cells to treat AIDS.

All gene therapy is still in the phase of research and clinical trials but the approach holds much promise for the future.

References

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Porter DL, Levine BL, Kalos M, Bagg A, June CH. (2011). Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med.* 365:725-733 (2011).

Regenerative medicine - new body parts

Regenerative medicine is the process of generating human cells, tissues or organs in the laboratory, for the repair of diseased or damaged tissue in the body. Normally, the repair and replenishment of tissues takes place from resident tissue-specific stem cells but there may not be enough of these in the right place, and in the right conformation, to carry out the repair when tissues are injured or diseased. Scientists can harvest tissue-specific stem cells in some cases, e.g., bone marrow stem cells have been used for some time now to treat leukaemia.

Other sources of stem cells with even wider potential are being discovered. These may be coaxed to differentiate along a number of different specific cell pathways. For example, there is a move to bank cord blood at birth for later use in life as a source of stem cells for repair. Encouraging results with cord blood stem cells have been obtained with diabetes, cardio-vascular injury, brain injury and stroke, and there is evidence that the cord cells migrate to the site of injury. Olfactory epithelial stem cells have been used to successfully repair a damaged spinal cord in a rat model system and recently a trial for embryo stem cell repair of spinal cord injury was started in the States.

The most powerful stem cells are embryonic stem cells which by definition are totipotent – i.e., capable of making all tissues of the body. Stem cells similar to embryonic stem cells can be created in a culture dish by injecting cells from the patient (e.g. skin cells) with several embryonic genes that convert these cells into induced pluripotent stem cells (iPSCs). This discovery avoids the use of human embryos as a source of these most powerful stem cells.

Scientists are able to use appropriate scaffolding to mould the growth of the patients own stem cells into specific organs in the laboratory (e.g., wind pipe or bladder). In June 2011, an international collaboration enabled a successful synthetic windpipe transplant in a cancer patient. The lead surgeon was Professor Paolo Macchiarini (Karolinska University Hospital, Stockholm, Sweden). The synthetic replica windpipe scaffold of nanocomposite polymer was constructed by a team led by Professor Alexander Seifalian at UCL London, and teams from USA and Germany covered the windpipe scaffold with the patient's own bone marrow stem cells.

Regenerative medicine is an exciting new field. It has the potential to solve the problem of the shortage of organs available for patients that require life-saving organ transplantation, as well as to solve the problem of rejection (since the cells used will be derived from the patient).

Reference

Interview with Paolo Macchiarini in November 2011.

Bioartificial trachiobronchial transplantation *Regen Med.* 6:14-15 (2011).

Vaccine safety report

Following a review of 1,000 published research papers the US Institute of Medicine has published a report which concludes that vaccines are largely safe. The report, reviewed by Erika Check Hayden in the journal, Nature, addresses research on eight vaccines – chicken pox; influenza; hepatitis; human papillomavirus; diphtheria, tetanus and pertussis (DTaP); measles, mumps and rubella (MMR); hepatitis A; and meningococcal disease. The report finds rare adverse effects, viz., 'a range of infections associated with the chickenpox vaccine; brain inflammation and fever-induced seizures related to the MMR vaccine; allergic reactions to six of the vaccines and fainting or local inflammation caused by injection of any of them' but 'many only occur in children with weakened immune systems'. In many other cases where adverse effects are claimed, there was 'inadequate evidence to accept or reject a casual relationship'.

The main message is that, although vaccination can be associated with adverse effects, these are very rare and have to be weighed against the harm caused by failure to vaccinate against common diseases which may have much more devastating effects. One hundred years ago life expectancy was around 40 and many children died in infancy from diseases now almost eradicated by vaccines. In countries where vaccination is currently low, life expectancy is also low and many children die of the common diseases which vaccines prevent.

The report also concludes that there is no evidence that vaccines cause autism or diabetes. The 1998 paper by Andrew Wakefield (now struck off the UK medical register) that claimed a link between vaccines and autism was retracted last year by The Lancet. But some parents who still believe there is a connection between vaccination and autism refuse or delay vaccinations for their children, leading to outbreaks of diseases such as measles and whooping cough.

Reference

Erika Check Hayden (2011). Vaccines given a clean bill of health. Report finds 'very little evidence' of serious harm from vaccines. *Nature* August 2011.

Stress in the city

It is well known from longitudinal studies that living in cities is associated with increased levels of stress and associated increased incidence of mental illness, e.g., schizophrenia. Lederbogen, Meyer-Lindenberg and colleagues (Central Institute of Mental Health, University of Heidelberg/Medical Faculty Mannheim, Germany) have measured stress levels during different tasks in individuals from cities (>100,000 people), towns (>10,000) and from rural country environments, and correlated stress levels with functional magnetic resonance imaging to measure activity in different brain regions. They find greater stress in cities than in towns, and in towns compared to country living, and that higher stress levels are correlated with increased amygdala activity. They also find that an urban upbringing is associated with activation of the perigenual anterior cingulate cortex, a key region for regulation of amygdala activity. The amygdala has been previously associated with anxiety disorders and depression. More than half of the world's population now lives in cities, making the creation of a healthy urban environment a major policy priority.

Reference

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Making sperm from embryonic stem cells

Scientists in Japan (Hayashi, Saitou et al, Kyoto University, Japan) have succeeded in making sperm from embryonic stem cells or from induced pluripotent stem cells (made by injection of several embryonic genes into a somatic cell, e.g., skin cell). The embryonic stem cells were incubated with a combination of proteins from the preceding stages of embryonic development in a progressive fashion to the stage where primordial germ cells (PGC) are usually derived. The PGC-like cells obtained by this culture method expressed integrin- 3 and SSEA1 which serve as markers to distinguish the isolation of PGC-like cells with spermatogenic capacity from tumorigenic undifferentiated cells. The PGC-like cells created from the embryo stem cells were then injected into the testis of a sterile male mouse where they successfully developed into mature sperm capable of siring offspring.

It is possible that the technology may be used in the future to treat infertile men.

Reference

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Humans and chimps differ when it comes to sharing resources.

Humans share more equitably when sharing the spoils obtained by collaborative effort.

Hamann and coworkers (Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany) observed the sharing behaviour of children of different ages in three situations – resources obtained following a windfall, resources obtained by individual effort, and resources obtained by cooperative activity with others, e.g., situations that could be compared to 'collaborative foraging'. Children of 3 to 5 years of age will keep a windfall mostly to themselves but share more equitably resources obtained from collaborative activities. They understand that resource distribution should depend on how the resource was obtained. However, by 5 to 7 years of age, children will share equitably in all three situations, indicating that human sharing is governed by social norms of fairness. In contrast, sharing in chimpanzees, a primate relative, is not influenced by prior collaborative effort.

Reference

Hamann K, Warneken F, Greenberg JR, Tomasello M. (2011). Collaboration encourages equal sharing in children but not in chimpanzees. *Nature* 476:328-331 (2011).

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