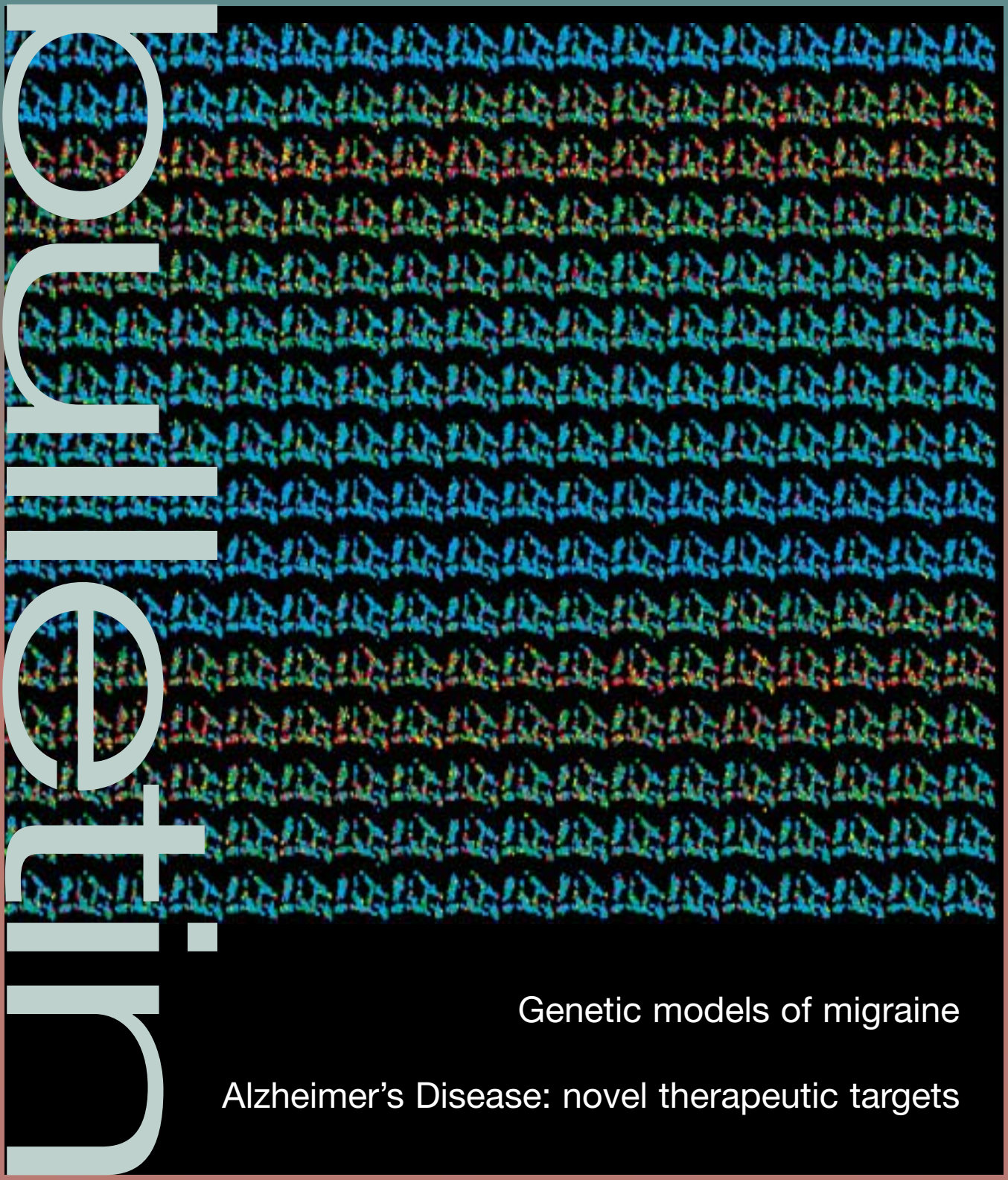
BRITISH NEUROSCIENCE ASSOCIATION

a newsletter for members of the BNA

Opinion

SPRING 2007 Issue 56



Genetic models of migraine

Alzheimer's Disease: novel therapeutic targets

INSIDE

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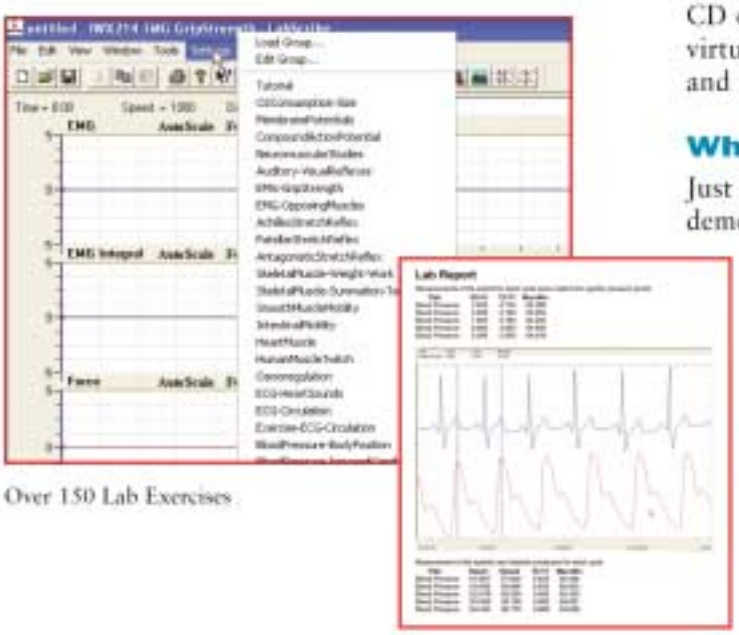

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BNA BRITISH NEUROSCIENCE ASSOCIATION
Bulletin

SECRETARY'S REPORT

DEBBIE DEWAR

● Our Christmas Symposium held at the Royal Society was, as always, well attended and very enjoyable. In addition to the wonderful science offered to us by an impressive line-up of speakers, the audience was also treated to a very striking illustration of how research can be translated into effective treatments for the devastating conditions that affect the nervous system. Mike Robins, the recipient of the BNA Award for Public Service, gave a dramatic and personal demonstration of how deep brain stimulation is alleviating the symptoms of his Parkinson's disease. Mike made the point vividly that successfully translating research through to treatment can have a profound impact on the quality of people's lives.

● As we highlighted in the previous Bulletin, translational research is being promoted by the Wellcome Trust, through their newly initiated Masterclasses in Clinical Neuroscience. At that stage it was difficult to predict what the level of interest in running these courses from basic and clinical scientists would be. However, it was clear from the response to the first call that there is a lot of enthusiasm for the scheme, with considerable interest in having BNA as the partner learned society. Proposals were submitted for a number of different clinical conditions including motor neuron disease, stroke, traumatic brain injury and autism. We look forward to supporting the first round of Masterclasses and hope that the scheme will continue in order to enhance interactions between basic scientists and clinicians in a wide variety of clinical conditions.

● By the time this Bulletin is published our National Meeting will be almost upon us. The core of the meeting is, of course, the extensive scientific programme of plenary lectures, symposia and poster viewing which the programme committee hopes will cover the interests of the majority of BNA members. However, there is a series of special events that should appeal to those also interested in the other activities the BNA aims to promote, including neuroscience teaching, winning grants and career paths for junior scientists. The Public Awareness of Science Group will host a café-bar discussion chaired by the Radio 4 presenter, Quentin Cooper. At the last national meeting in Brighton, the café-bar forum proved to be a great way of promoting lively debate while relaxing with a drink after a day at the meeting. Another special event has been organised to commemorate the 10th anniversary of European Dana Alliance for the Brain (EDAB) and will include discussions between neuroscientists and artists about how the two can interact. No doubt the free wine will help these discussions get under way. A free lunch should also be an added incentive to attend the AGM during the meeting and members are encouraged to come along if they have views about the BNA they wish to air. If you haven't already registered for the meeting, you can always come along to Harrogate and do it on site.

● I will be stepping down from the BNA Committee at the Harrogate meeting and this is my final contribution to the Bulletin. It has been a fun being on the BNA committee and I would like to thank past and present colleagues for making it one of the few committee meetings I actually looked forward to. I am delighted to hand over the tasks of introducing this wonderful publication and reporting on various BNA activities, to Colin Ingram, our new Honorary Secretary.

A montage of low resolution images of human neuroblastoma (SH-SY5Y) cells responding to nicotine using Fura-2 calcium imaging. Two responses to the same dose of nicotine are shown. Shifts to the red end of the colour spectrum indicate a rise in intracellular calcium. Such experiments are being used to dissect the pathways whereby activation of nicotinic acetylcholine receptors protect neurones from amyloid toxicity in a hunt for possible new drug targets for the treatment of Alzheimer's Disease. See Steven Buckingham review (pages 22/23)

DATES FOR YOUR DIARY: BNA EVENTS 2007

● **1st – 4th April, 2007:**
19th National Meeting, International Centre, Harrogate, North Yorkshire, in association with Neuroscience Ireland

● **9th May, 2007:**
One Day BNA-Promemoria Symposium and Workshop: Functional Cellular Neuroimaging and Microscopy, at The Open University, Milton Keynes

● **27th June, 2007:**
Controversial Issues in Neuroscience: Talking therapies – all in the mind?, a café-bar discussion at The Dana Centre, London, SW7

● **13th - 17th July, 2007:**
IBRO World Congress, Melbourne, Australia

● **4th – 8th September, 2007:**
8th European Meeting on Glial Cells in Health and Disease, at Imperial College, London

● **26th September, 2007:**
Controversial Issues in Neuroscience: Mind wars, a café-bar discussion at The Dana Centre, London, SW7

● **17th October, 2007:**
One Day Symposium: 'Bench to bedside in acute stroke: 'Finding our way' or 'Lost in translation?', University of Edinburgh

● **12th December, 2007:**
The Christmas Symposium, at The Royal Society, London, NW1

The British Neuroscience Association Bulletin is published regularly and distributed to over 2,000 members of the BNA. The views expressed in the Bulletin are the authors' own and are not necessarily the opinion of the BNA committee.

DEADLINE FOR SUBMISSION OF ITEMS FOR THE NEXT BULLETIN: Ist JUNE 2007

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INTERVIEW

Laurie Pycroft is only 17 years old yet has already made quite an impact since the founding barely two years ago of *Pro-Test*, a campaigning group supporting animal research for the advancement of medical and scientific discovery. He is clearly a very busy young man, hence the brevity of his answers, but this succinct reply to the *Bulletin* at least gives us an insight into the thoughts and aspirations of someone willing to take a stance in such an increasingly vitriolic debate.

‘I have no regrets, and the few offensive e-mails that I do get really don't bother me’

Laurie, can you tell us a little about yourself - have you always lived in Oxford? What are your interests at school? What do you hope to do at college/university in the future?

I actually live in Swindon, and have done since I was very young, before which I lived in Holland, where I was born. I'm very interested in all areas of science, especially neuroscience, nanotechnology, anatomy, pharmacology and various others, as well as computing. I hope eventually to study medicine.

What inspired you to form Pro-Test? What is the extent of this organisation now? Has its rapid growth surprised you? Alarmed you?

I formed Pro-Test as a result of the monopoly that the "animal rights" activists seemed to hold over the animal research debate. I felt it's important that people hear the facts about animal testing. The speed at which Pro-Test has grown has really surprised me, and I'm still astounded by how successful we've been.

This must be a major commitment for you now. Are you often asked how you find time for your schoolwork? What do you say to this?

I'm actually not attending school at the moment- I'm taking some time out to get some real-world work experience and to concentrate on working with Pro-Test.

You have clearly mobilised much support for animal research. Do you feel satisfied? Is there more you would like to achieve? Is there an 'end-point' to your campaign?

I'm very glad with all that Pro-Test and other advocacy groups have achieved over the last year in the animal research debate, and I just hope that we are able to carry on spreading the truth. I don't think that there is a real end-point where Pro-Test is concerned, but eventually I do hope to take a more hands-off role, so that I can engage in advocacy of other issues.

Do you have any regrets? How are you coping with the abuse from those opposed to your views? Has your family been involved too? Are they supportive?

I have no regrets, and the few offensive e-mails that I do get really don't bother me. My family were initially quite worried about possible reprisals, but they've always been very supportive, and we all feel a lot safer now.

Is there anything you would like to say to BNA members in particular? How can the BNA help you?

I'd like to thank the BNA's members for improving the health of this country in spite of not being given the respect and pay that they deserve, and I'd especially like to thank all the nurses who attended both our demonstrations. Currently, we don't have any specific plans that we need help with, but please do keep supporting us, and if you wish to make a donation (always very appreciated!) then please go to our website (www.pro-test.org.uk).

OPINION

GM, stem cells and nanotechnology – **is neuroscience next?** Science communication in the 21st Century

‘Good science communication is a collaboration, not a battle between press and academia. And researchers find that using the media gains wider recognition for their academic work, which in turn leads to international awareness, better research links with other international institutions, and ultimately gets them access to grant funding and collaborations’

Myc Riggulsford is a science journalist and managing director of The Walnut Bureau where he runs an annual programme of science communication and media training courses in the UK and beyond for research councils, universities, the European Commission, charities and learned societies. He also hosts science events for public and teaching audiences including Science on Stage, UK science festivals, and café scientifique, and is currently one of the international judges for the European Science Teacher of the Year awards. Here, from his Devon smallholding, he muses on the importance of science communication and explains how and why there is much to be gained for scientists who indulge.

Putting a Factor 45 sunblock on your baby’s skin when you finally get time for that much needed holiday in the sun seems a sensible precaution. But you may not know that you are probably using nanotechnology, and the cream may contain tiny mirror particles so small that they could pass straight into your child’s skin cells, with all sorts of unknown future health implications.

If you feed processed and pre-prepared baby foods to your infant, do you check to see whether it contains genetically modified soya extracts, or possibly dangerous pesticide residues? And if you do check the labels and sources of these products, do you understand the science enough to know what risks you are taking with your child’s health?

I’d expect neuroscientists and other readers of *BNA Bulletin* to understand medical risks, pressure group hype, and the limited conventions of newspaper reporting well enough to make informed decisions about these types of concerns. But does the public have sufficient information? And do the politicians and grant bodies who decide on the funding and other resources which will allow effective neuroscience research to continue in the NHS and at academic institutions in the UK in the future understand your current problems and needs?

Of course, if you are a sophisticated reader of tabloids, our national daily newspapers, you will understand the convention of the question mark in my title. Apart from its apparent mission to test every single substance in the universe and divide it into either cancer causing or cancer curing, the *Daily Mail* has made one other great contribution to scientific debate – the question mark headline.

When a scientist writes ‘Does eating hedgehogs prevent migraines?’ then the answer is usually ‘Yes, our study seems to indicate so’. But when the *Daily Mail* writes a headline such as ‘Is breakfast tea the cure for cancer?’ you can bet that the answer is ‘No’. Otherwise the headline would read ‘Tea is the cure for cancer’. I am indebted to my friend, former *Mail* writer and current *Daily Telegraph* consumer affairs editor, David Derbyshire, for this succinct analysis and indicator of the completely diametric gulf between ordinary public readers and the scientific community.

So is neuroscience likely to become as controversial as stem cell research or GM foods in the near future? – No, probably not. But are your future medical advances in our understanding of drug and alcohol addiction, anorexia, Parkinson’s and obesity likely to be misinterpreted by the public, media and alternative medical practitioners? – Yes, very likely.

So what can we do to make sure that the public (and funding bodies, concerned relatives, nurses, government ministers and all the other meddlesome and legitimate tax paying members of our society) understand the implications of scientific findings so clearly and so accessibly that neuroscience gets the credit and support it so obviously deserves and needs?

Public mistrust has driven an explosion in scientists’ efforts to communicate their work in the last twenty years, along with a hunger from the public, industry and government to understand them. If we, the taxpayers are, paying for the work, then we have a right to know what is being done in our names.

Our physicists, chemists, biologists and other science experts have had to learn to communicate better if they are not to lose even more public confidence, faced with outrage and protest from pressure groups and the public over health scares, pollution and personal safety issues. Newspapers, radio and television have also had to find journalists who can understand and interpret jargon and the highly technical reports which often contain vital information affecting our future lives.

You might expect that government and industry would resist any attempts to make the scientists’ work understandable, especially since investors and decision makers are a focus of the pressure groups’ anger. However, British and European politicians and senior scientists have realised that, if society is to benefit from new types of jobs and ways of working using mobile telephones, the internet and all the other modern technologies, and gain the full benefits which science, technology and medicine can deliver for society, then people need to understand science better. Which means engaging us in dialogue, not simply telling us after decisions have been made.

At the same time, businesses and industry have realised that, if they want shareholder confidence,

foreign and domestic investment, and the benefits from adopting new cleaner technologies, then they too will have to start being more open and accountable in their practices. And explain and publicise the science they are using - especially if they want public confidence and the freedom to operate in a democracy.

British (and European) science receives little recognition and support compared with American or Japanese research efforts and results. This means our country risks losing its most talented scientists in a brain drain, many of whom feel they lack funding, jobs and modern technologies through lack of investment, and lack of proper access to useful collaborations, grants, investment and links with the international research community.

In Britain during the last twenty years, science communication has developed into an important part of our lives. People are eager to hear about the latest developments, medical advances and environmental threats. We expect news reports about the latest science, medicine and technology. And we expect them to be so well written that they are as easily readable as the rest of the news. However, this is not as simple as it sounds. Our opinion makers and leaders in the science community became aware a few years ago of the mismatch between public confidence in science and technology, and the economic and social benefits which would be available through better public understanding. The initial reaction of traditionalists was to try to 'educate' the public by making them understand more science, but in the way that scientists view the world. However, it quickly became apparent that this approach does not work effectively, and is not what we the public necessarily want.

This top down 'deficit' model of communication – based upon scientists' belief that the public is at fault and should simply know more facts - was fairly quickly abandoned by the best science communicators, and a 'dialogue' model was adopted instead. Instead of increasing the volume of teaching science or medical technicalities to the public, efforts are being made in Britain to improve the quality of communication. Scientists now want open dialogue with the public, exploring our fears and concerns about science and making more of an attempt to help us understand why research needs to be done, and how it is relevant to our everyday lives.

In return, doctors and scientists have had to learn better communication skills, use informal channels of communication such as the web, newspapers, radio and television, and be receptive to public fears, even though these may often appear trivial or irrelevant. Scientists find the dialogue approach more challenging as it involves a mental shift from being insiders and having specialist knowledge that the public does not share, to being partners in a collaboration for the benefit of all our society. Most science in the UK is done using public money, directly or indirectly taken from taxpayers, and scientists must learn to view themselves as being responsible to the public for these funds and for the trust put in them by our public. This requires greater effort from researchers to make their work accessible and understandable to the public, and a responsibility to learn how to make their communication effective. It also means embracing the idea that research is only truly useful once it is communicated to a wider audience within the scientific community and to key decision makers, industry partners and our general society.

As scientists' attitudes have changed and science communication has become more professional, the debate has moved 'upstream' in the scientific and technological development process. In some rare cases, this is now allowing the public to go further than two-way dialogue and actually influence what research is done. The UK has held public debates about controversial technologies such as stem cell research, nanotechnology and GM foods, for instance, in new attempts to improve relationships between science and society.

In Britain, we also have a competitive environment amongst universities and research institutes, each striving to gain a share of the overall science research funds provided by public money through government channels, charities and investment from industry. This competitive environment encourages individual scientists, research departments and institutes to issue high quality press releases explaining their successes in science and medical research and the benefits these will bring to society, so gaining recognition for their expertise and attracting further funds for research to their own establishment, as well as the best students.

The different sectors of UK funding bodies similarly issue their own high quality press releases about research results. From the public sector, these justify the use of taxpayers' money and encourage continued political support for research efforts. From charities, they explain what successes have been achieved using publicly donated funds and enable fundraisers to continue their efforts. From industry, they build shareholder confidence and help attract further investment. This means hundreds of good quality press releases arrive daily at newspapers, radio, television and online media through conventional post, email and internet websites from funding bodies and many individuals. This lets journalists choose the most interesting stories, most significant advances and most clearly written press releases as the basis for their own news stories, which must then compete with other sources of news and topics to make it into the media, making interesting news for our readers and listeners.

This double competitive pressure means that British science is well written about and clear, and has recently stimulated the growth of a new profession of science communicators and press officers within UK academic institutions to act as bridges between scientists and the media or public. It has also encouraged the rise of a new specialism within the media of 'science journalism', people who are experts in understanding and explaining the context and significance of scientific advances.

This treatment of science by experts within the British media has further increased the confidence of doctors and scientists in dealing with journalists, and encouraged public discussion of previously difficult concepts such as climate change, nanotechnology, biodiversity or genetic modification. The more that interesting science appears in the media, the greater the appetite from news media and the public. Once more, we are learning to trust our scientists because we can now understand what they are doing. And we are sometimes allowed to have our say in what they do next.

In the UK, we have clear distinctions between feature stories, comment and analysis, news reports and advertising space. Filling these different parts of a newspaper is the responsibility of different editorial departments. In other countries, science reporting sometimes contains elements of opinion, comment and commerciality that would be absent from British news coverage. Interestingly, this helps bolster our UK scientists' international reputations for being fair, impartial and honest.

Good science communication is a *collaboration*, not a battle between press and academia. Science and environmental journalists can help to open the public debates that are vital to a democracy. And researchers find that using the media gains wider recognition for their academic work, which in turn leads to international awareness, better research links with other international institutions, and ultimately gets them access to grant funding and collaborations. Oh, and readers get better stories in their papers.

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Welcome to 2007!

Richard Dyer, Chief Executive of the Biosciences Federation begins the new year by describing his concerns about the proposed abolition of peer review panels and the introduction of a metrics only-based RAE.

BIOSCIENCES FEDERATION

Another New Year has arrived. I hope that it brings you all the important things you seek and few of those that you do not.

> 'The BSF holds the view that it is potentially dangerous to rely on an algorithm for an activity as critically important as the RAE. We think it essential that there is some wise evaluation of the quality of the data fed into the formula.'

From a political point, of view I fear that the latter will not be true. The discussions about the future of the RAE have now reached a critical point. The momentum towards the abolition of peer review panels and the introduction of a metrics only-based RAE continues. This change is supported strongly by many of your employers! External to Government, the main supporters of the metrics only approach are University Vice Chancellors and The Academy of Medical Sciences. All other "academies", including The Royal Society, The Royal Society of Chemistry, The Institutes of Physics and Biology, and – of course – The Biosciences Federation are strongly opposed to the abolition of peer review panels. We want these panels maintained and we want them informed by robust metrics including those relating to output.

The main argument for change is to reduce costs – including those costs associated with time. We agree that strenuous efforts should be made to implement clear and substantial reductions in the bureaucracy associated with the RAE and believe that there should be serious discussion about how can this be achieved. A metrics only approach will achieve a cost reduction but this is not at all the right route to follow. Why do I write this?

First, because the BSF holds the view that it is potentially dangerous to rely on an algorithm for an activity as critically important as the RAE. We think it essential that there is some wise evaluation of the quality of the data fed into the formula.

Second, because the BSF thinks that a metrics-based formulaic approach will disadvantage some areas of the Biosciences. We are particularly concerned about those important disciplines where research is truly excellent but grant income is low and outputs may be relatively sporadic. Research in Systematics is an example where these anxieties are relevant.

Third, and following from the previous point, the BSF thinks it likely that Vice Chancellors will inevitably move to support most those areas of the Biosciences most suited to whatever algorithm that emerges. These areas will, of course, "do well".

And finally, and personally, because I have had too many computer generated letters from non-existent Bank managers based on incorrect information or a "mistake". I have always managed to receive an apology and charges reimbursed. I doubt that you will get (m)any apologies out of the RAE!

What can you do about this situation? Well, of course you can continue to support the BSF and I would welcome your ideas about how costs can be reduced effectively and peer review panels maintained. Some of you could also start an interesting discussion with your employer!

There are quite a few issues emerging that will have an effect on your professional lives. By the time that you read this, I will have met with a Task Force to discuss the BSF response to a paper published by the Research Councils on Peer Review and our response will be on our web site. If you haven't seen the Research Councils' proposals, you might like to download www.rcuk.ac.uk/research/peer/efficiencypr.htm . I don't wish to prejudge our response to these proposals, but I am 100% confident that we will not be 100% supportive – and nor will you!

I am anticipating a busy year. However, I don't want all the activity to be reactive. A proactive position, taken at the right time, can often be more influential than "fire fighting". Ideally, I should like some of the issues where we should trigger debate to come from the Member Organisations. If you have thoughts about important matters to address in the next year or so please let us have them via your Council.

We are quite pleased by the number of "hits" our jobs link page received during 2006. You may remember that this was a new initiative for us and is aimed to provide a resource for postdocs. I write "quite pleased" because we are fully aware that all web sites can be improved. If you – or junior colleagues not members of the Society – have a thought about how improvements could be made please contact Dr Emma Southern (esouthern.bsf@physoc.org). In fact, please contact us about any bright ideas that you may have concerning the BSF. I don't promise to pursue them all, but I do promise to "cherry pick" the very best for consideration!

Dr Richard Dyer
Chief Executive.
Biosciences Federation
www.bsf.ac.uk

This year's BNA Award for Outstanding Contribution to British Neuroscience went to **Professor Horace Barlow FRS**, a fellow of the Trinity College in Cambridge, for his lifelong contribution to the research into the mechanism of visual perception. His pioneering work that studied neuronal activity using single-cell recordings has been instrumental to our understanding of visual inhibition, the process whereby a neuron firing in response to one group of retinal cells can inhibit the firing of another neuron, which allows perception of relative contrast. In 1961, he published a seminal article in which he addressed the issue of the computational properties of the visual system. This and his subsequent work have laid the foundations for the burgeoning field of computational neuroscience.

The BNA Awards, 2006

The BNA Award for Public Service was presented to **Mr. Mike Robins** in recognition of his tireless work in promoting the value of animal research in benefiting human health. "I owe my quality of life to this small device," said Mike Robins, pointing to an electronic controller in his jacket pocket. He switched it off and his right hand began to shake violently and uncontrollably. Mr Robins developed Parkinson's disease in his early fifties and, for eight years, his condition worsened until he could no longer feed or dress himself. Thanks to the successful treatment using deep-brain stimulation, his life has changed beyond recognition. "Now I can have a proper conversation, go out on my own, and drive to work," he said. "Every morning I wake up and marvel that I no longer shake."

Both awards were presented by Professor Richard Frackowiak at The Royal Society in London, on the occasion of the annual Christmas Symposium. This was the last function Richard Frackowiak will undertake for the BNA as he now retires from the presidency and Graham Collingridge takes up this challenging role.

Karen Luyt

Congratulations to our BNA prize winners for 2006:

Sophie Buglass (Undergraduate prize) and **Karen Luyt** (post-graduate prize), closely followed by runners up Holly Griffiths and Amos Fatokun.

Sophie Buglass

Sophie Buglass completed an intercalated degree in Neuroscience last summer at the University of Leeds, deservedly gaining first class honours after an exceptional performance in her examinations and thesis. For her final year project, she investigated the modulation of calcium homeostasis by hypoxia and β-amyloid to explore possible mechanisms of cell death in Alzheimer's disease. Described by her supervisor, Chris Peers, as 'one of the best students I've had the pleasure to supervise', Sophie produced publication-quality data in less than eight weeks. She has now returned to her medical course but feels the insight she has now gained into neuroscience has broadened her career prospects immensely such that she might return to the laboratory bench again one day. **She'd be very welcome!**

Karen Luyt was also an exceptional student, not averse to winning prizes and medals during her PhD, and publishing a number of papers in quality journals for her outstanding research. Supervised by Elek Molnar at the University of Bristol, Karen investigated the cellular and molecular mechanisms of white matter injury in the immature brain, concentrating in particular on the identification and function of metabrotropic glutamate receptors and GABA receptors in oligodendrocytes, implicated in the cell death, proliferation and differentiation of these cells. Identifying their presence and receptor sub-type might offer the possibility of pharmacological intervention to mitigate the effects of premature birth on myelination, Karen hopes.

Since returning to her consultant's position in neonatal medicine, she feels the experience of her PhD has greatly enhanced her understanding of white matter development and injury in the immature brain, and hopes to see translational research directing clinical management strategies one day. Her qualifications in both clinical neonatal medicine and basic neuroscience are an increasingly essential requirement, she feels, for a successful translational approach.

So, heartfelt congratulations from the BNA to both Sophie and Karen! But we should also mention two close runners-up: Holly Griffiths, a first class student at the University of Manchester, for the Undergraduate prize; and Amos Fatokun, another outstanding PhD student, at the University of Glasgow. Their nominations gave the judges much angst in their decision-making but also much reassurance in the quality of undergraduate and postgraduate teaching and research in the UK.

BNA NEWS

BNA NATIONAL COMMITTEE: NOMINATIONS SOUGHT

Nominations are now invited for election to the BNA National Committee for TWO vacancies that arise this autumn. Nominees should be proposed and seconded by extant BNA members and sent to the BNA Office (y.allen@bna.org.uk) by 1st JUNE, 2007. Members of the BNA Committee perform a vital role in influencing the goals and ambitions of this vibrant society. Would you like to contribute for the next three years? Informal enquiries are very welcome **(y.allen@bna.org.uk; tel, 0151 794 5449).**

Yvonne Allen with Duncan Banks (left) and Peter Woodhams at the BNA stand in Atlanta last year. The BNA exhibits at SfN meetings every other year to promote the society on the world stage and say 'hello' to members, past and present, and to tout for new ones. It is still a sad fact that many more BNA members go to the American meeting than support their own national meeting, or even the biennial FENS gatherings.

Where have all the SfN abstract slots gone?

In 2005, the Society for Neuroscience decided to change the way it distributed sponsored abstracts to other neuroscience societies that may have implications for the future allocation of these to BNA members. Although the BNA was one of the first societies to negotiate this 'deal' whereby BNA members could present as non-members at the SfN annual meetings, many other national societies were then also keen to claim a similar allocation. It was fast becoming a chaotic mess so, to simplify the procedure, SfN decided to give a (still generous) allocation instead to FENS to distribute to constituent FENS members on its behalf. BNA members still wishing to obtain one of these are now requested to contact the FENS office directly. However, the FENS Council then decided to impose its own rules and regulations on their distribution, such that priority goes to students and early career post-docs only, disproportionately to smaller societies and to poorer countries. The outcome of this was that, although BNA members fulfilling the criteria appear to have been awarded sponsored abstracts with no problem, there was still a proportion of the entire allocation unused.

SfN has changed the allocation practice for slots. In 2006 FENS was appointed as the unique distributor of slots for entire Europe.
The total number of slots that FENS distributed in 2006 is **419**. Only Ph.D. students and postdocs were eligible.
Taking into account the requests of some, especially the smaller, financially compromised countries,the Executive Committee of FENS decided to distribute the slots according to the following scheme:

Category I: Societies with 300 or less members: 126 slots
Category II: Societies with 301 to 1000 members: 126 slots
Category III: Societies with 1001 and more members: 126 slots

41 slots remained at the disposal of the Executive Committee.

363 slots have been distributed (every eligible applicant received a slot

Germany	93	Georgia	6
UK	56	Denmark	4
France	50	Czech Rebublic	3
Switzerland	23	Finland	3
Israel	22	Norway	3
The Netherlands	19	Romania	3
Portugal	18	Austria	1
Italy	15	Croatia	1
Belgium	11	Serbia and Mont.	1
Hungary	11	Sweden	1
Spain	11	Turkey	1
Poland	7		

Figure 1:

Upon request, the FENS office released the figure (above) to describe how the 'slots' were allocated for the Atlanta meeting last year. Clearly, BNA members would be wise to still apply (even if they do not necessarily meet all the criteria) and request to go on a waiting list to receive one of the 'leftovers' this time round.

Engaging the public down under

The Manchester Science Group (www.manchesterscience.blogspot.com), comprising lecturers Dr Ellen Poliakoff (School of Psychological Sciences, University of Manchester) and Dr Stuart Allan (Faculty of Life Sciences, University of Manchester) and Science Communicators Dr Erinma Ochu and Dr Michelle Lockwood, will be running a series of public engagement activities at the IBRO World Congress of Neuroscience in Melbourne, July 12-17 2007.

The group were invited to submit a proposal to the Local Organising Committee and this was accepted. The proposed events build on existing activities developed by the group over the last couple of years, and include a 'Brain Discovery Stand' in Federation Square, one of Melbourne's foremost public spaces (www.fedsquare.com) The group will also be hosting an interactive pub quiz, 'You Know it Makes Sense', which has run successfully at Café Scientifique events in Manchester and Nottingham. A poster will be presented as part of the main congress where the group will share with the other delegates their experiences of developing and delivering public events for diverse audiences.

If any members of the BNA are attending the IBRO Congress and are interested in taking part, even for a few hours, in any of these activities then please contact Stuart Allan (stuart.allan@manchester.ac.uk).

PLUS – Neuroscientists are invited to participate in our European Dana Alliance of the Brain DAY IN THE LIFE project, where scientists give the public an insight into their lives. Check the blog or email: mansci@googlemail.com for more details.

Four for the price of one!

The BNA regrets that it must raise the annual subscription fee from 1st March, 2007, for all members by a modest £5 per year, to reflect inflationary increases in its operational costs over the last year that, in many cases, have risen by nearly 10%. Unfortunately, we now have to ask for 10p per week from everyone to help us maintain and improve the service we can offer. This means the annual subscription for full members paying by direct debit will be £69 per annum, and the student fee will be £35.

Please remember that this fee also includes your membership subscriptions to FENS, IBRO and the Biosciences Federation that the BNA pays on your behalf – four for the price of one! And some of these subscriptions rose by a staggering 200% this year! So, younger members especially should remember to include membership of all these societies as well on their CVs.

The benefits of BNA membership now include:

(1) FREE admission to many events throughout the year including 'One Day Symposia' and the ever popular Christmas Symposium

(2) Reduced registration fees (up to 30%) to the National Meeting

(3) Regular *BNA Bulletin* and other relevant mailings

(4) Regular 'BNA Email Alert' service

(5) Student prizes, and bursaries for attendance at BNA and FENS meetings

(6) FREE on-line access to *European Journal of Neuroscience*

(7) Concessionary (SfN membership rate) registration fees and sponsored abstract forms for Society for Neuroscience annual meeting (now handled by FENS)

(8) FREE advertising in the *BNA Bulletin* and on the BNA Website

(9) FREE Inclusive membership of the Federation of European Neuroscience Societies (FENS), the International Brain Research Organisation (IBRO) and the Biosciences Federation (BSF).

We do hope you agree that this is tremendous value for money and that you continue to support as many of our events as possible.

For further information on any of these benefits, contact: membership@bna.org.uk

ANNUAL GENERAL MEETING 2007

The BNA will be holding its Annual General Meeting this year during the 19th National Meeting in Harrogate:

1.00pm, Tuesday, 3rd April, 2007, Conference Suite, Harrogate International Centre.

All members are invited to attend

BNA NEWS

Drugsfutures – can BNA members help?

BNA members with a long (perhaps chemically-enhanced) memory may recall Drugs Futures 2025, the Foresight project on *Brain Science, Addiction and Drugs*. Set up by the government's Office of Science and Innovation, it took a 20-year look at the possibilities for drugs both legal and illegal, for both therapy and pleasure. It reported in 2005, but the story does not end there.

Instead, the government has asked the Academy of Medical Sciences to see what happens next, and this is where we would like your help.

The AMS is concentrating on three main areas of concern about future drug use.

They are

- Cognition enhancers.
- Future legal and illegal recreational drugs
- Drugs for mental health

It is asking for detailed submissions on the issues these topics might raise over the coming 20 years. If you would like to contribute, as an individual or via an organisation, start by taking a look at the guidelines, which are at www.acmedsci.ac.uk. The AMS will report to government by the end of 2007.

In addition to seeking the opinions of experts such as the members of the BNA, the study is also gathering views more widely.

Public engagement

January 31 saw the launch, at the Dana Centre in London, of *Drugsfutures*, an innovative consultation occurring both online and in person. The aim is to get an idea about future developments from both experts and a wide range of the public. Managed by the OPM (Office for Public Management) with partners including the British Association for the Advancement of Science, it is running until the end of March.

There is a range of ways to get involved. One is by invitation only. Defying the insights of Alexei Sayle, who says that nobody should be able to say they are running a workshop unless they are engaged in light engineering, we are running some workshops. They will invite the public (recruited to reflect the olve "the public" in the sense of a sample of individuals recruited to match the population as a whole) to discuss and debate the issues. at large. But we will also be talking to other people who are experts in some aspect of drug use. They include groups such as young people, drug users, and people who care for others with mental health problems.

Each of these groups will be asked to explore a specific aspect of drug use. They will be helped along the way by a background note on the future possibilities, including a scenario for future drug use, that is intended to help their thinking without railroading it. We will also be inviting some experts to the events, to provide further information.

Each workshop will focus on one of these five following themes:

- Drugs and the law
- Drugs and society
- Drugs and young people
- Drugs and mental health
- Drugs for a smarter brain

During the workshops, people will be be asked to explore topics questions such as the regulation and control of drugs, including the balance between regulating addiction via the health system or via criminal justice. For example, how far should the use of cognition enhancers be allowed to go? Should they be illegal for anyone who does not have a demonstrable clinical need for them? Should they be compulsory for anyone who runs a nuclear power station, flies a plane or drives a bus? What about job interviews? If you use a cognition enhancer to look clever at the interview, will you feel obliged to take it once you get the job?

A related set of issues will arise when Drugsfutures considers our emerging knowledge of neuroscience and genetics. We are starting to find genuine genetic markets for susceptibility to addiction, confirming the centuries-old wisdom that drunkenness runs in the family to a degree that social settings alone cannot explain. At the same time, we may reach the point of being able to tell whether an individual expresses gene combinations that make them susceptible to addiction.

One issue we shall explore with the public is how to handle knowledge such as this. For example, what sort of counselling is right for a five-year-old with dangerously high levels of drug susceptibility? He or she might become a problem gambler, a heroin user, or a heavy smoker, depending what influences they are exposed to. But it is hard to imagine locking them away from all possible exposure to potential addiction. Almost as tricky is the advice to give people with a low susceptibility to addictive harm. Can they try any behaviour they like with impunity?

Previous OPM work for the Foresight project showed that the public is less panickedvery able to consider the issues raised in this project. by the possibilities of drug use than one might imagine. They often think that people have a right to try drugs out, and would be reluctant to have their own children vaccinated against addiction even if it became technically feasible.

To ensure the sample we need, the workshops will not be public events. But Drugsfutures has an online life in which we hope you will participate, at www.drugsfutures.org.uk. There you will find an online consultation where you can register painlessly and then let us know what you think.

Also at that address you will find the *Drugsfutures Blog*, where you can join in discussions of topical issues to do with addiction and treatment. You will need to register separately for the blog. We would welcome your comments, questions or suggestions for themes to be discussed.

The team would very much welcome your participation in Drugsfutures and we look forward to your first contribution.

By Martin Ince
Science writer and editor of the Drugsfutures Blog
Drugsfutures@martinince.com

Members of the ECBR launch committee: Mary Rice (EBRA), Magda Chlebus (EFPIA), Mark Matfield (EBRA)

The Launch of the European Coalition for Biomedical Research (ECBR)

Members of the ECBR launch committee: Duncan Banks (BNA), Domenico Spina (BPS) and Alan Bateson (BPS)

The ECBR, with a current membership of 42 scientific institutions from 19 countries across the EU, representing 44,000 scientists, held its inaugural meeting in Brussels on November 8th 2006. It elected an Executive Group (Prof. Edith Olah, Chair, Dr Mark Matfield, General Secretary, and three Executive Members, Prof Peter Janssen, Dr. Duncan Banks, and Prof. Christine Giudicelli), and adopted a Manifesto setting out concerns about the proposed revision of the EC Directive 86/609 which regulates the use of animals in research across EU member states. The website (www.ecbr.eu) provides ongoing updates on activities and links to member organisations.

Background

The ECBR was initiated by EBRA specifically to coordinate response to the revision of the EC Directive 86/609. This revision was proposed in a report from the Environment Committee in December 2002, which set up a Technical Expert Working Group drawn from European professional bodies (e.g. EBRA, EFPIA, FELASA), but excluding representative from Patient groups. The Expert Group planned to draw up a report by the end of 2003, but this was delayed for a year by EU elections. A Swiss company, Prognos, was then commissioned in 2004 to assess the impact of the proposals, and mounted a hasty preliminary consultation, which attracted only 66 replies, followed by a long internet questionnaire sent to experts, plus requests for views from the general public. The questionnaire/consultation document provides a clear indication of what might be in the final revision. While the ECBR supports many of the objectives, the factual mistakes and the bias of some questions in the consultation document prompted the ECBR to draw up its Manifesto to raise particular concerns and to suggest changes in wording. The projected timetable for rolling out the Draft Revision of Directive 86/609 include delivery of the final Prognos Opinion in November 2006, inter-service consultation in December 2006, leading to release of the Draft legislation early in 2007, under supportive German presidency of the EU.

Adoption of the revised directive will depend on agreement of the final version by all three European legislative bodies: the Commission, the Parliament and the Council. The rounds of consultation between these bodies and the Environmental Committee will afford vital opportunities for ECBR members to lobby and consult with relevant members to enhance their understanding of the critical issues involved.

Why should the ECBR be concerned about the revised directive?

The ECBR supports legislation to improve animal welfare and the harmonisation of welfare practice across the EU. However, current evidence suggests that the revisions may include legislation which could be detrimental to biomedical research, without achieving increased welfare benefits, or promoting the 3Rs. Problematic proposals include:

- A ban on first generation bred non-human primates (NHPs)
- Extension of cover to some invertebrates (cephalopods, decapods)
- Increased regulation of transgenic animals and xenotransplantation.
- Extension of cover to fetal and embryonic forms
- Extension of cover to animals killed for tissue.

Further possible revisions include provisions that are effectively in place in several EU countries (including the UK), and which the ECBR would seek to clarify and promote:

- Compulsory cost/benefit analysis
- Ethical review process
- Minimum animal/technician ratio
- Standardised pain/suffering assessment
- Standardised procedures for analgesia
- Specified methods for euthanasia (ban on CO2)
- Implementation of the 3Rs
- Regulations for use of animals in education and training.

Although the details of the draft amendments to Directive 86/609 have not been released, the ECBR is taking proactive measures:

- To alert scientists to the possible negative impact of some of the proposals
- To inform EU legislative members about potential implications in terms of increased costs and administrative burdens without achieving improvements in animal welfare.
- To suggest amendments to the proposed revisions of Directive 86/609 in its Manifesto

The ECBR Manifesto

The Manifesto was finalised at the launch meeting and can be seen in full on the website. The key elements include the following issues:

1. Inclusion of 'recital' statements to emphasize the

- Importance of freedom of research for scientific enquiry
- Importance of harmonisation of national controls on animal experimentation across EU member states

2. Euthanasia

- All animals to be killed by a competent person using a humane method.
- Animals bred for tissue should not be included in the scope of the Directive
- Ban on the use of CO2 for euthanasia is not justified.

3. Authorisation

The ECBR supports the proposed system for authorisation and ethical review, but wants time limits and avoidance of duplication in the process to be clearly specified, as follows:

- A deadline of 60 days for completion of local and national authorisation, to start from the date that projects are submitted to the local ethical review process
- A statement that the review process must not duplicate any of the project assessments made initially by the local ethical review body.

4. Caging and welfare standards

The Council of Europe Convention ETS123 has recently revised standards for caging and welfare that member states must adopt, at an estimated cost of over one billion Euros for upgrading. This will cause problems especially for academic institutions which will need time to raise funding. The ECBR proposes that the Directive should allow

- A minimum of 10 years before institutions are required to comply with ETS123 standards

5. Transparency

The proposal that all relevant non-confidential information from the authorisation process be made public would involve huge administrative and legal costs. The ECBR proposes that transparency would be more effectively and efficiently served by

- Publication of a summary of the research couched in easily understood language ('lay summary')

6. Non-Human Primates (NHPs)

The proposed ban on use of first generation (F1) purpose-bred NHPs is based on the erroneous view that most NHPs are F2. Currently, only New World NHPs, constituting 13% of research use, are from F2+ stock. Most EU research (87%) uses F1 Old World NHPs, and F2 animals are not available. Welfare would better served by improving breeding conditions, rather than setting up long-term breeding colonies, which breeders are not prepared to undertake. The ECBR proposes that

- The ban on use of F1 NHPs should be lifted
- The EU should set up a system for inspecting NHP suppliers, and approving their breeding and conservation practices
- NHPs should only be obtained from EU approved suppliers.

7. Multiple sites

To avoid duplication and conflict the ECBR proposes that where projects run across several sites

- Ethical approval obtained from any one institution should be accepted by the other institutions involved

Training

In order to facilitate communication between laboratories and harmonise training standards the ECBR proposes that the directive should charge the EC to set up an Expert Group on training to

- Set up training standards and curricula for EU members
- Require member states to adopt and mutually recognise these standards and curricula.

What happens next?

The draft Directive is expected to be issued in April 2007. The EC has already (Jan 18) issued a working document which has incorporated several of the suggestions in the ECBR Manifesto. This document is confidential, but in general terms there are still issues to resolve, for example

- Frequency of project reporting to ethical review committees
- Use of non-human primates
- Training requirements
- Funding for research on alternative approaches

Therefore, the ECBR will continue to work to publicise the manifesto, and inform EU administrators and legislators about the issues.

The overall strategy involves:

- Enlarging the coalition and forming alliances with other interested bodies
- Keeping ECBR members and allies informed
- Targeting MEPs and convincing them to put down amendments which reflect ECBR proposals
- Lobbying MEPs and members of the Commission and Council to support these amendments

What can individual ECBR members do?

Send a message (Fax and email) to your MEP stating

- The problem
- The amendment
- Arguments for the amendment

The coordination provided by the ECBR will be much more effective than lobbying by individuals or single associations. As Mark Matfield commented 'the larger the coalition, the more effective it can be' Working together we can achieve EU legislation that will enhance the quality of care for experimental animals, without imposing undue increases in costs and administration. Improved welfare will enhance the quality of the science that results.

By Duncan Banks and Helen Hodges
(d.banks@open.ac.k; h.hodges@kcl.ac.uk)

RDSNEWS 06

UNDERSTANDING ANIMAL RESEARCH IN MEDICINE

WINTER 2006

In this issue: Animal Procedures Committee report for 2005 - page 2. Helping institutions communicate - page 3. Tackling cybercrime - page 4. Arrests and prosecutions on the rise - page 5. The growing need for information security management - page 5. Anaesthetics: 40 years on - page 6. 50% rise in animal research web statements - page 6. Book Review - *Testing Treatments: Better Research for Better Healthcare* - page 8. One university's TV experience - page 9. Research News - page 10. New European coalition - page 12. RDS staff roles - page 12. RDS membership direct debits - page12.

GPs back animal research

More than 19 in 20 GPs (96%) agree that animal research has made an important contribution to many medical advances. The results were announced by Health Minister, Andy Burnham, in October last year.

Animal experiments have made an important contribution to many advances in medicine

Safety tests should be carried out on animals before human trials

Medical research data can be misleading

Strongly agree | Agree | Disagree | Strongly disagree

0 10 20 30 40 50 60 70 80 %

The latest opinion poll also sought doctors' views about safety testing of medicines. Almost 9 in 10 GPs (88%) agree that safety tests should be carried out on animals before human trials of new medicines are conducted. The remainder disagree or are undecided.

George, said: "The BMA believes that at present animal experimentation is necessary to develop a better understanding of diseases and how to treat them. However, wherever possible alternative experimental methods should be used. It is essential that regular inspection takes place to ensure that animal welfare is protected within current legislation. It is very important that the public is fully aware of how animal experimentation is vital in fighting disease and illness in both humans and other animal species. The BMA strongly condemns the illegal and intimidatory action taken by certain groups opposed to the legal use of animals in medical research."

It is clear that the overwhelming majority of GPs appreciate that animal research is crucial for the treatments they prescribe to patients every day. This exposes the anti-vivisection claims that doctors are sceptical about the need for animal research.

The third poll question commissioned by RDS asked whether GPs agree that "medical research data can be misleading". 93% of the GPs polled agreed. This puts into context a leading question in an anti-vivisection group poll of doctors in 2004. The group, European for Medical Progress, found that 82% had a "concern ... that animal data can be misleading when applied to humans". In fact it seems that most GPs think that medical research data in general can be misleading.

The Chairman of the British Medical Association's Board of Science, Sir Charles

EMP only published half the results it obtained from its poll, and produced a highly suspect interpretation of the remainder. It has since been claiming the support of 'at least 80% of GPs, ever least in last year's Early Day Motion 92 in Parliament.

Previous polls of doctors' views were conducted by Medix UK for *Hospital Doctor* magazine in 2004 (500 hospital doctors) and by the BMA in 1993 (334 doctors working in hospitals, GP practices, community and public health). Both revealed over 90% agreement that animal research and testing is important for medical progress.

Barbara Davies
Communications Director

"If we hadn't taken on the animal rights extremists, we might well have lost essential scientific research to Britain with incalculable economic damage to the country, to say nothing of the value of the research in the treatment of disease."
Tony Blair, 3 November

"The NHS could not function effectively without medicines and treatments developed or validated through animal research. These interventions are saving lives, relieving pain and other symptoms, and preventing disease."
Andy Burnham, Health Minister, 9 October

BNA NEWS

The RDS: Defending the use of animals in research and testing

The use of animals in research has been in the news frequently in the past year, with the People's Petition earlier in 2006 to the more recent publication of the Weatherall report in December supporting the use of non-human primates in research of biological or medical importance. Indeed, as neuroscientists, you know all too well that animals are still necessary in medical and scientific research and need to be aware of the arguments in favour and against as well as the current status of the debate.

The Research Defence Society (RDS) is the leading UK organisation that represents doctors and scientists in the debate concerning experiments on animals. It recently commissioned an opinion poll of GPs that showed 96% of family doctors agree that animal research has made an important contribution to many medical advances. The results were announced by Health Minister, Andy Burnham, in October last year.

RDS is the only organisation which brings together the academic and commercial sector to work on policy, representation and communications. RDS engages in dialogue with stakeholders, and interacts with legislators, regulators and government.

It has about 5000 members, both individuals and organisations. Members are entitled to advice, information and assistance on all aspects of animal research, such as dealing with administrative bodies or the media. All members receive regular information through publications and meetings, and may sign up to the RDS Email News Service. RDS educational material, produced primarily for schools and colleges, is also available to members.

Most of the activities of the RDS fall into four categories: communications, policy and lobbying, information and networking, and support for members. It publishes:

- a quarterly members' newsletter, *RDS News*, which is essential reading for all those interested in animal research and animal rights issues
- leaflets and more extensive reports
- monitors both media and parliamentary coverage of relevant issues, as well as animal rights groups' publications
- provides supporting material to other organisations

Last year the RDS set up a Resource Centre to help research institutions deal with actual or potential animal rights extremism and produced a series of good practice guides which give practical advice to help prevent, prepare for, and minimise the effects of extremism. More recently, the Research Centre expanded its activities to cover communications, helping research institutions (Universities and Charities) communicate openly and effectively about the use of animals in research.

The annual subscription for full individual membership is currently £25 per annum payable by direct debit. A membership form is included in this edition of the *BNA Bulletin* and may also be downloaded and printed from the RDS web site. (www.rds-net.org.uk).

For more information:
Corina Hadjiodysseos,
Communications Officer, RDS
Email: corinah@rds-net.org.uk;
telephone: 020 7478 4333

RDS believes that research using animals should be well regulated, conducted humanely and only when there is no alternative. Not all medical research needs to use live animals - useful results are also obtained by using computers, studying cells and tissues, and some studies that are done on patients and human populations. RDS puts the research processes in context, to explain when animals need to be used.

RDS would like to see a time when animal research that causes pain, suffering or lasting harm is no longer required, at least in many areas of research. However, society has unmet medical needs and there are gaps in our knowledge. RDS considers that current technical and scientific limitations mean that full replacement is unachievable in the foreseeable future.

The RDS was founded in 1908 by Dr Stephen Paget, at a time of intense public interest in medical research and animal welfare. Its comprehensive website contains useful information on animal welfare, the number of animals used in research, the types of animal and the research areas in which they are used. The number of animal experiments has halved over the last 30 years and is now roughly stable as the increasing use of genetically modified animals offsets reductions in the use of wild-type strains. The website lists some of the key medical benefits derived from animal research over the past century and also the benefits for animals themselves, mainly through the development of vaccines. It also has a recently-introduced hot topics and policy section that addresses current issues.

Richard Dyer, Chief Executive of the Biosciences Federation, receives an OBE

The British Neuroscience Association would like to congratulate Richard Dyer on the receipt of an OBE in the Queen's New Year Honours List. Richard receives the award for services to biology, particularly his contribution to the Babraham Institute and Babraham Research Campus.

Richard Dyer joined the Babraham Institute in 1974 as a neuroendocrinologist, becoming Head of Department in 1985. His distinct scientific contributions were on understanding how specialized nerve cells in the brain regulate hormone production and thereby control the female reproductive cycle. In 1986, he was awarded the Annual Medal of the UK Society for Endocrinology and, 1987, the Medal of the Polish Physiological Society. In 1994, he was appointed Director and led the Institute through a period of great change.

In 2005, just before his retirement as Director, the Institute was highly praised for the excellence of its research and scientific training in an independent assessment for the BBSRC, the Institute's main sponsoring Research Council. Richard Dyer's vision of an integrated campus, with researchers from both the academic and commercial ends of the biotech spectrum working in close proximity, has been realised. The "Babraham Research Campus", with its Bioincubator, is now the UK's most active location for start-up and emerging biotech companies, with another building due to open in late 2007 which already has multiple expressions of interest.

Dr Dyer is now Chief Executive of the Biosciences Federation, an umbrella organization representing the UK's biological expertise and providing independent opinion to inform public policy and to promote the biosciences. He is also Vice President of the European Science Foundation and continues as a member of the Babraham Bioscience Technologies Ltd. Board.

Dr John Bicknell, former Acting Director, said "I am delighted that Richard's contribution to the Babraham Institute and to the conception of the Babraham Research Campus has been recognized in this way. Richard was the prime mover in bringing the Institute to its current, highly respected status as a vibrant international research centre for discovery biology in the 21st century with its promise and potential for applications in biomedicine. This award to Richard is a richly deserved tribute from which his colleagues at the Institute will take great pleasure"

Genes to Cognition:
a neuroscience consortium for the scientific community

The Genes to Cognition (G2C) Programme (www.genes2cognition.org) is a systematic integrative research program that bridges basic and clinical neuroscience and was initiated by support from the Wellcome Trust. G2C is a consortium of scientists primarily based in the UK, studying synaptic molecules and their role in behaviour and disease. The G2C Programme collects and integrates data in the areas of psychiatry, human and mouse psychology, cellular neurophysiology and cell biology, proteomics and biochemistry, molecular biology, human and mouse genetics and genomics.

As neuroscientists, we seek to tackle one of the great scientific challenges - understanding the mechanisms of human behaviour – as well as help relieve the enormous burden of neuropsychiatric disease on our community. Lessons learned from the study of cancer and cell growth have told us that there were far more molecules, cell biological processes and, ultimately, disease types than ever expected. Importantly, these insights have emerged not from one technique or investigator but from integrating a diverse range of studies. There is no reason to suppose that the biology of brain diseases will be any less complex.

In several areas of biology it is now clear that large scale projects with publicly available data and distributed resources make an important contribution alongside traditional individual projects and collaborations. Large scale projects, through economy of scale, can expedite progress and remove the need (and cost) for many basic experiments in specialist laboratories. For example, we no longer need to perform in situ hybridisation to document the basic expression pattern of genes in the mouse brain because of the Allen Brain Atlas; we no longer need to manually clone and sequence a piece of genomic DNA from humans, mice and other species because of genome projects.

It is very early days for large scale projects in neuroscience. One type of program is where a single methodology is extensively employed (e.g in situ hybridisation). Another type of program is where multiple technologies or areas of study are integrated. Systematic programs that link basic and clinical neuroscience may be particularly useful to a broad sector of the neuroscience community.

G2C scientific strategy

The central theme of the G2C project is the study of multiprotein complexes, called NRC (NMDA Receptor Complex) or MASC (MAGUK Associated Signaling Complex), found at excitatory synapses in the mammalian brain. These complexes were isolated from mouse brain and found to have a surprisingly large number of proteins (~185). Over 50 of these have been implicated in human diseases. In experimental animal models such as the knockout mouse or drug studies there have been ~50 genes reported to alter the properties of synaptic plasticity and forms of behavioural plasticity. These behaviors include learning and memory, pain, visual and somatosensory plasticity amongst others. The NRC/MASC set of proteins is clearly very important for human diseases and animal models of those diseases. G2C scientists are conducting a systematic study of mutations and polymorphisms in mouse and human genes encoding postsynaptic proteins, and exploring how these genes influence a broad range of phenotypes - especially cognition.

Modular organisation of the consortium

The consortium has a modular architecture where different modules include specific scientific disciplines or activities (see Box 1). Details of people involved with these modules can be found on the G2C website. These modules provide a natural way for collaborators to join the program.

The connection between mouse and human genetics is central to the strategy. In brief, the human genetics involves clinical investigators interested in diseases of the brain (e.g. cognitive disorders; mental retardation, schizophrenia, bipolar disorder) and normal cognition (e.g. cognitive ageing and individual differences). Human DNA samples are sequenced and analysed for the NRC/MASC genes and variants identified. Because of the extensive information on these molecules in the G2C program from basic science studies the human genetic variants can be rapidly evaluated. Thus, there are several complementary aspects to the collaboration between clinical and basic scientists.

The study of the genes in mice typically involves the generation of knockout mice and examination of their behaviour (e.g. learning and memory tasks), neurpathology and electrophysiology studies. The data and all reagents are made available to collaborators and widely distributed. One important vehicle for distribution of data is the G2Cdb.

G2Cdb: an integrative databases for synapse biology

The G2C program has created an integrative database (G2Cdb) that links multiple databases (see Box 2). We are curating a comprehensive database of all mouse knockouts that have been studied in synaptic plasticity. Similarly we have built a knockout mouse behaviour database. We aim to make these databases repositories for published data (curated manuscripts), data generated in the G2C program as well as place for data submission directly by external groups. There is a linked database on the human genetics and disease affecting synaptic proteins. This in turn is linked to a further database on synapse proteomics.

Education and Training in G2C

Scientific research into the basis of behaviour and disease is of great interest to lay people. We recognise the importance of education on all aspects of the research program and rather than develop educational material after the research has been completed we are developing that material from the outset. The major collaborator in the educational program is the DNA Learning Centre at Cold Spring Harbor (www.DNALC.org). They are developing an education website and materials for schools and colleges called 'G2C Online'. This website will contain extensive information, videos and interviews that informs on all aspects of the G2C research program.

Participating in the G2C program

The G2C program welcomes new collaborators. The interactions, sharing of information and reagents through the program are proving to be very helpful in speeding progress. Using the modular framework of the program provides a simple way to identify connections. There are also training opportunities for students and scientists wishing to learn new methods. Send any enquires directly to Seth Grant (sg3@sanger.ac.uk) or through the website contact our collaborators.

By Seth Grant (email: sg3@sanger.ac.uk)

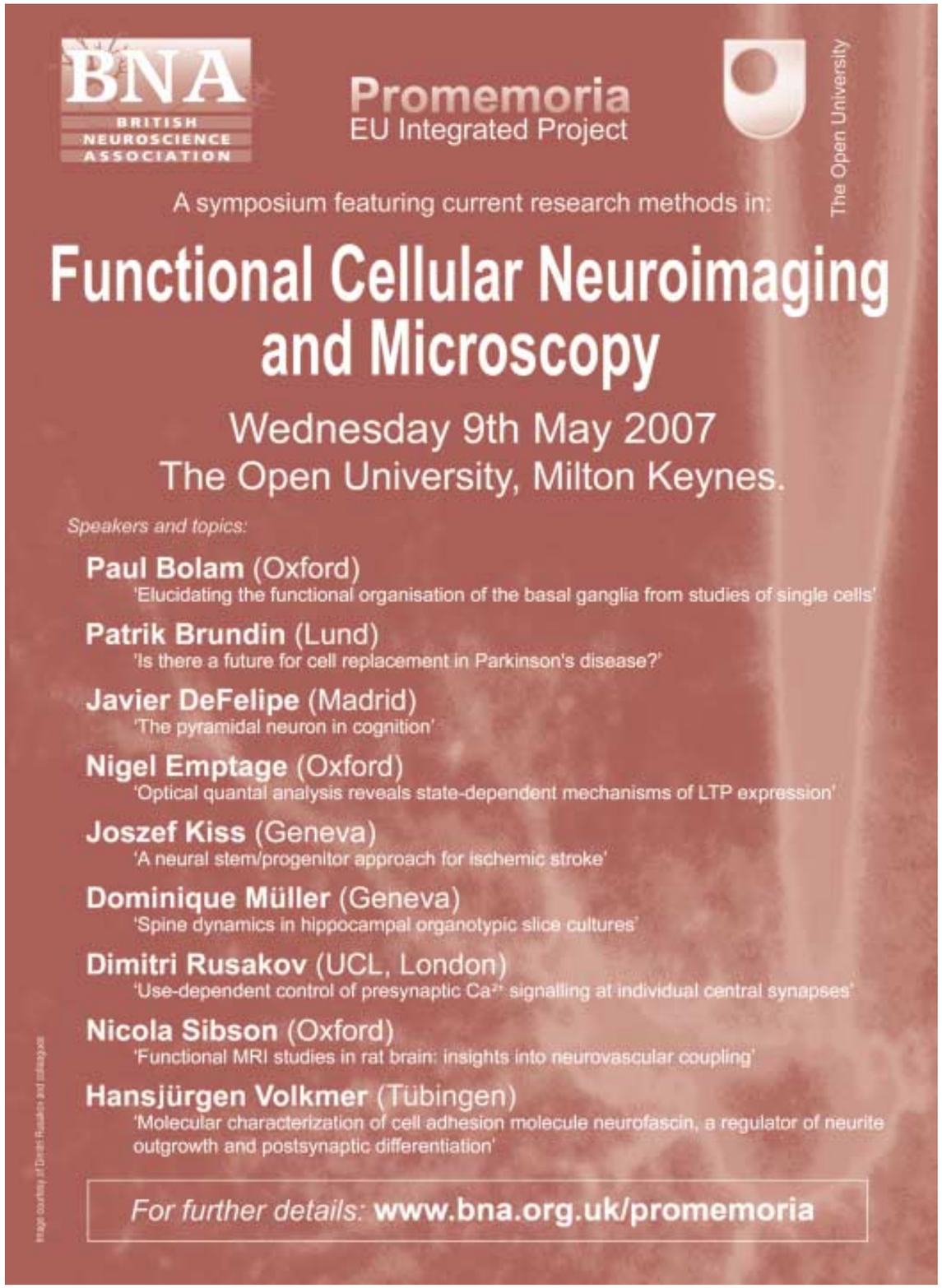
Box 1: Research modules

Human studies:
- Psychiatry & Psychology
- Clinical studies
- Sample collection
- DNA analysis

Mouse studies:
- Creation of mutants
- Molecular: RNA and proteomics
- Anatomy: Neuropathology
- Electrophysiology
- Behaviour

Box 2: Data resources

Database: G2Cdb
- Mouse genetics of synaptic plasticity
- Mouse genetics of behaviour
- Human genetics of synaptic proteins
- Synapse proteomics



Controversial Issues in Neuroscience

Talking therapies

all in the mind?

6.30pm for 7.00pm,
Wednesday, 27th June, 2007
at The Dana Centre
165 Queens Gate, London SW7

Join us for a lively café – bar discussion between therapists, psychiatrists, psychologists and others to discuss whether talking therapies can alter the brain as well as the mind.

Chaired by Adam Zeman (Professor of Psychology, Exeter).
Speakers will include Hanno Koppel (Psychotherapist, Director of Dover Counselling Centre), Chris Brewin (Psychiatrist, KCL) and Brid Hendron (Dentist, hyponotherapist).

Tickets are FREE but must be ordered in advance: contact - *tickets@danacentre.org.uk*

This is part of a series of continuing collaborative events between the European Dana Alliance for the Brain (EDAB) and the BNA

One Day Symposium

Bench to bedside in acute stroke – "Finding our way" or "Lost in Translation"?

A timely symposium to review the current status of clinical and preclinical stroke research and the current success of translating preclinical research to clinical efficacy

Wednesday, 17th October, 2007, at The Royal Society Edinburgh

Programme

- **9.30 to 11.00 Stroke treatments – where are we now?**

Chair – Richard Morris (Edinburgh)

- What treatments are available at present?
  Gary Ford (Newcastle)
- What treatments have been tested, and why have they failed?
  Philip Bath (Nottingham)

- **11.30 to 13.00 Stroke treatments – identifying therapeutic targets**

Chair: Charles Warlow (Edinburgh)

- A view from industry
  Richard Green (AstraZeneca)
- Inflammation
  Nancy Rothwell (Manchester)
- Novel Routes to Novel Targets
  James McCulloch (Edinburgh)

- **14.00 to 15.30 Bench to Bedside – from laboratory to ED**

Chair: Peter Sandercock (Edinburgh)

- The epidemiology of candidate neuroprotective drugs
  David Howells (Melbourne, Australia)
- Study quality in preclinical stroke studies
  Bart van der Worp (Utrecht, The Netherlands)
- Does study quality matter?
  Malcolm Macleod (Edinburgh)

- **16.00 Public lecture**
  Animal models of neurological disease – doing well, getting better?
  Richard Morris (Edinburgh)

Tickets will be FREE for members of the BNA and will include refreshments, lunch and evening reception (non-members, £65; student non-members, £30).
For further information and ticket reservations, contact: events@bna.org.uk, or tel: 0151 794 4943/5449.

GLIAL CELLS in health and disease

The VIIIth European Meeting

Imperial College, London
4th to 8th September, 2007

An international meeting that will examine neuron-glial interactions in development, health and disease, and the role of glia in stem cell biology and regeneration. Imperial College is one of London's largest academic venues, located in the heart of the museum and cultural district.

There will be nine plenaries, twenty-one symposia, lively themed poster sessions, an exhibition and a full range of social events.

PLENARY LECTURERS:

Dwight Bergels (Maryland, USA)
Marie Filbin (New York, USA)
Peter Brophy (Edinburgh, UK)
Ron McKay (Washington, USA)
Helmut Kettenman (Berlin, Germany)
Bill Richardson (London, UK)
Patrick Charnay (France)
Pierre Magistretti (Lausanne, Switzerland)
Linda Watkins (Colorado, USA)

SYMPOSIA:

- Neurotransmitter signalling to oligodendrocytes and neurological disease
- Microglia: agents of neurodestruction or neuroprotection?
- Signals from the extracellular matrix in glial development
- Cancer stem-like cells in malignant gliomas
- Repair in CNS demyelinating disease
- Glial migration in the developing and pathological brain
- What can we learn from insect glia?
- Fate decisions in neural stem and progenitor cells
- Ependymal cells and the cerebrospinal fluid
- Diverse regulatory roles for gliotransmitters at the tripartite synapse
- Glial cells in acute neurological diseases: novel approaches to understand pathophysiology and endogenous glial repair mechanisms.
- Glial regulation of chronic pain
- Functional role of Bergmann glia-purkinje cell signalling
- How do glial-axonal interactions impact the organization of the node of ranvier?
- Neuroinflammation: a two-edged sword
- Transcriptional control of differentiation in myelinating cells
- Glia in spinal cord injury and regeneration
- Mechanisms of myelination
- Pannexins: an alternative pathway for cell-cell communication
- The role of astrocyte dysfunction in epilepsy
- The molecular pathology of myelination

ABSTRACT DEADLINE: 1st May, 2007

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RECENT PROGRESS IN MIGRAINE RESEARCH

Simon Kaja is a Postdoctoral Research Associate in the laboratory of Professor Terrance Snutch at the University of British Columbia, Vancouver, having recently obtained his PhD from the University of Leiden. He is interested in the pathophysiological mechanisms of epilepsy and familial hemiplegic migraine, amongst other things, and his many awards and prizes include the BNA's Undergraduate Award 2002/2003 for his outstanding achievements at Durham University, supervised by Dr Chris Thompson. Here, he describes how genetic models for migraine are enhancing our understanding of the pathophysiology of the disease and have defined a molecular basis for migraine on which to focus research efforts.

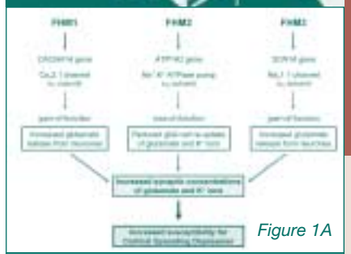

Figure 1A

Figure 1A. Mutations in all three known loci for FHM result in increased levels of the neurotransmitter glutamate, resulting from increased glutamate release from the pre-synaptic terminal (FHM1 and FHM3), or reduced clearance of glutamate and K^+ ions from the synaptic cleft by astrocytes (FHM2). As a result, FHM brains are more susceptible to cortical spreading depression (CSD), which underlies migraine aura and is a potential migraine trigger (modified from[10]).

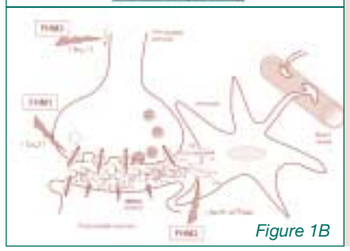

Figure 1B

Figure 1B. A glutamatergic synapse. The locations of the three known FHM loci are indicated. Cav2.1 channels mediate the calcium influx required for glutamate release; Na^+,K^+-ATPases are expressed in astrocytes and involved in maintaining Na^+ and K^+ gradients, required for the active re-uptake of glutamate; Nav1.1 channels mediate the generation of pre-synaptic action potentials. Upward arrows indicate a gain-of-function of the protein (FHM1 and FHM3), the downward arrow a loss-of-function (FHM2). Modified from[9].

We have all heard about migraine. And with more than five million migraine sufferers in the UK alone, we probably all know at least a few of them. However, what do we know about migraine as a disease? The answer is probably not very much and this is not in the least surprising, as, unless we or someone in our household suffers migraine, we are unlikely ever to witness the extent of a full-blown migraine attack. This has, in the past, prevented the broad social acceptance of migraine as a severe and very disabling disorder. In this short review, I shall briefly describe the clinical features of migraine and highlight recent research on currently available genetic models of migraine.

Clinical Spectrum and Epidemiology

Migraine is an episodic neurovascular disorder that affects approximately 6-8% of men and up to 25% of women in the general Western population. It is estimated that approximately 12% of the general population have 18 migraine days per year, which poses a substantial burden on the affected individual and society. Within the European Union, the annual cost associated with migraine exceeds £6 billion. The World Health Organization, therefore, ranks migraine amongst the twenty most-disabling disorders. Since 1988, migraine has been defined by diagnostic criteria established by the International Headache Society[5] and is commonly grouped into migraine without aura and migraine with aura. As such, a migraine attack can consist of up to three phases: 1) the *prodrome*, with symptoms preceding the headache and suffered by about one-third of patients; 2) the migraine *aura*, experienced by about 25-30% of migraine sufferers; and 3) the characteristic severe, unilateral (one-sided) and often pulsating *headache* that can last anywhere between hours and days.

Typical symptoms suffered during the prodromic phase include retention of fluids, craving for certain types of food and mood changes. This phase signals the onset of a full-blown migraine attack. Those suffering migraine with aura will experience an aura phase. The migraine aura is characterised by neurological symptoms, which are typically perceived as visual impairments (seeing dots, flashing lights, or blind spots), but which can also include speech and movement difficulties or affect sensation. The migraine headache associated with an attack takes the shape of a severe, unilateral throbbing pain occurring around the eyes and temples. The headache is accompanied by nausea and increased sensitivity to light (photophobia) and/or sound (phonophobia).

Migraine Pathophysiology

The migraine headache appears to result from the activation of the trigeminovascular system, consisting of the meningeal and superficial cortical blood vessels, which are innervated by the trigeminal nerve. Projections of the trigeminal nerve through the brain stem (specifically the trigeminal nucleus caudalis) activate higher order pain centres resulting in headache pain[4].

A series of carefully conducted experiments both in the rodent and human brain have led to the now generally accepted hypothesis that migraine aura arises directly from a phenomenon termed cortical spreading depression[7] (CSD). CSD is characterised by a slowly propagating wave of strong neuronal depolarisation across the cortex that is followed by a long-lasting neuronal suppression. Once CSD reaches the visual cortex, the ensuing neuronal silencing results in the characteristic visual aura symptoms.

Specific medication for migraine is available. However, only about 50% of migraine patients respond satisfactorily to the drugs. The design of effective and prophylactic migraine treatments is hampered by our lack of detailed mechanistic knowledge on how migraine attacks are initiated. It has been suggested that CSD itself may be an initial migraine trigger, and recent animal experiments indeed provide some evidence for a potential link between CSD and migraine headache. Specifically, experimentally-induced CSD in rats was shown to activate the trigeminal system and evoke changes in the meninges and brainstem consistent with the development of headache pain[1]. However, direct evidence for such a causative relationship between CSD and trigeminal activation is still lacking in humans.

Migraine Genetics

Migraine (both with and without aura) shows a strong genetic component and is thought to be of multifactorial origin. However, to date no direct gene involvement could has been shown. It is generally assumed that a genetic pre-disposition reduces trigger thresholds for migraine. However, as knowledge of the nature of migraine triggers is lacking, research efforts have focussed on a severe and very rare inherited form of migraine: familial hemiplegic migraine (FHM). FHM is characterised by attacks of migraine with aura, associated with ictal hemiparesis (half-sided body paralysis during the attack). FHM is generally considered a valid model for the more common forms of migraine, especially since FHM patients frequently suffer attacks of 'common' migraine. Three distinct genetic loci for FHM have been identified to date; all resulting in dysfunction at the synaptic level (Figure 1).

> 'Within the European Union, the annual cost associated with migraine exceeds £6 billion. The World Health Organization, therefore, ranks migraine amongst the twenty most-disabling disorders.'

Mutations in the CACNA1A gene, encoding the alpha-1 subunit of neuronal Cav2.1 calcium channels, are associated with FHM1[8]. These channels are expressed widely in the nervous system, where they are directly involved in the release of neurotransmitter molecules from synaptic nerve terminals. Following an electrical stimulus, the synaptic membrane depolarises allowing Cav2.1 to open and to mediate an influx of calcium ions into the synapse. These calcium ions cause vesicles containing neurotransmitter to fuse with the outside membrane resulting in the release of neurotransmitter molecules, such as glutamate. FHM1 mutations result in increased calcium influx through the mutated Cav2.1 channels, and hence, augmentation of neurotransmitter release.

The FHM2 locus is the alpha-2 subunit of Na^+K^+-ATPase (ATP1A2)[2]. Maintaining a fine homeostatic balance between essential ions (by transporting Na^+ out of and K^+ into the cell), these pump proteins also play an important role in astrocyte ion balance that allows for clearing neurotransmitter from the synaptic cleft following its release from the pre-synapse. It is perceivable, how FHM2 mutations that result in a loss-of-function of ATP1A2 lead to reduced astrocytic uptake of neurotransmitter.

The recently identified FHM3 locus is in the neuronal Nav1.1 sodium channel, encoded by SCN1A[3]. Nav1.1 channels are required for the generation and propagation of pre-synaptic action potentials, thereby directly influencing likelihood and frequency of neuronal firing. Those SCN1A mutations identified to date result in an enhanced recovery of Nav1.1 channels from the inactivation that occurs after their opening by depolarisation, allowing for a higher frequency of pre-synaptic action potentials.

It appears thus that each of these FHM mutations cause altered ionic homeostasis that ultimately results in increased levels of neurotransmitter (mostly of the excitatory neurotransmitter glutamate) in the brain; either by the increased release of glutamate (in the cases of FHM1 and FHM3) or by reduced clearance of glutamate by astrocytes in the case of FHM2 (Figure 2).

Genetic Migraine Models

One of the biggest challenges to migraine research has been the unavailability of sensitised or genetic (animal) models. Recently, however, transgenic knock-in mice have been engineered to carry mutations, originally found in FHM1 patients, in the orthologous mouse Cav2.1 channel.

Knock-in (KI) mice carrying the human CACNA1A R192Q mutation (a single amino-acid change from arginine to glutamine in the Cav2.1 channel) do not show any overt neurological or anatomical phenotype and appear healthy[11]. However, electrophysiological recordings of neurotransmitter release both in the central and the peripheral nervous system showed significantly enhanced neurotransmitter release[6,11].

Cerebellar granule neurones isolated from brains of R192Q KI mice have increased neuronal calcium currents. At the peripheral neuromuscular junction (a synapse almost exclusively dependent on Cav2.1 channels for acetylcholine release), R192Q KI mice had increased evoked and spontaneous neurotransmitter release under conditions similar to those occurring in the brain during CSD (i.e. low extracellular Ca^{2+} and high K^+ levels). These changes in neurotransmission have been demonstrated to be functional, resulting directly from altered biophysical properties of the FHM1-mutated Cav2.1 channel rather than originating from e.g. morphological abnormalities. Heterozygous FHM1 R192Q KI mice show an intermediate synaptic phenotype in accordance with the autosomal dominant inheritance pattern in humans. Experimental studies in R192Q KI mice revealed both a reduced threshold and an increased velocity of CSD, indicating that Cav2.1 channel mutations can influence the initiation and propagation of CSD.

A second FHM1 KI mouse model (carrying the serine to leucine amino acid change at position 218) has been generated and is currently being studied. However, no genetic models for either FHM2 or FHM3 are available yet. Taken together, FHM1 R192Q KI mice and other transgenic FHM KI mice can serve as useful models to investigate migraine pathophysiology and will be instrumental in discovering migraine triggers and testing novel therapeutic approaches.

Conclusion and Outlook

The identification of FHM-associated mutations in genes encoding two ion channels and an ion-transporting ATPase has increased our understanding of the pathophysiology of the disease and defined a molecular basis for migraine, on which to focus research efforts. A further boost has come from the generation of genetically sensitised mouse models. These new genetic models will aid research efforts into the nature of migraine triggers and the increased sensitivity to them in migraine patients. These insights will be instrumental for developing in particular novel prophylactic migraine therapies.

Acknowledgements:

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Links: The Migraine Trust (www.migrainetrust.org)

(See page 22 overleaf for references)

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Nicotinic acetylcholine receptor signalling and Alzheimer's Disease: exploring new targets for therapy

Steven Buckingham is a senior research associate at the MRC Functional Genetics Unit where he has been a regular collaborator with David Sattelle for many years. He is interested in invertebrate and human cell-line models of Alzheimer's Disease, and uses electrophysiology, calcium imaging and bioinformatics as tools to explore patho-physiological mechanisms. Here, he discusses how an understanding of the roles of nAChRs in particular, and their associated signalling proteins, may assist the discovery of new targets for the treatment of Alzheimer's disease.

A summary of neuroprotective and Aβ-associated degenerative pathways at the cholinergic synaptic terminal. Activation of α7 nicotinic acetylcholine receptors by nicotine activates the PI3K/Akt pathway which protects neurons from Aβ toxicity. Aβ acts upon nAChRs to activate MAPK/ERK pathways resulting in cell death. Several drugs currently used in the treatment of AD reduce the breakdown of ACh by acetylcholinesterase (AChE), thereby elevating the quantity of ACh available to activate nAChRs. One of these, galantamine, can also act directly on nAChRs to evoke the neuroprotective pathways. For clarity, α7 nAChRs are shown on the presynaptic neuron only: although most brain α7 nAChRs are thought to be presynaptic, they can be located postsynaptically at certain synapses. Note that although memantine is known to act primarily through glutamate receptors, there is also evidence that it also has actions at ACh receptors.

Alzheimer's Disease (AD) is a debilitating neurodegenerative disease involving degeneration of predominantly cholinergic neurons, particularly in the basal forebrain inputs to the hippocampus and cortex [46]. The Alzheimer's Society estimates that dementia currently affects over 750,000 people in the UK, some 55% of which is AD, and by 2010 the problem is likely to be exacerbated with an expected 870,000 cases in the UK (http://www.alzheimers.org.uk/News and Campaigns/Policy Watch/demography.htm). However, current therapies are of limited effectiveness, and so the discovery of new drug targets is a matter of urgency. A key step in identifying such targets is to develop a clearer understanding of the pathways that cause neurodegeneration in AD as well as those that protect cells against damage by peptides associated with disease pathology. It is clear that oligomers or aggregates of the β-amyloid peptide (Aβ) play an important role in the development of AD and recent studies indicate that brain nicotinic acetylcholine receptors (nAChRs) not only are affected by Aβ, but also initiate signalling pathways protective against Aβ toxicity. Thus, understanding the roles of nAChRs and their associated signalling proteins may assist the discovery of new targets for the treatment of AD.

Nicotinic acetycholine receptor loss

Brain nAChRs are ligand-gated ion channels consisting of five subunits that form a central, cation channel which opens in response to the binding of the neurotransmitter, acetylcholine (ACh). Brain nAChRs are generated from α (α2-10) and β(β2-4) subunits. The 3 most important brain receptors are composed of α7, α4β2 and α3β4 subunits. Brain nAChRs have been the subject of studies on the development of AD for the following reasons: 1) the most vulnerable neurons in AD appear to be those expressing high levels of nAChRs, particularly those containing the α7 subunit [9]; 2) the numbers of nAChRs and some of their associated proteins change in AD; 3) nicotine and acetylcholinesterase (AChE) inhibitors (currently used for treatment for AD) can protect cultured neurons from amyloid toxicity via nAChRs [1, 2]; 4) Aβ binds with high affinity to α7 nAChRs [45]; and 5) polymorphisms of neuronal nAChRs may be linked to AD [43]. It is clear that AD involves loss of cholinergic neurons in the brain [11, 31] as well as an overall reduction in nAChRs [32-34] and that different subunits are differentially up- or down-regulated in AD in a tissue-specific manner [18], although there are conflicting data on the details of the subunit- and tissue-specificity of these changes.

Direct actions of Aβ on nAChRs

Aβ affects nAChRs directly, and most reports indicate that Aβ is an antagonist at nAChRs: for example, Aβ inhibits single channel nicotinic receptor currents in rat hippocampal interneurons [35] as well as α7 receptors heterologously expressed in Xenopus oocytes [17, 36]. However, Aβ activates a mutant (L250T) of the α7 receptor - this mutant conducts current in the desensitized state, indicating that Aβ may exert its antagonistic action through receptor desensitization [17]. In addition, Aβ action on nAChRs depends on subunit composition, as it has been reported to block α7, transiently potentiate α4β2 prior to blocking and have no action on α3β4 [36].

Although most studies report the absence of agonist actions of Aβ, there are some reports of Aβ acting as an agonist at low concentrations (1-100 pM) and blocking at higher (nM) concentrations [13]. Similarly, Aβ has been shown to activate α7 nAChRs in rat basal forebrain neurons [16] and to cause a calcium responses in presynaptic terminals isolated from rat hippocampus and neocortex [15]. Again, despite numerous reports of a block of α7, one study indicated that Aβ failed to block α7, even though it blocked α4β2α2β2 and α4α5β2 receptors [24]. Some of these conflicting reports are likely to arise either from differences in the aggregation state of the Aβ used, which is notoriously sensitive to the method of preparation and storage. In addition, complex interactions with receptor-associated proteins and/or intracellular signalling pathways that modulate nAChRs may account for differences between native receptors from different cell types and the various host cells used for recombinant receptor expression. Furthermore, although Aβ binds with high affinity to α7 receptors heterologously expressed in Xenopus oocytes [45], indicating that some at least of Aβ's actions on nAChRs are the result of direct binding to the receptors, the possibility remains that Aβ actions on nAChRs are indirect, via other functionally-linked proteins.

Aβ evokes signalling cascades via nAChRs

Aβ initiates intracellular signalling cascades via nAChRs, including the MAPK kinase signalling pathway, resulting in cell death. In hippocampal slices, Aβ activates extracellular signal-regulated kinase (ERK2) isoforms of the ERK mitogen-activated protein kinase (MAPK). The sensitivity of this effect to block by α7 nAChR antagonists confirms that Aβ evokes this cascade through α7 [14]. Which pathway is activated by Aβ depends upon the time of exposure to the amyloid peptide: chronic applications of oligomeric Aβ to hippocampal slice cultures activate the JNK MAPK pathway but inhibit the ERK MAPK pathway, whereas acute applications of Aβ oligomers do not activate JNK [4]. In neuroblastoma cells, as well as cultured hippocampal neurons, Aβ activates JNK and ERK and blocking these stops Aβ hyperphosphorylating tau, as does α7 antisense oligonucleotides or α7 antagonists, suggesting that Aβ may trigger tau phosphorylation through ERK and JNK via α7 receptors [44].

nAChRs mediate neuroprotection

Nicotine and its mimetics can protect neurons against Aβ toxicity [23], and α7 receptors play a particularly prominent role in nicotine protection. This protective effect is blocked by the nicotinic antagonists, dihydro-β-erythroidine and mecamylamine [22, 41], including the α7-selective antagonist methyllycaconitine [30], indicating that the protective action of nicotine is exerted through nAChRs, notably α7. In addition to nicotine, donepezil, rivastigmine (acetylcholinesterase inhibitors currently used as treatments for mild or moderate AD under the brand names of Aricept and Exelon) also protect cultured neuroblastoma cells from the toxic effects of Aβ and this effect is blocked by antagonists of α7, but not of α4β2 receptors [2]. Curiously, although most studies agree that nAChRs need to be activated for their protective effects to occur, mouse cortical neurons are protected by the α7 antagonist methyl lycaconitine [30], raising the possibility that neuroprotection by α7 agonists may be through desensitization rather than activation of this rapidly desensitizing receptor. This is of interest and consistent with the α7-dependent activation of intracellular signalling pathways by Aβ [4]. Activation of nAChRs also protects against other aspects of Aβ action: nicotine inhibits free radical accumulation and calcium dyshomeostasis in cultured hippocampal neurons [28].

Nicotinic neuroprotection pathways

The PI3K/Akt pathway

The PI3K/Akt pathway is a well-established anti-apoptotic pathway and has been identified as one important component of nicotine neuroprotection [22]. The neuroprotective effects of nicotine are blocked by inhibitors of either PI3K or SRC-family kinases, and nicotine evokes an increase in levels of phosphorylated Akt, Bcl-2 and Bcl-x [38], which are downstream in the PI3K/Akt pathway. The protective effects of acetylcholinesterase inhibitors on neuroblastoma cells is prevented by a blocker of the phosphoinositide 3-kinase (PI3K)-Akt pathway [2]. Janus kinase (JAK2) is another early target in the nicotine neuroprotection pathway and may mediate signalling between the nAChR and the PI3K pathway [37]. Indeed, JAK2 may play have a wider role in neuroprotection as it also appears to be involved in erythropoietin neuroprotection against hypoxic stimuli [12, 40]. JAK2 is also activated by nicotine in non-neuronal cells such as keratinocytes [3].

How does activating the PI3K pathway by nAChRs protect neurons? One route is through upregulating the expression of the anti-apoptotic protein, Bcl2. The AD therapeutic AChE inhibitors donepezil, galantamine and tacrine increase Bcl2 expression when applied to cultured neuronal cells [41]. However, nAChR-mediated neuroprotection may also involve pathways other than those regulating apoptosis. For instance, over-expressing PI3K in Drosophila neurons *in situ* resulted in an increase in functional synapses as well as synaptic sprouting [29]. So it is possible that nicotine's neuroprotective pathways include PI3K upregulation resulting in increased synaptic stability. The pathways linking nAChRs and synaptic stability may provide new drug targets for treating AD.

Tyrosine-kinases

Members of the SRC-family kinases, such as SRC and FYN, are physically associated with nAChRs [22], but their potential role in Aβ toxicity and nicotine protection is unclear. FYN expression is increased in AD brains, specifically in a subset of neurons with

elevated hyperphosphorylated tau protein [39], but it is unclear whether this increase in FYN contributes to hyperphosphorylation of tau or is a protective response to it. In extracts of human AD brains, soluble FYN increases with cognitive score and synaptophysin levels and inversely with the tangle count, suggestive of a protective role for FYN [19]. It has also been shown that FYN can activate the PI3K/Akt cascade, thereby inhibiting apoptosis [42]. Furthermore, SRC inhibitors also prevent nicotinic protection of differentiated PC12 cells against serum-deprivation-induced cell death [26] and inhibitors of FYN or JAK2 block the neuroprotection against Aβ toxicity of therapeutic acetylcholinesterase inhibitors [41]. However, FYN may paradoxically also play a role in Aβ toxicity. Indeed, Aβ activates both FYN and the PI3K cascade [47], while germline knockout of FYN is neuroprotective in mice [6, 25]. More research is therefore needed to determine the complex roles of this potential therapeutic target in AD and neuroprotection.

One receptor, two opposite outcomes

How can nAChRs mediate both the toxic actions of Aβ and the protective actions of nicotine? Perhaps there is some way in which these ligands operate different signalling pathways. The simplest explanation might be that Aβ's antagonist actions block the therapeutic effect of nAChR activation. Setting aside the controversy over the actions on nAChRs of Aβ, this explanation is unlikely to offer a full explanation because Aβ alone evokes the ERK/MAPK signalling cascade through α7 nAChRs. Nicotine activates the ERK pathway but via a different route to Aβ, involving PKA [4]. Thus, α7 receptors appear to be differentially coupled to different downstream signalling pathways depending on which ligand is bound and, in the case of Aβ, on the aggregation state and time of exposure. Further studies are required in order to understand more fully how the balance of signalling cascades can determine the survival of neurons.

nAChRs and calcium signalling

The nAChRs may provide a link between Aβ and disruption of calcium homeostasis, which is also thought to play a part in AD. The α7 subtype may be of particular relevance since it is much more permeable to calcium ions than most nAChRs. Acute application of Aβ to the human neuroblastoma cell line results in a rapid increase in intracellular calcium ions which is dependent upon both α3β2 and α7 nAChRs. This calcium signal arises from three sources: influx of extracellular calcium through voltage-gated calcium channels, release of calcium from intracellular stores, and calcium influx through the α7 receptors. It has been shown that the α7 receptors, but not the α3β2, specifically trigger calcium release from intracellular stores by activating ryanodine receptors [10]. Such a specific functional coupling of α7 receptors and ryanodine-sensitive stores may provide another site of therapeutic intervention.

Conclusion: nAChRs as a route to new therapies

While it is clear that Aβ kills neurons and nicotine protects them against Aβ toxicity, much remains to be resolved to unravel the mechanisms by which death or survival is the outcome. Intracellular signalling initiated by Aβ and nicotine is complex and involves much cross talk between diverse signalling pathways, arguing for a systems-based approach to understanding precisely how nicotine or Aβ can determine a cell's fate. Such a task could be facilitated by the deployment of mutant suppressor and RNAi screens as well as the ease of transgene production, afforded by invertebrate model genetic organisms [5, 7, 8, 20, 27]. Identifying new components of these pathways offers the prospects of new targets for the treatment of AD. In addition, because α7 receptors are present in human lymphocytes, AD-related alterations in expression of the receptor and/or key associated proteins in these cells may form the basis of a biomarker for early detection of AD or evaluating progression of the disease and responsiveness to drugs [21].

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National Brain Science Writing Prize 2006
Winning entries

As part of our commitment to communicating progress in brain research to a wider audience, the BNA last summer again joined forces with 'Your Amazing Brain' website and the European Dana Alliance for the Brain (EDAB) to host another national 'Brain Science Writing Competition'. There were two categories: a **researcher category**, open to anyone actively engaged in neuroscience research, from postgraduate students to professors; and a **general category**, for anyone at all with a passion for writing about science. The brief was to communicate something inspiring and informative in maximally 750 words, and in a style that would be accessible to all, much like a national newspaper article. The result was a fascinating array of essays, including a wonderful collection from Year 10 pupils at Tudor Hall School, Banbury, Oxfordshire. On behalf of the three judges, Dr Penny Fidler (Your Amazing Brain website), Dr Yvonne Allen (BNA) and Elaine Snell (EDAB), we hope you enjoy reading the winning entries in each category and a couple of those deemed 'highly commended', including one from a sixth former.


REBECCA POOLE

General Category – 1st Prize

The truth, the whole truth and nothing but…?

Have you ever witnessed a crime or wondered how good a witness you would be? If a person pushes past you on your way home one night and it later becomes apparent they had just committed a crime, would you be able to recall their age, build, hair colour and clothing? Many people find themselves a witness to a crime and are called upon to provide evidence which often replies upon their ability to remember tiny details about a person or event.

Most people forget information either temporarily, for example when you can't think of a particular word, or more permanently, where details of an experience are lost over time. However, even when our memories can be recalled with vivid detail, they are not necessarily an absolutely true account of what happened. For example, memories of something we do regularly, like shopping, can become blurred into one generic recollection. Perhaps more fascinating is the observation that we can unwittingly fill in gaps in our memory with an imagined detail and, even if we initially remember correctly, our memories can later be overwritten with new false memories. These observations beg the question, how reliable are our memories and how easily can they be manipulated? A question which is of great significance for the validity of eyewitness accounts of crimes.

Dr. Giuliana Mazzoni, Reader in Psychology at Plymouth University, believes that it is all "too easy" to manipulate a person's memory and has demonstrated the mere suggestion that an individual has witnessed or experienced something can be enough for them to create a memory of it. Although this research was carried out under strictly controlled laboratory conditions there is some suggestion that this can also happen in the 'real world'. In 2002, one of the major news stories was of the sniper attacks in Washington DC, where 10 people were killed. Eyewitnesses reported seeing a white van leaving several of the crime scenes. The perpetrators were later caught and found to have been using a blue car. It seems that a white van was seen in the vicinity of one of the first attacks and the constant reporting of this by the media is thought to have influenced the memories of the witnesses to the later attacks who also 'remembered' seeing a white van fleeing the scene. By expecting to see a white van, the witnesses to the later sniper attacks had invented a memory to fit in with what they were primed to believe might happen.

In addition to the media, other witnesses, or even the interviewer taking eyewitness statements, can influence memories of an event as demonstrated by Professor Maria Zaragoza of Kent State University, USA. By forcing individuals to make up answers to questions about scenes they had not witnessed, memories of the fictitious events were generated and, during later questioning, recalled and believed to be true.

Dr Mazzoni's and Dr Zaragoza's research suggests that during the interview process it would be extremely easy for the interviewer to impose their beliefs on the interviewee, either by subtle suggestion, or by inflicting pressure to provide answers to questions, which could result in the generation of false memories. The implications of which are far reaching. For example, if part of an eyewitness' testimony proves to be wrong, their entire account could be dismissed, even if the remainder is good. And, worryingly, Dr. Mazzoni believes, "A good interview is a relatively rare phenomenon, still",

What's most puzzling is how false memories are recalled as though real and yet no memory exists of the forced responses, or even the knowledge that originally you simply couldn't remember that detail. Dr. Mazzoni suggests that this "can be due to the fact that people remember the content, but forget the source of the content". How many times have you recalled a fact, but have been unable to remember how or why you would know that piece of information? False memories are further strengthened by the very act of producing them, resulting in very strong traces that are indistinguishable from real memories.

While it seems false memories are virtually unavoidable, it is clear that more care should be employed when taking witness statements and that, for high profile cases, the potential influence of the media should not be underestimated. If you are unfortunate enough to witness a crime, there is a simple piece of advice - try to write down what you saw as soon as you can.

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By Rebecca Poole
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Rebecca Poole graduated with a degree in Biology from Southampton University in 1999. She stayed at Southampton to study for a PhD. in Plant Pathology and, in 2003, joined the Functional Cereal Genomics group at Bristol University to investigate genetic factors that influence bread making quality in wheat. Rebecca enjoys the challenge of science communication and currently volunteers for the Bristol and Bath branch of the British Association for the Advancement of Science.

General Category – 2nd Prize: Genes for alcohol use turn up in drunk worms and Cheapdate flies

BY KATE HOLDEN-DYE

Inebriated worms and drunken flies are helping researchers pick the genetic locks that drive some of us to drink. At Southampton University, scientists are busy studying the wriggling of worms in alcohol. The worms in question aren't the familiar earth worms you dig up in the garden, “they are natural soil dwellers like earth worms”, says Prof Holden-Dye, “but these worms are much smaller. They are only just visible to the naked eye”. *C. elegans* are in fact just over 1 mm long. Somewhere way back on the path of evolution, they went their way and we went ours. Interestingly for researchers, however, these worms behave in much the same way as any of us after one too many. “What's been previously observed by other scientists is that worms initially become overexcited in alcohol, but then as the amount of alcohol increases they get sluggish”, says Prof Holden-Dye. Other researchers are using fruit flies instead of worms to demonstrate the same effects. Fruit flies positively love a drink it seems, perhaps not that surprising considering their fondness for rotting fruit. Scientists measure how unsteady on its feet a drunken fruit fly is by watching how quickly it tumbles through an aptly titled device, the “Inebriometer”. The drunker the fly, the more quickly it emerges out of the bottom.

So what is it exactly that scientists are hoping to learn by observing drunk worms and flies? “There is evidence that some worms are better at holding their drink than their others, essentially there is variation as to how quickly they get drunk,” says Prof Holden-Dye,” other worms aren't good at building up tolerance to the effects of alcohol; worms that have become tolerant are more resistant to the effects of alcohol after more than one exposure”. The same is seen in flies. It has been known for some time that these two factors, initial sensitivity to alcohol and tolerance, might be linked to the development of alcohol abuse problems in the general population. “ This definitely isn't the full story”, says Prof Holden-Dye, “but they are obviously important factors that we can look at in worms and other organisms like fruit flies and that might say something about how we deal with alcohol. We still don't really know that much about how alcohol acts on our brains”.

The Holy Grail is to find genes that are tied up with how the brain is affected by alcohol and those which may play a part in making some of us more likely than others to develop a dependency problem. The human brain is jaw-droppingly complex with billions of neurones, the specialised cells that comprise the brain and nervous system, and trillions of synapses, the junctions between neurones that act as communication gateways. It performs tasks of unimaginable complexity in the blink of eye. Frankly, our brains stick two fingers up at even the most sophisticated of computers we have today. By comparison, *C. elegans* has a relatively reserved 302 neurones, each one of which has already been exquisitely mapped by scientists. These substantially more simple organisms are Nature's gift to those in the genetics business. In much the same way as it's advisable to learn your alphabet before you start on the great works of Shakespeare, scientists are starting their search for interesting genes in worms and flies. So far this approach is proving fruitful. *Cheapdate* (does what it says on the tin, a *Cheapdate* fly gets drunk very quickly) and Hangover are two genes that have been identified in fruit flies and numerous others have wriggled their way into the spotlight in worms. Excitingly, some of these genes are also known to be at least partly responsible for governing how these organisms respond to certain stresses, adding credence to the long held belief that stress and drug and addiction behaviours are linked in all of us. The hard task now is to pin down exactly what these genes and others like them do, so we can begin to unravel how alcohol really works it magic or wreaks its havoc on our brains.

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***Kate Holden-Dye** obtained a BSc in Biochemistry and is now finishing off a PhD at the University of Bristol in the School of Medical Sciences. Her PhD focuses on the stability of an integral membrane protein.*

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Researcher Category – 1st Prize: Scientists reveal that autism and hyperactivity have the same cause


ANGELICA RONALD

Although Dustin Hoffman gave one of the most famous portrayals of autism in *Rainman*, his co-star Tom Cruise's hyperactive performance on Oprah Winfrey's sofa more recently may also be a good depiction, if recent science is to be believed! Amazingly one in three individuals with autism are hyperactive and inattentive, a condition known as ADHD (attention deficit hyperactivity disorder).

Perhaps a lead role involving both autism and ADHD would be too ambitious even for Dustin, but off-screen, autism and ADHD are closely linked. Both conditions begin in childhood and are associated with differences in the brain. It might be, however, that brain differences do not cause autism or ADHD, but arise as a consequence of living with autism or ADHD. On the other hand, we know that genes play a part – but until now we didn't know whether the same genes cause autism and ADHD.

That is why my colleagues and I at the Institute of Psychiatry carried out a study on autism and ADHD in over 6000 pairs of twins. No study until now has had the scope to tackle this issue. TEDS (the Twins Early Development Study) included identical twins, who share all their genes, and fraternal twins, who share half their genes.

Double trouble

We compared how alike one twin's level of autistic behaviours were with the other twin's amount of ADHD behaviours. If the same genes cause both autism and ADHD it is expected that in identical twin pairs, who share all their genes, the level of autistic behaviours in one twin and the amount of ADHD symptoms in the other twin will be the same. Less similarity between autistic and ADHD behaviours would be expected in fraternal twins because they do not share all their genes. This is what we found.

The results showed that at the genetic level, autism and ADHD weren't so different. It became clear from our findings that more than half the genes for one were also influencing the other.

Symptom-specific effects

Of course, it is not that simple. A complication is that both autism and ADHD consist of several different types of symptoms. Odd social interaction, communication problems and obsessive and repetitive behaviours are all part of autism, and ADHD includes inattentiveness and hyperactivity. Earlier work by our group has shown that the different autistic symptoms are caused by mostly different genes. So as well as just looking at the overlap between autism and ADHD as a whole, we needed to look at overlap between the separate symptoms.

In this next stage, we found that it was the communication difficulties in autism that were caused by the same genes as ADHD. In contrast, the obsessive and repetitive behaviours showed very little overlap with ADHD.

As Professor Robert Plomin, a co-author on the study and the deputy director of the Social Genetic and Developmental Psychiatry centre, commented, 'It's startling that there appears to be greater genetic overlap between autistic communication difficulties and ADHD than there is genetic overlap within autism itself'. In other words, children with autism appear genetically to have much more in common with children with inattention and hyperactivity than previously expected.

Back to the Brain

Why is this important? The findings will help figure out better treatments for autism and ADHD, through providing a clearer understanding of changes that occur as a result of these genes. It is likely that the genes that influence autism and inattention and hyperactivity will have effects in the brain. It will be important to understand these changes in brain development that may underlie both conditions. For example, brain areas thought to be affected in autism, such as those involved in processing social information like faces, might also be involved in ADHD.

Finally, these findings may change the way we view and study autism and ADHD. Autism is five times more common in males and recently Professor Simon Baron-Cohen put forward the extreme male brain theory. He says that we can understand autism better if we think of it as an extreme form of male characteristics, such as being good at figuring out systems and focussing less on empathising. Could we suggest the same theory might apply to ADHD then, given that it is also five times more common in males?

That, says the professor, is 'an important question for future research.'

By Angelica Ronald

After completing her undergraduate degree in Experimental Psychology in 2000, Angelica Ronald spent a year in advertising selling snack food. Yearning for a more academic life, she returned and did her PhD at the Social Genetic and Developmental Psychiatry Centre at the Institute of Psychiatry, London, on the causes of children's social development and cognitive ability. Her thesis focused on the causes of autism spectrum conditions. She is currently working as a postdoctoral researcher on genetic research into autism and related conditions.

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Researcher Category – 2nd Prize

Stimulating the brain

BY NADA YOUSIF

Sounding either like something from science fiction or something rather barbaric, deep brain stimulation (DBS), uses electricity applied directly to the human brain in order to successfully treat neurological disorders. And recent advances with computational modelling could help us to understand how it actually works.

DBS is extensively used to treat different types of movement disorders, most commonly the tremor (a repetitive uncontrollable movement of a body part) associated with Parkinson's disease. Parkinson's disease is a degenerative disease, and occurs due to the loss of a particular type of brain cells which contain a chemical called dopamine. Dopamine is extremely important in the part of the brain which controls movement (the motor system), and without it patients may develop a tremor, and may eventually become unable to initiate movement.

Such problems of the motor system are thought to occur due to abnormal electrical activity in the brain. This is because brain cells communicate with one another using essentially electrical signals. DBS is able to treat such problems by one or two electrodes being surgically implanted in specific areas of the patient's brain, and an electrical current being applied through these electrodes. This arrangement is shown in Figure 1, where we can see the electrodes implanted, and wires leading to the battery powered stimulator (a device similar to a pacemaker) which is implanted in the chest. The electricity injected during DBS can then disturb the abnormal electrical signals in the patient's brain, and ease their tremor.

Figure 1: The electrodes are surgically implanted into the patient's brain, and a stimulator is implanted in the chest to deliver the electrical current.

Figure 2: A scan of a patient's brain with an implanted DBS

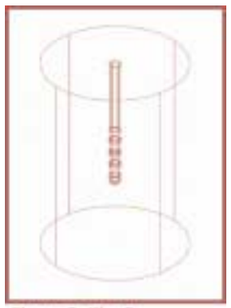

Figure 3: The 3-dimensional model, which features the DBS electrode and a cylinder

At present, one in 500 people suffers from Parkinson's disease, and every year 10,000 people are newly diagnosed with it. Since DBS was pioneered over a decade ago there have been over 35,000 implantations worldwide, and the estimate is that as many as 80% of people who receive this treatment will experience a reduction or complete suppression of their often disabling symptoms. The decision to allow a patient to undergo this surgery depends on a number of factors, and is usually made only after trying the non-surgical option of drug treatment to replace the lost dopamine.

And yet, although DBS is widely used and successful at achieving therapeutic benefits, the precise way in which the injected electrical current affects the electrical activity of the brain is not fully understood. The difficulty is that although we can produce accurate images of where the implanted electrode is inside the brain, as shown in the MRI scan in Figure 2, there is no way that we can see or measure exactly how the current spreads in tissue, and how this current is interacting with the brain's own electrical signals.

Another way to try to understand what exactly is going on in the human brain during DBS is to use mathematics. As part of a team at Imperial College London, I am interfacing the clinical research undertaken by my colleagues, with the development of 3-dimensional computational models of the implanted electrode and the surrounding area of brain. Simple models, like the one shown in Figure 3, can be used to visualise the electric field created around the electrode. These computational models can then be used to study how the injected current interacts with the surrounding brain tissue.

The goal is to use mathematical modelling to better understand how the current influences the brain's activity and predict how to use this procedure more effectively. Our recent results from theoretical models explains the difference in the electric fields created by two commonly used stimulation approaches, and therefore can help doctors to better target the abnormal activity that exists as a result of disease. The final challenge will be to use such computer models within routine clinical practice in order to predict the best settings for the current applied to each individual patient, as and when they require the intervention.

As the use of this procedure spreads to new ailments such as epilepsy, depression, and bipolar disorder, the number of patients who may benefit from this surgical intervention will also surely increase. But in order to understand more about how the electrical current is achieving the observed effects, theoretical research hand in hand with clinical research needs to be undertaken.

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By Nada Yousif
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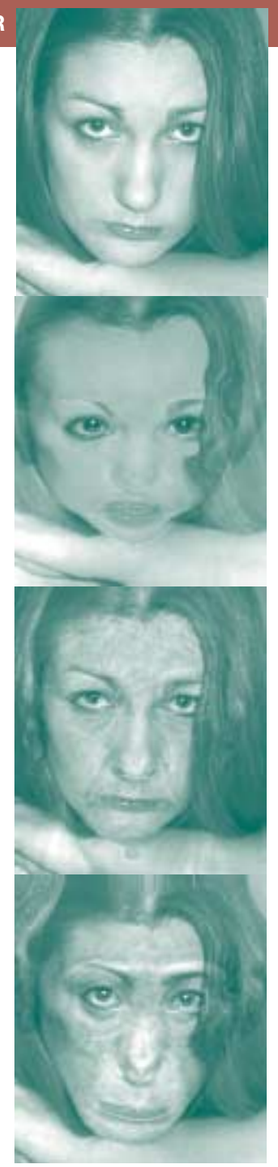
Nada Yousif graduated from Imperial College in 1998, leaving with a keen interest in the workings of the brain. She went on to study thalamocortical networks, and completed her PhD in Computational Neuroscience at the University of Plymouth. She returned to Imperial in 2005 to work on theoretical modelling of deep brain stimulation, and is currently in the first year of a 3-year post-doctoral fellowship funded by the Medical research Council.

Highly Commended – Changing the face of our lives: how our innate interest in faces can change the choices we make

BY GILLIAN PEPPER



Gillian Pepper as herself, baby morph, aged morph and 50% chimpanzee using St Andrews University Face Transformer.

Faces are important to people. They are strongly linked with our sense of identity. Anyone who has been watching the news lately will be aware of the surgical pioneering work into full face transplants. These are not without risk: patients undergoing transplants will have to take immunosuppressant drugs throughout their lives to prevent their bodies from rejecting the new facial tissue. Nevertheless, people unlucky enough to have suffered facial damage are willing to take the risk. So, why are faces so important to us?

Studies have demonstrated that looking at faces produces greater brain activity than looking at strings of letters or textures. Furthermore, newborn infants appear to pay greater attention to faces than to arbitrary objects. Such evidence has prompted researchers to suggest that our interest in faces is innate.

If indeed we are predisposed to focus on faces, it may be for good reason. If we were unable to identify others as friend or foe, we would quickly run into trouble. People suffering from prosopagnosia, the inability to recognise faces, do encounter such difficulties. Dr Brad Duchaine of the Institute of Cognitive Neuroscience explains: "Imagine failing to recognise your boss in the elevator or walking right past your boyfriend. Even worse, imagine picking up the wrong child at daycare or failing to recognize yourself in mirrors or photos. These sorts of incidents occur regularly for people with face recognition problems, and not surprisingly lead to serious social problems."

So we may be predisposed to pay attention to faces because this confers a social advantage. Indeed it's possible that faces guide us in deciding whom we can and cannot trust. Research by psychologists in Canada has demonstrated that we are more likely to trust individuals whose facial features are similar to our own. This is possibly because we use facial resemblance as a cue to detect kin and are hardwired to cooperate with family. Furthermore, scientists in New York have found that we are disposed to remember the faces of individuals who cheat in "social contract" games - exercises such as borrowing money and returning it when promised. Naturally, remembering cheats is important if you wish to avoid them in future. Dr Anthony Little, an evolutionary psychologist and face expert explains: "We are able to retrieve a huge amount of information about past deeds and reputation based on only a brief viewing of a known face - we know who has been nice to us or can help us so we can turn to them, and conversely we know who has cheated us or others in the past and avoid them."

So faces help us to recognise friends and to avoid cheats, but why else should they be so significant? A growing body of research demonstrates the importance of facial cues in what might be one of the most important decisions of our lives – our choice of partner. Evidence suggests that we unconsciously use features such as facial symmetry and masculinity to judge the quality of potential mates. For example, a symmetrical face is thought to indicate good health, and therefore "good genes", which ought to be desirable in a potential mate if we hope to produce healthy offspring. There can be a conflict of interests for women however, since masculine characteristics indicate good genes, but more feminine features convey a caring personality – one more likely to invest in rearing children. Research has found that generally, young women prefer men with slightly feminised features, but that when their fertility is at its peak, a masculine face is more attractive.

Our innate interest in faces is used by advertisers to sell products. Research from the Center for Consumer Marketing has shown that a smiling face on an advert can lead consumers to a positive attitude towards the company using the advert, making them more likely to patronize the company and to recommend them to others.

Faces really are important. They help us to decide who to trust, with whom to mate, even what products or companies to trust. Those who are unable to recognise faces can suffer for it. Those who have lost their faces feel lost without them. Not even faces it seems should be taken at face value.

By Gillian Pepper
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Gillian has a BSc in Zoology with Evolutionary Psychology from the University of Liverpool, where she hopes to return to further study in 2007. Since graduating in 2005, Gillian has completed a variety of work experience projects related to science communication, including work with the Science Media Centre, BBC Focus Magazine and Newton's Apple, and has also spent four months in India working as a volunteer. She is now one of the UK co-ordinators for Yearoutindia, a company that sends volunteers to do charitable work at various sites in southern India.

Highly Commended: The real cause of obesity: addicted to food

Telling obese people to 'just eat less' is the equivalent of advising a chronic heroin addict to 'cut down a bit', say scientists.

According to research carried out at New York's Brookhaven National Laboratory, obesity is literally an addiction to food. The findings may offer clues to why current strategies to combat obesity are failing. The condition is as much a psychological problem as a physical one and should be treated accordingly, scientists urge.

It has previously been shown that drug addicts and alcoholics have fewer receptors for dopamine, a neuro-transmitter associated with feelings of pleasure and satisfaction, than non-addicts. The Brookhaven team, lead by Professor Gene Jack Wang, has discovered that obesity causes the same kind of changes in brain chemistry. The results imply that obese people consume more food to stimulate the release of 'pleasure' endorphins in the brain, just as addicts feel compelled to take drugs to obtain a 'high'. If you find this hard to believe, think about the feeling when you devour that first mouthful of chocolate.

In the experiment, the brains of 10 severely obese people and 10 individuals of normal weight were examined. The subjects were injected with a radioactive chemical tag, made to bind to the dopamine receptors. Positron Emission Tomography (PET) was used to pick up the radioactive signals, the strength of which was proportional to the number of receptors. The obese group were found to have significantly fewer receptors. The study further revealed that there is an inverse relationship between weight and the number of dopamine receptors. That is, the more obese the individual, the fewer their dopamine receptors.

The advice given to obese people on the NHS Direct website is "Try not to overeat – listen to your body and stop when you're full." However, in an obese person, there may be an overriding message from the dopamine receptors in the brain saying, "carry on eating!"

Whether the observed differences in brain chemistry determine obesity or are caused by obesity is unclear. "It's possible that obese people have fewer dopamine receptors because their brains are trying to compensate for having chronically high dopamine levels, which are triggered by chronic overeating," said Professor Wang.

"However, it's also possible that these people have low numbers of dopamine receptors to begin with, making them more vulnerable to addictive behaviours including compulsive food intake." This question is a current area of investigation.

This research revolutionises our understanding of obesity. The focus needs to switch away from 'which diet' to the question of how to tackle food addiction. One possibility is prescribing drugs that artificially alter dopamine levels. However, these drugs are highly addictive and would only be appropriate when a person's weight is an immediate risk to their health. A better alternative is exercise. Not only does it have the direct physical effect of weight-reduction, but it also provides the all-important dopamine high.

So what is my point? Stop feeding the ever-expanding diet industry and get the nation on a bike!.

Sources:

Brookhaven National Research Laboratory www.bnl.gov

By Flora Devlin

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Flora Devlin is a sixth form student at St Bedes College, Manchester. She is currently studying for AS levels in Maths, Further Maths, Physics and Economics. Last year, she achieved 10 A's in her GCSEs. She is hoping to study Economics or Maths at university, and wants to be a civil servant. Her main hobbies are sport and music. She plays both piano and percussion to a high level and is a regular team player at school. She is a keen follower of the modern music scene, especially local Manchester groups and musicians.*

The future of A' Level Psychology – discuss!

On the behalf of the BNA, Helen Hodges, Emeritus Professor of Psychology, Institute of Psychiatry, attended an important workshop on the future of A level Psychology and plans to introduce AS/A2 level Neuroscience, hosted at the National Science Learning Centre, York University Campus, 26th – 27th October, 2006. It was convened by Professor John Holman and supported by The Wellcome Trust and The Royal Society.

Representatives from teaching, publishing, examination boards and professional societies converged for a brainstorming meeting about the future of A level Psychology at the National Science learning Centre in York, in October. The NLCS team and speakers (including Annie Trapp, John Holman, and Jeremy Airey) devised stimulating group activities centred on how to deepen scientific understanding within A and AS level courses. Raj Persaud's keynote address on motivation illustrated just how to communicate science. The meeting ended with a list of recommendations to the Qualifications and Curriculum Authority (QCA) and other stakeholders, which emphasised the importance of reducing the load of course contents in favour of exploring scientific methodologies. Our wish list also contained resource banks, a dedicated website for teachers, outreach activities, improved careers advice, and recruitment of A level students into relevant professional societies (BPS, BNA). Participants left with a sense of achievement, feeling that the points made would be heard and might even make a difference. As Matt Jarvis wrote in the ensuing (and ongoing) email discussions: *'unquestionably an excellent day, really well planned and organised. It is also clear that this type of genuine multidisciplinary dialogue can achieve something very distinct from what happens at other conferences'*

Too little, too late?

Despite the enthusiasm, the timing of the meeting was not ideal. The QCA (responsible for curricula) has *already* issued criteria for the sciences, and the exam boards are revising the syllabuses for September 2007. This leaves very little time for our recommendations to feed through to the QCA and then to the boards, even though seeds may be sown for the future. Of particular concern is the loss of the Psychology Project in the current QCA proposal of four assessment units, all to be externally examined. The project is a key way for students to learn about experimental design, data collection and analysis. Class or group investigations will not contribute directly to assessment, and it is difficult to see how exam questions will compensate for direct hands-on experience of research. It is unlikely that the strong support for projects at the meeting will rescue them in time.

Too many sciences?

The aim of the meeting was to strengthen the scientific content of A level Psychology. However, QCA proposes five core areas (cognitive, social, developmental, individual differences, and biological) each with its own methodologies. This large content has two damaging effects. First, different exam boards differ in the prominence given to each area. While this might offer more course choice, the lack of a common knowledge base weakens the standing of A level Psychology in the universities. There was a strong perception that Psychology A level students arrive poorly prepared for a degree course in Psychology. Second, a crammed syllabus reduces the time available for understanding scientific methods and developing transferable skills such as critical thinking and scientific writing. Course planners should think about how to build core areas around analysis of a few key studies, rather than offering broad superficial coverage.

Should we have a Neuroscience A level?

Neuroscience fares badly within Psychology A level courses; the biological component is mainly confined to stress, motivation and emotion. Teachers considered that students attracted to Psychology might be put off by a larger neuroscience element. However, neuroscience is rapidly advancing and offers a host of flexible, exciting career options. Separate A/AS level neuroscience courses could have a well-structured and focussed programme of direct relevance to understanding science at work or in continuing education. This would offer opportunities that are not possible within the framework of current A level Psychology or Biology courses.

Ageing Research – the new dynamics

New Dynamics of Ageing (NDA) Research Programme was launched on 1st November, 2006, at the Queen Elizabeth Conference Centre, London. This multi-disciplinary research initiative aims to improve the quality of life in later years by funding 'the largest and most ambitious research programme mounted in the UK.' NDA combines the resources of five research councils (ESRC, EPSRC, BBSRC, MRC and AHRC), six Government Departments, and seven charities (linked already into the 'Funders Forum' for ageing research). Leading members of the government, research councils and ageing research institutions (including Lord Sutherland of Houndwood, Royal Commission on Long Term Care of Elderly; Lord Hunt of King's Heath, Minister for Work and Pensions; Ian Diamond, Chair RCUKEG, CE ESRC; Tom Kirkwood, Director, Institute for Ageing and Health, Newcastle University; Alan Walker, Director of NDA programme; Michael Lake, Chair of Funders Forum) explained and pledged support for the goals of NDA.

NDA Goals

NDA aims to change perceptions and experiences of ageing through direct engagement with older people. The objectives are three-pronged and centre on

(1) *understanding views of ageing* (dynamic influences, cultural and individual diversity of experiences)
(2) *generating new knowledge of ageing processes* (by supporting inter- disciplinary and international research)
(3) *contributing to the development of policies, practices and products* to help people achieve an active and independent later life.

The stark reality is that as older people survive longer they are supported by a relatively static or even declining proportion of younger people in employment – the upside down population pyramid. The elderly are therefore often seen as an increasing and unproductive burden. However, older people have a wealth of experience and skills that, with creative management, could extend and develop their career paths or involvement in voluntary work. The NDA is committed to changing negative perceptions and enabling the elderly to participate fully in work and social activities.

'Life expectancy is increasing at a rate of five hours per day', Tom Kirkwood explained. However, healthy life expectancy is six year less than actual life expectancy, so people in later life experience periods of significantly reduced capacity and poor health, rather than enjoying their extra years. The NDA will foster research into ageing processes and factors contributing to the maintenance of good health.

NDA first and second round funding

The NDA initiative has already identified five projects for funding, and The Launch Meeting was treated to an impressive round up of progress to date:

- **Sara Arber** (University of Surrey) has gathered together six academic partners in six disciplines for work on optimising the quality of sleep of the elderly in care homes, and will work with four non-academic partners to develop use of blue light, and involve relatives and residents associations.
- **Ruth Hancock** (University of Essex) is engaged in modelling the needs of old people up to 2030. This comprehensive project will recruit government departments (e.g. Pensions Policy Unit, Census Office), health services, industrial partners

(e.g. BT), statistical experts, and a host of other sources to provide a rational, knowledge-based perspective for future policy making.

- **Diana Kuh** (UCL Medical School) is making full use of the UK Life Course cohorts, including the 1921 Lothian cohort, to plot pathways to healthy ageing from molecular to social contexts.
- **Diana McCann** (University of Wales, Newport) is re-directing her expertise in smart clothes for sport to developing 'wearable technology' for old people: clothes that make people feel good, manage moisture, control temperature, protect and insulate, and enable them to present an attractive and confident outer face to the world.
- **Leela Damodaran** (University of Loughborough) is making use of the pervasive influence of IT to develop ways of 'adapting support to sustain autonomy' There is a lot of help online already, for example for shopping and finding out about local or national services. However, this help is not used effectively by the elderly as they lose confidence in coping, forget PIN numbers, or are impeded by tremor or failing eyesight. The Lougborough proposal will develop solutions for user problems, and build an easy access network for supplying information and contact details about a range of specialist services.

Future (stage 2) programmes start with funding for a year to form networks (national and international) between researchers to establish a basis for collaborative research which will subsequently form the platforms for full grant applications.

The 'Silver Revolution'

The UK research councils have demonstrated commitment to research on ageing. The ESRC's 'Growing Older' programme launched in May, 1999, which funded 24 projects was the direct forerunner of the NDA initiative, whilst the MRC's life cycle approach ensures the needs of ageing receive specific, if more limited, attention. However, it will take a massive shift in research effort and public awareness to push through a 'silver revolution' through which the elderly can participate fully in all aspects of life, instead of being marginalised. The NDA initiative will certainly work towards achieving an independent and healthy life for the elderly. However, this will crucially depend on the full involvement and participation of the elderly themselves, to create and sustain momentum.

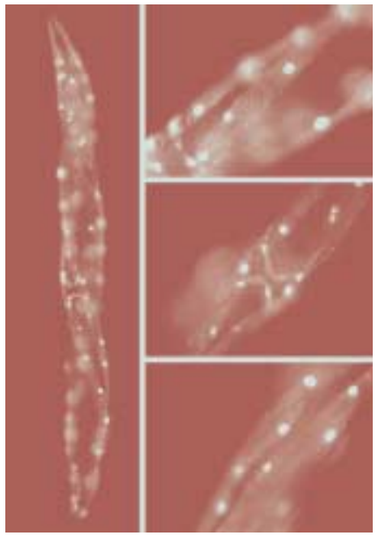
> 'This multi-disciplinary research initiative aims to improve the quality of life in later years by funding the largest and most ambitious research programme mounted in the UK'

By Helen Hodges
Emeritus Professor of Psychology
Institute of Psychiatry, London

Genes and Synapses:
New insights from studies on Invertebrates
ONE DAY SYMPOSIUM 8th November, 2006, Oxford

Research on invertebrate organisms has already made outstanding contributions to Cellular Neuroscience, providing access to uniquely identifiable neurons, sometimes of large diameter, facilitating electrophysiological and biochemical studies on neural signaling mechanisms and the integrative physiology of neural networks. Invertebrate neuroscience has been further empowered by the sequencing of the first animal genome for the nematode *Caenorhabditis elegans* and the development in that same model organism of gene knockdown by RNA interference. UK-based research, which takes advantage of inverterbrates, continues to be strong and 85 neuroscientists participated in a lively one day BNA Meeting (9 lectures and 25 posters) at St John's College in Oxford on November 8th, 2006, organised by David Sattelle (MRC FGU Oxford), Lindy Holden-Dye (Southampton) and Mark Darlison (Nottingham Trent), in collaboration with Sam Potts and Yvonne Allen in the BNA Office.

This meeting demonstrated, yet again, the strengths of invertebrates as experimental models. They offer easy-to-manipulate genetic tool kits to pinpoint gene functions underlying complex behaviours. Having a short lifespan and generation time, invertebrates such as the worm *C. elegans* are readily amenable to forward and reverse genetic screens to correlate gene activity with certain behavioural characteristics. Genetic manipulations, such as gene overexpression or deactivation using knockdown by RNA interference, are relatively simple and, in the case of *C. elegans*, have even been performed on a genome-wide scale. Thus, many aspects of neurobiology, including genetics, biochemistry and electrophysiology, can be readily studied in invertebrates providing an excellent first step in the study of gene function.



Muscle cells of the nematode Caenorhabditis elegans labelled with green fluorescent protein, courtesy of Michael Briese, MRC Functional Genetics Department.

Mario de Bono showed how the worm continues to be an excellent model for establishing the neural circuitry involving foraging behaviour and the important role played by oxygen sensing. Also deploying the worm, **Lindy Holden-Dye** reported on new work showing how neuropeptides regulate important aspects of behaviour. Work on another important genetic model organism, Drosophila melanogaster, was well represented. **Mary O'Connell** described RNA editing in the fly nervous system and showed how this can add greatly to functional diversity in voltage-gated and ligand-gated ion channels. **Mathias Landgraf** showed exquisite images depicting dendritic development and connectivity in the embryonic fly nervous system. **Michael O'Shea** described a fascinating example of natural antisense regulation of NOS and its role in memory formation. **David Shepherd** described one example of what is a growth area, the use of invertebrate models to study aspects of human neurodegenerative disorders by modelling tauopathies in Drosophila.

Andrew Jones and **David Sattelle** reported on molecular and functional diversity in nicotinic acetylcholine receptor gene families, taking advantage of the new invertebrate genomes currently emerging (bee, mosquito, flour beetle as well as additional fly and nematode genomes). **Richard Baines** described exciting work on the regulation of neuronal excitability via Pumilio dependent control of a sodium channel gene. **Steve Nurrish** brought us back to the worm at the end of the day describing studies on the regulation of neurotransmitter release by GTPases. Finally, **Robert Walker**, a pioneer in invertebrate neurophysiology and always a passionate advocate of such work in the UK, explored some of the common threads in current themes and speculated on some key areas where work on invertebrates can contribute in the immediate future.

It emerged that invertebrates can be used to study not only basic neuronal signalling, but also more complex phenomena that underpin behavioural plasticity. A large cohort of other post-graduate students attended and we listened to a variety of excellent talks, ranging from behavioural through to biochemical studies, accompanied by some beautiful images and descriptions of elegant scientific techniques. This friendly and informal meeting provided students especially with a great opportunity to network, comparing experimental approaches and sharing our enthusiasm. For this, we thank all the speakers and poster presenters, and above all, the organisers and the BNA.

By Zara Luedtke (Southampton) and Michael Briese (Oxford)

Butterflies of the Soul: The BNA Christmas Symposium
The legacy of Golgi and Cajal: past, present and future
14th December, 2006
Royal Society, London

By Jane Qiu

The year 2006 marks the 100th anniversary of the first Nobel Prize for Physiology or Medicine, which was shared by Camillo Golgi and Santiago Ramón y Cajal for their key contributions to the understanding of the nervous system. Golgi discovered a new histological staining method that allows neurons and their processes to be darkly labelled. By using this revolutionary technique, Cajal's meticulous studies of the entire nervous system led to the Neuron Doctrine, which marked the birth of modern neuroscience. He famously likened nerve cells to the "butterflies of the soul" – an insightful conjecture that mental processes are a result of activity of nerve cells in the brain. The BNA's annual Christmas symposium was held to commemorate their outstanding achievements in neuroscience. Jane Qiu reports.

The symposium, chaired by Richard Frackowiak of University College London, got underway with a presentation by **Javier DeFelipe** of the Institute of Cajal, Madrid. He gave a historical overview of research that led up to Golgi's and Cajal's discoveries and hypotheses, many of which are still largely relevant to neuroscience to this day. In the 1850s, scientists already realized that there were many types of cortical neurons that are different in their size and morphology. It was thought that the network of continuous nerve branches is crucial for the function of the nervous system, whereas the cell body serves only to provide nourishment – a hypothesis called the Reticular Theory. It was not until 1873, when Golgi discovered his "reazione nera" ("black reaction"), was it possible to conduct detailed studies of the nervous system.

Cajal discovered this important method in 1887 and made a series of discoveries in the following few years. In contrast to the Reticular Theory, he proposed that axons and dendrites ended freely without continuity with other nerve cells, and that the currents flowed "in much the same way that electric current crosses a splice between two wires" – an embryonic version of the notion of synaptic cleft, which was discovered in the 1950s as a result of the advances in electron microscopy. It was based on this idea that several scientists, including Cajal, drew up the first detailed circuit diagram of the cerebral cortex. This had important implication for understanding brain function, as Cajal explained to an audience in the Croonian Lecture during his first visit to the Royal Society in 1894. He also discovered dendritc spines, noting, "The surface of [the dendrites of Purkinjie cells] appears covered with thorns and short spines". His conception of plasticity as well as theories regarding nerve degeneration and regeneration are extremely insightful and are roots of some of the most exciting discoveries in neuroscientists today.

Sam Potts welcoming delegates.

The following speakers presented their areas of research, highlighting how the scientific insights of Golgi and Cajal have had a significant impact. **Alain Prochiantz**, of the École Normale Supérieure in Paris, focused on the role of a family of transcription factors called homeoproteins in the spatial and temporal regulation of neural development. He showed that the expression of the homeoprotein Pax6 instructs the development of the eye in zebrafish, and how a gradient of homeoprotein Engrailed is established along the rostrocaudal axis of the tectum (or the target field of retical projection). This gradient is crucial for establishing the retino-tectal topography: temporal retinal axons project to the tectal regions with low levels of Engrailed expression; nasal retinal axons have the opposite preference.

This is confirmed by *in vitro* studies which show that Engrailed repels growth cones – a notion that was put forward by Cajal in

1909 – of temporal axons but attracts that of nasal axons. Dr Prochiantz went on to demonstrate the role of another homeoprotein Otx2 during the critical period of visual development. He showed that the onset of the critical period in the binocular visual cortex of mice coincides with the transfer of Otx2 between neurons from the dorsal thalamic to the visual cortex. This passage is dependent on visual activity and specifies the timing of the critical period. Manipulating the expression of Otx2 by gain-of-function or RNA interference results in opening and closure of the critical period, respectively.

The third speaker **Thomas Klausberger**, who holds a position at the MRC Anatomical Neuropharmacology Unit, Oxford University and an honorary position at the Centre for Brain Research in Vienna, demonstrated how single neurons contribute to global activity in the hippocampus. Although Cajal and his contemporaries had noted the myriad of neuronal types with distinct morphology, the extent of this diversity has not become fully appreciated until the advances in molecular biology and electrophysiological recordings. As Dr Klausberger explained, the proper functioning of the cerebral cortex requires neural networks formed by projection neurons and interneurons that primarily use the neurotransmitters glutamate and GABA respectively.

Interneurons have an important role in modulating cortical output and plasticity. In the basic hippocampus circuitry, for example, the principle cells are innervated by 14 types of GABAergic neurons, which themselves are innervated by 4 types of interneuron-specific cells. Dr Klausberger illustrated the anatomical details of such connections and how various GABAergic interneurons with distinct firing patterns are involved in communicating with different parts of the brain. He concluded that different classes of interneurons evolved because distinct subcellular domains of the pyramidal cells require different GABAergic modulation in time and that specialised GABAergic cells transmit information about network rhythm and phase to other brain areas.

The discussion on GABAergic neurons was continued by **Annette Dolphin** of University College London. She has studied the role of calcium channels in spontaneous activity of Purkinje cells – a subtype of GABAergic neurons in the cerebellar cortex – and how channelopathies might contribute to cerebellar ataxia. Professor Dolphin focused on the $\alpha_2\delta$ subunits of voltage-gated calcium channels, because loss of expression of $\alpha_2\delta$-2, which is strongly represented in Purkinje cells, has been associated with cerebellar ataxia and epilepsy. Furthermore aberrant expression of $\alpha_2\delta$-1 is associated with neuropathic pain. She showed that the $\alpha_2\delta$ subunits can increase current density of calcium channels. This is mediated by the metal-ion-dependent adhesion site in the Von Willebrand factor-A domain of the subunits, which is responsible for trafficking calcium channels to the plasma membrane.

Professor Dolphin went on to demonstrate to the audience that the integrity of the $\alpha_2\delta$ subunits is crucial for proper brain function. Mutations in the gene Cacna2d2, such as Cacna2d2^{du} and Cacna2d2^{du2J}, that encodes the $\alpha_2\delta$-2 subunits result in the so-called ducky mice characterized by spike-wave seizures and cerebellar ataxia. Those mutant mice also have slow degeneration of selective regions in the central nervous system and the animals do not survive beyond postnatal day 35. In du/du and du^{2J}/du^{2J} Purkinje cells, Professor Dolphin observed a reduction in calcium currents as well as in spontaneous and depolarisation-induced firing rates compared with their normal counterparts. There are also abnormalities in dendritic arborisation, in the mutant Purkinje neurons. These observations have provided insight into the molecular mechanisms whereby mutations in the calcium channel $\alpha_2\delta$-2 subunits result in cerebellar ataxia.

In the next presentation, **Antoine Triller**, also of the École Normale Supérieure in Paris, discussed surface trafficking of neurotransmitter receptors between synaptic and extrasynaptic membranes. He explained that the number of neurotransmitter receptors at synapses, which partly determines synaptic strength, is controlled by dynamic interaction with intracellular scaffold proteins. Most receptors are inserted and removed at non-synaptic locations, and the process of receptor trafficking into and out of synapses is regulated during development and by plasticity. New insights into this area of research have been facilitated by the advent of semi-conductor quantum dots because these new nanomaterials enable measurements at the single-molecule level with high signal-to-noise ratio.

Dr Triller showed that the scaffolding protein gephyrin is crucial for the assembly and the dynamics of receptor clusters in the synaptic and non-synaptic membranes by connecting the cytoplasmic domains of those receptors to cytoskeletal systems. Manipulation of gephyrin expression has an effect on the lateral diffusion of neurotransmitter receptors in and out of the synapse. In addition, this dynamic behaviour is regulated by intracellular calcium concentration and by the cytoskeleton in response to synaptic activity. Intriguingly, lateral diffusion of neurotransmitter receptors is also regulated by the length of the spine neck as well as spine morphology, which in turn vary with plastic processes. Dr Triller conjectured that receptor movements in the membranes as a result of neuronal excitability might underlie the mechanism of excitation-inhibition homeostasis.

The topic of the final talk, presented by **Michael Coleman** of the Babraham Institute in Cambridge, was axonal degeneration. One type of axonal degeneration was first observed by Waller in 1850 after nerve fibres of the peripheral nervous system (PNS) were severed. He noted that "It is particularly with reference to nervous disease that it will be most desirable to extend these researches", and that the purpose of this degeneration process, which was later coined as Wallerian degeneration, was to prepare for regeneration. In 1913, Cajal published a book titled "Degeneration and Regeneration of the Nervous System", in which he detailed many histological drawings and his hypotheses. Dr Coleman remarked that "there is little to observe in fixed, wild-type tissue that Cajal did not already report" and, indeed, many researchers have often ended up "reinventing" his discoveries.

However, the development of novel, powerful experimental approaches, such as living imaging, new disease models as well as molecular and genetic tools, has allowed researchers to break new grounds, explained Dr Coleman. For example, the slow Wallerian degeneration mutant mouse (Wlds), in which the degeneration process is delayed to 2-3 weeks, has been used to show that both physical injury and a blockade of axonal transport trigger a proactive axon death programme. The Wld^s gene, which was identified using positional cloning, encodes a fusion protein consisting of a fragment of UBE4B (ubiquitination factor E4B) and the complete coding region of NMNAT1 (NAD$^+$ synthesising enzyme nicotinamide adenylyltransferase 1). This has been explored further using transgenic mouse lines YFP-H and GFP-S, where Wallerian degeneration has now been imaged along 3cm lengths of individual PNS axons. The fluorescent proteins in the neurons of these mice make it possible to "bring the Golgi stain to life" and follow in real time movies what happens to axons as they degenerate. By understanding how various pathways fit together, it is hoped that novel therapeutic interventions will be developed for treating axonal disorders.

By Jane Qiu, a science writer who divides her life between London and Beijing (jane@janeqiu.com)

The Regenerating Brain

Phil Trans B, Royal Society (Biological Sciences),
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A Theme issue organised and edited by Geoffrey Cook[1], James Fawcett [1], Roger Keynes[1] and Marc Tessier-Lavigne[2]

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2 Center for Brain Development, Howard Hughes Medical Institute, San Francisco, USA.

The volume contains twelve papers organised into seven topics encompassing:

- Neurogenesis (Goldman and Windrem on cell replacement therapy; Sohur et al. on adult neurogenesis and repair with neural progenitors)
- Circuits, axon growth, guidance, regeneration and rearrangements (Pasterkamp and Verhagen on Semaphorins in axon regeneration; Mueller et al. on repulsive guidance molecules in adult and embryonic CNS)
- Developmental plasticity of axonal connections (Low and Cheng on axon pruning)
- Neurotrophic factors (Reichardt on neurotrophin-related signalling pathways)
- Intrinsic control of axon elongation in the embryo and after injury (Filbin on developmental recapitulation to promote axonal regeneration; Zhou and Snider on intracellular control of developmental and regenerative axon growth)
- Extrinsic control of axon regeneration after injury (Liu et al. on extracellular regulators of axonal growth in the adult CNS; Meier and Schwab on factors affecting spouting, regeneration and circuit formation in the injured spinal cord)
- Plasticity of connections in the adult brain (Cai et al., on plasticity of functional connectivity in the adult spinal cord; Rossignol on plasticity underlying locomotor recovery after central and peripheral lesions in adult mammals)

This is a really useful collection of papers on factors affecting axon extension, although there is a certain amount of overlap (e.g. on inhibitory factors in myelin, extracellular matrix, and repulsive guidance molecules). There are some helpful figures and diagrams, for example summarising embryonic and adult axon guidance (Liu et al.), and developmental vs. regenerative processes (Maier and Schwab). Overall, some important themes emerge, which include factors contributing to and limiting adult neurogenesis, neurotrophin signalling pathways, opposing and complementary interactions between Trk and P75 NT receptors. Sohur et al. gave warnings about difficulties in identifying newborn cells in brain using single markers plus nestin, but were nevertheless optimistic about the potential for neurogenesis to be induced and amplified in non-neurogenic regions after neurotoxic or ischaemic insults (e.g. Nakatomi H et al., Cell 110, 439-441, 2002).

The papers identified several different levels for potential therapeutic interventions to repair or reduce axon degeneration, partly informed by differences between the neonatal and myelinated brain where axon regeneration is severely limited. Zhou and Snider, for example, argue that distinct signalling pathways mediate developmental as opposed to regenerative axon growth at both cell body gene expression levels and at the growth cones which act as local assembly units. Understanding these differences will help us to intervene more effectively. Filbin outlined strategies for increasing the permissiveness of the extra cellular environment by blocking inhibitors such as Nogo or chondroitin sulphate proteoglycans (CSPGs) by antibodies, peptides, or digestive enzymes (e.g. Bradbury E.J. et al., Nature 416, 636-640, 2002), and by blocking intracellular signalling cascades or activating alternative pathways, so that neurons would fail to recognise inhibitory signals. Relatively little attention was given to possibilities for cellular repair by transplanting stem, precursor or progenitor cells. However, Goldman and Windrem set out guidelines for impairments which might be usefully addressed, which emphasised selective neuronal loss as in Parkinson's disease, circumscribed damage as in spinal cord injury, or well understood deficits as in lysosomal storage deficits or demyelinating diseases. However, there is also evidence for stem cell graft efficacy following large non-selective lesions (for example in rodent models of stroke: Modo M. et al. Stroke 33, 2270-2278, 2002), and differential mechanisms for graft repair of selective and non selective lesions would have been an interesting extension to this discussion. Maier and Schwab presented a comprehensive overview of sprouting, regenerative and transplant contributions to spinal cord repair. Emphasis was laid on combined treatments, but possibly more could have been made of evidence for effectiveness of olfactory ensheathing grafts in SCI (Raisman G. in Neural Transplantation in Neurodegenerative Disease, Wiley, Chichester (Novartis Foundation Symposium 231), 94-109, 2002).

Opportunities for maximising recovery of motor functions were stressed in terms of the malleability of circuitry, and functional rather than strictly anatomical circuits controlling movement (Cai et al). Hence the attempts of previously silent pathways to take on new functions after injury can be fostered by selective training, including the use of robotic devices, and pharmacological treatments such as quizapine. Rossignol clearly illustrated improved walking in cats after intensive treadmill training, despite spinal lesions.

The take-home message from the 'Regenerating Brain' is optimistic. Although regeneration of CNS axons after injury is minimal, there are elements of endogenous plasticity and neurogenesis to exploit, opportunities to engraft stem cells, to augment neurotrophic activity, and to block inhibitory factors in glial scars and ECM, and to divert cell signals that recognise and engage with inhibitory and apoptotic mechanisms. The challenge of promoting axon regeneration in adult CNS is to integrate molecular, pharmacological and behavioural approaches into biologically complementary and multifaceted therapies.

By Helen Hodges
Emeritus Professor, Institute of Psychiatry, London

Conferences at:

Wellcome Trust Hinxton Hall Campus

Spring, summer and autumn, 2007

Microbial Genomes 2007:
11 - 14 April 2007

Organisers: Julian Parkhill, Siv Andersson, Gordon Dougan, Claire Fraser, Vivek Kapur, Frank Kunst, George Weinstock.

Humanising Model Organisms to Understand the Pathogenesis of Human Disease: 1 – 4 May 2007

Organisers: Roland Wolf, Nadia Rosenthal, Steve Brown, Riccardo Fodde, Rudi Balling, Nick Hastie

Animal Biotechnology and its Application to Animal and Human Health:
14 – 16 June 2007

Organisers: Helen Sang, Jim Kaufman, Michel Georges.

Genomics of Common Diseases:
7 – 10 July 2007

Organisers: Tim Aitman, David Altshuler, Eddy Rubin, Myles Axton. Keynote speakers Francis Collins, Leena Peltonen.

Molecular Biology of Hearing and Deafness: 11 – 14 July 2007

Organisers: Karen Steel, Guy Richardson, Allen Ryan.

Interactome Networks:
29 Aug – 2 Sept 2007

Organisers: Marc Vidal, Ewan Birney, Anne-Claude Gavin.

Mouse Molecular Genetics:
5 – 9 Sept 2007

Organisers: Tony Wynshaw-Boris, Bill Skarnes, Hiroyuki Sasaki, Kathryn Anderson. (This meeting was previously held between CSHL and Heidelberg, but will be hosted at Hinxton this year).

Evolution of Brain and Behaviour:
12 – 16 Sept 2007

Organisers: Seth Grant, Nicky Clayton, Svante Paabo.

Integrated Approaches to Brain Complexity: 26 – 28 Sept 2007

Organisers: Nathaniel Heintz, Seth Grant, Jeffrey Noebels. Includes the Francis Crick Lecture on Neuroscience by David Hubel.

Pharmacogenomics: 18 – 21 Oct 2007.
Organisers: Steve Leeder, Munir Pirmohamed, Dick Weinshilboum, Roland Wolf.

For further information, contact:
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email: d.carley@wtconference.org.uk

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VACANCIES VACANCIES JOBSJOBSJOBSJOBSJOBS

Royal College of Surgeons Ireland, Dublin
Centre for Human Proteomics

Post-Doctoral Researcher
Protein-Interaction Mapping and Neuronal NF-kappaB/ Survival Signalling

The Centre for Human Proteomics (CHP) applies proteomics technologies to identify proteins, their modifications and their role in disease progression. We employ mass-spectometry, fluorescence resonance energy transfer imaging, and protein array technologies for the identification of protein-protein interactions involved in diverse biological processes such as receptor signalling, survival signalling and apoptosis.

We are seeking an ambitious post-doctoral researcher to elucidate protein interactions of IKKs and the NF-kappaB inhibitor IkappaBalpha in neurons, using protein array technologies (http://chp.rcsi.ie/) and proteomics approaches. We have recently provided evidence for a selective enrichment of phosphorylated IkappaBalpha and IKKbeta in the axon initial segement of neurons, and their release upon injury. The successful candidate will learn to use present protein array technology for the identification of protein interactions and will be expected to examine the molecular role of these interactions in neurons.

The applicant should have a Ph.D. in molecular biology or a related field and be confident with basic techniques in molecular biology and protein biochemistry. This post is particularly suited for individuals with an interest in signal transduction and neuroscience. Practical experience with proteomics, neuroscience or analysis of array data are advantageous, but not required. Enquiries and/or applications (a letter of interest, a CV and a list of up to three referees) should be sent to Prof. Jochen Prehn (prehn@rcsi.ie).

Prof. Jochen Prehn
Centre for Human Proteomics
Royal College of Surgeons in Ireland, 121 St. Stephens Green, Dublin 2

NYU Medical Center, New York, USA

Postdoctoral Research Fellowship in Cortical Electrophysiology and Genetics

The Fishell lab is looking to hire an experienced electrophysiologist to work on an ongoing project investigating the genetic determination of cortical interneurons. Ideally candidates should have 2-3 years experience of whole cell patch clamp and be capable of working in a semi-independent manner. The successful applicant will be responsible for defining the direction of the electrophysiology research but will work in close collaboration with other members of the lab experienced in developmental genetics. There will also be the opportunity to gain experience in genetic methods.

Informal inquiries are welcome. A full CV and letters of recommendation should be sent to Prof. Gord Fishell at the following email address:

fishell@saturn.med.nyu.edu
Lab website: http://saturn.med.nyu.edu/research/dg/fishelllab/
Smilow Neuroscience Program, NYU Medical Center, New York, NY10016, USA.
Closing date: until position is filled.

Voluntary Services Overseas

VSO is an international development charity that works through volunteers. Our vision is a world without poverty in which people work together to fulfill their potential. We bring people together to share skills, creativity and learning to build a fairer world. VSO welcomes volunteers from an ever increasing range of countries, backgrounds and ages. National agencies in Canada, Kenya, the Netherlands, the Philippines and India recruit volunteers from many different countries worldwide. This international approach allows us to combine and learn from a rich variety of perspectives. In all the countries where we work, VSO is represented by a Programme Office. Staff and volunteers in our Programme Offices work together with local partner agencies, and increasingly with the people whose interests VSO aims to serve, to agree a programme of development priorities in their country and region.

Financial support

We cover all the costs for you. Our financial package for volunteers includes: Salary, return flight , accommodation, medical and travel insurance cover, national insurance contributions, pension contributions, visas and work permits grants and guarenteed holidays.

For information on how to apply go to http://www.vso.org.uk/volunteering/stepthree and complete our online application form or call us 020 8780 7500 or email: enquiry@vso.org.uk for more details.
You must be living in an EU country to apply for these positions. Please specify your interest in this particular job when you apply and add the reference code to your application form.

University of Edinburgh, Doctoral Training Centre

PhD studentship: 4 YEAR PhD IN NEUROINFORMATICS and COMPUTATIONAL NEUROSCIENCE

This is a 4 year programme with a strongly interdisciplinary character and is ideal for students who want to apply their computational and analytical skills to problems in neuroscience and related fields. The first year consists of courses in neuroscience and informatics, as well as projects based in experimental labs. The first year is followed by a 3 year PhD project. The PhD project is commonly done in collaboration with one of the many departments and institutes affiliated with the DTC.

The DTC programme is made up of 3 themes:
1) Computational and Cognitive Neuroscience.
Computational, mathematical, and experimental studies of information processing in the nervous system.
2) Neuromorphic Engineering and Robotics.
Artificial sensor perception, neuromorphic modelling, spiking computation, and neurorobotics.
3) Data Analysis and Systems.
Imaging data analysis using machine learning, Bayesian methods, and neurally inspired software.

Edinburgh has a strong research community in these areas and leads the UK in creating a coherent programme in neuroinformatics. Edinburgh has been voted as 'best place to live in Britain', and has many exciting cultural and student activities.
Students with a strong background in either computer science, mathematics, physics or engineering are particularly welcome to apply. Motivated students with other backgrounds will also be considered.

About 8 full studentships are available to UK students and a small number of EU students.
The stipend is about 12,300 GB pounds per annum.

Applicants from outside the EU will need to provide their own funding and evidence thereof.
Full info and application forms can be obtained from:
http://www.anc.ed.ac.uk/neuroinformatics. • E-mail: neuroinformatics-phd@inf.ed.ac.uk
Contact: Mrs Pat Ferguson • Phone: (44) 131 650 3090 • Fax: (44) 131 650 6899
Address: School of Informatics, 5 Forrest Hill, Edinburgh, EH1 2QL. Scotland, UK
Applications received by March 30th, 2007 will receive priority treatment.

University of Glasgow, Division of Clinical Neuroscience

PhD studentship

MRC funded studentship in pre-clinical imaging in neuroscience (4 years)

Stroke is a major killer and can cause significant disability in survivors. Specific treatment options are currently limited (thrombolysis within 3 hours or aspirin). The time window for acute neuroprotection therapy depends on the length of time injured but potentially salvageable tissue (penumbra) survives in each patient. Magnetic Resonance Imaging (MRI) techniques improve diagnostic accuracy, and offer the opportunity for physiological brain maging. This project will involve the development and validation of a new MRI technique to identify penumbral tissue in the ischaemic brain using established rodent stroke models, imaged in a state-of-the-art 7T small animal MR scanner.

The 4 year MRC funded PhD studentship, will be available from 1st October 2007 with a stipend of £12,300 per annum. Applicants should hold or expect to gain a first or upper second class honours degree in a biological or biomedical science or related field. Eligibility requirements for MRC studentships are listed in the Studentship guide - (http://www.mrc.ac.uk/Careers/Studentships/Informationforstudents/index.htm)

For further information contact Professor I Mhairi Macrae (m.macrae@udcf.gla.ac.uk) Tel 0141 330 6978, Division of Clinical Neuroscience, Wellcome Surgical Institute, Garscube Estate, Glasgow G61 1QH, UK.
Applicants should submit a CV including e-mail addresses of 2 referees.
A closing date has not yet been set. Applications received by March 30th, 2007 will receive priority treatment.

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