

Model organisms and disease

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11 November 2008



Animals are used widely in medical research

- **to explore normal biological mechanisms**
- **to identify the genetic basis of both normal and pathological cellular mechanisms**
- **to provide 'models' of human disease to explore possible treatments**
- **to test the toxicity of possible treatments**



The arguments for

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Most medical researchers, clinicians and the general public accept that animal research is still essential for medical progress.

Supporters argue that it is ethically more acceptable than neglecting the suffering of sick people.

The arguments against



- **some are absolutely opposed on moral grounds to human benefit derived from animal suffering – the deontological argument**
- **others question the evidence base for animal use, challenging the validity of animal models and the reliability of treatment strategies based on the study of other species – the utilitarian argument**

Polarisation of debate

Opponents to animal use sometimes deploy biased and unsubstantiated arguments.

Supporters of animal research sometimes dismiss the moral objections and the undeniable inadequacies of some aspects of animal experimentation.




Poll of *Nature* readers




- **scientists who work on animals have a complex set of views**
- **the simplified pro-con debate makes it very difficult to communicate them**

**What is needed is
more nuanced and
evidence-based debate**



We need to tackle such questions as:



- **Do we have adequate ways of assessing the validity of animal models?**
 - **Is there more scope for the development of alternatives to animal use, and is sufficient funding available for such research?**
 - **Is medical progress being impeded by excessively bureaucratic regulation and by the negative impact of extremist activity?**
 - **How effective is the evaluation of evidence from animal research about new treatment before clinical trials are started?**
 - **How justified is the use of primates, genetic modification and techniques that cause considerable suffering?**
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Call for systematic reviews

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***Pandora Pound et al.
BMJ (2004)***

- **is much of animal research wasted because of lack of evaluation through systematic reviews?**
- **are some animal experiments poorly designed and irrelevant?**
- **to what extent can the results of research on animals be generalised to humans?**




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Funds research, raises awareness, collates and disseminates information, provides training, establishes partnerships

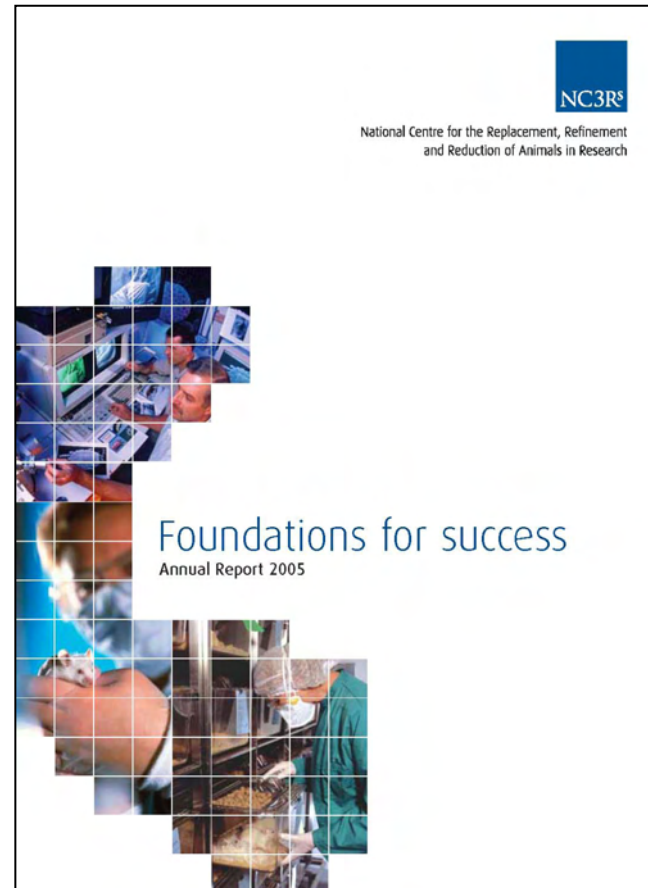
- **Replacement:** use of non-animal alternatives
 - **Reduction:** using minimum number of animals
 - **Refinement:** minimising pain and suffering
- 

NC3Rs

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- **budget for grants is more than £2m a year; extra money for resources**
- **award rate: 20% (roughly same as the MRC)**
- **funded by: MRC, BBSRC, Wellcome Trust, Home Office, Cancer Research UK, ABPI, Chemicals Industry**
- **established 3 years ago**




NC3Rs – examples of projects



- **diabetic wound healing: aims to develop a simple, reproducible, *in vitro* diabetic wound model system**
- **reduction of the numbers of animals in monoclonal and polyclonal antibody production: vaccinate each animal with more than one antigen**
- **identification of indicators of pain in rodents: aims to evaluate tumour-induced pain in rodents, and to develop a practical and reliable system for pain measurement**

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Excessive bureaucratic regulation?



Approval of Home Office licence applications still takes too long

Currently, regulators require tests on rodents with death endpoints, but they don't use the data

NC3Rs is trying to campaign with companies for change.



Impact of extremist activity?

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HLS exposed 10 years ago

The Guardian | Wednesday November 20 2006

SocietyGuardian Environment

Cagey questions

Zoe Broughton, 'laboratory technician' – journalist, secretly films tests on dogs

The outcry after a documentary about cruelty at Huntingdon Life Sciences laboratory brought about many changes in animal testing. **Zoe Broughton**, who exposed the abuses, looks at the situation a decade later

It is 10 years since I worked undercover on animal testing at Huntingdon Life Sciences (HLS). As a laboratory technician, I cleaned cages and held the puppies while tests were performed. I secretly filmed and caught on camera staff abusing the dogs so horrendously that the day after my article appeared in the Guardian, and the film was broadcast on Channel 4, the police turned up at the perpetrators' doors and arrested them.

After my exposé, the then chief executive of HLS, Christopher Cliffe, wrote a report titled *Dog Days in Huntingdon: Lessons From A Corporate Crisis*. In this he stated that "the managers thought that the scenes broadcast were tricks of the camera and that mitigating circumstances, such as the 'agent provocateur' behaviour of the infiltrator, would influence the outcome of any investigation".

I had clear video evidence showing staff hitting and shaking the puppies as they experimented on the dogs. The two technicians were convicted of cruelty to animals under the Protection of Animals Act 1986, pleading guilty to cruelly treating dogs. This was the first and only time in the UK that laboratory staff had been convicted of cruelty to animals. Both were sentenced to 60 hours' community service and ordered to pay legal costs.

Some of the tests I witnessed were mishandled. Staff didn't always measure out the capsule doses correctly, and on another test I saw them inject syringes straight into the leg where the blood



Trouble at HLS

Activists target organisations involved in animal research by attacking the individuals that work for them or the companies that supply them

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You are in: UK
Friday, 23 February, 2001, 16:35 GMT
Animal lab boss defiant after attack



Target: Attack on Brian Cass "linked to protest"

The head of an animal testing company says he is determined not to give in to "terrorism" after being hurt in an attack believed linked to animal rights protesters.



Arson...

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**Special
report**
Animal
rights

Animal rights extremists in arson spree

Sandra Laville and Duncan Campbell

Saturday June 25, 2005

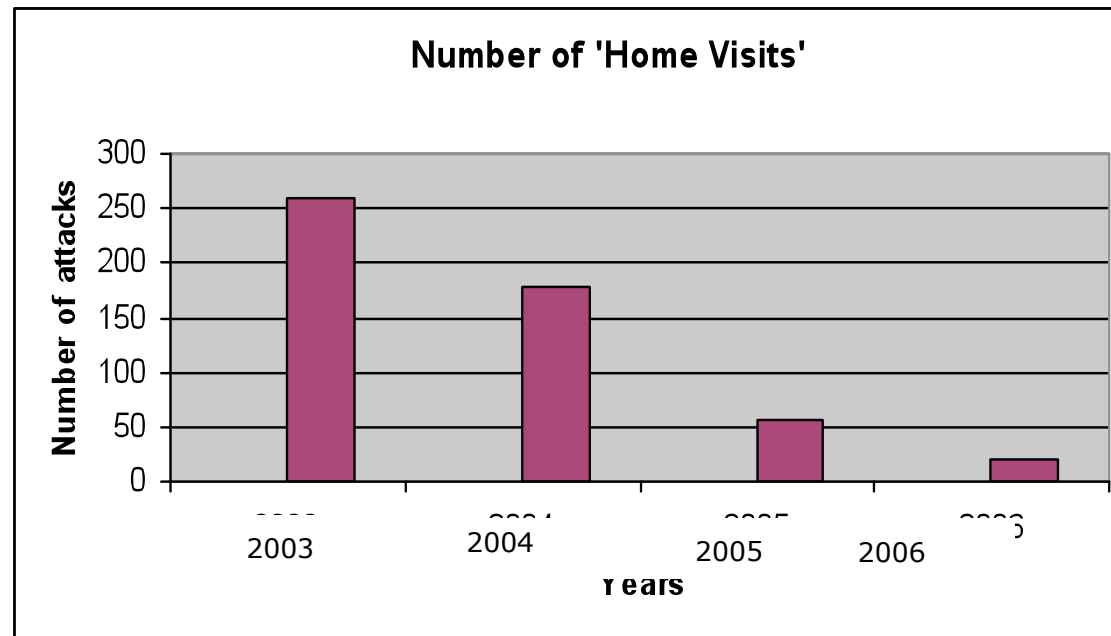
[The Guardian](#)

Animal rights activists have unleashed a new arson campaign in the run-up to the introduction of a law next month which could see them jailed for five years for economic sabotage.

Extremists are returning to the tactics of several years ago, using firebombs to attack anyone they perceive as having links to Huntingdon Life Sciences, the Cambridgeshire-based research laboratory.

Impact of extremist activity?


- **figures released by ABPI (Jan 2007): a “sustained downward trend in violent and intimidating animal extremism”**
- **in 2006 there were 20 ‘home visits’ – compared with a peak of 259 in 2003**



Source: ABPI

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Need better translation of animal tests into clinical trials



BMJ, 2006

- **how useful are animal experiments in predicting the outcome of human trials of new medicines?**
- **researchers looked at clinical trials of treatments for stroke and head injury, and assessed whether prior animal research had given similar results to human trials**
- **exposed problems with the models and the analysis of animal data**

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Weatherall report - 'The use of non-human primates in research'

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Published in December 2006

Concluded there is a strong scientific case for the carefully regulated use of non-human primates where there is no other means to address clearly defined questions



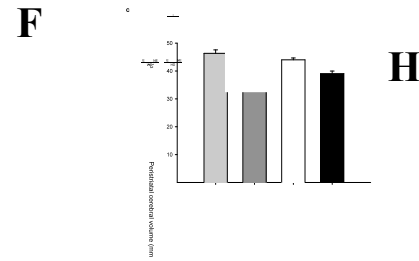
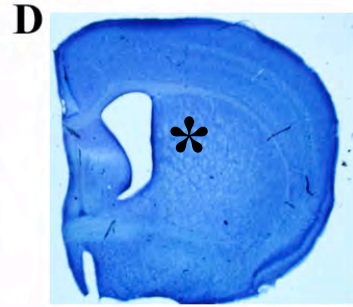
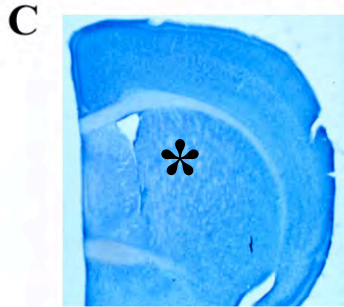
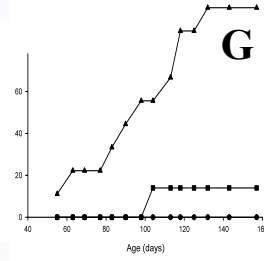
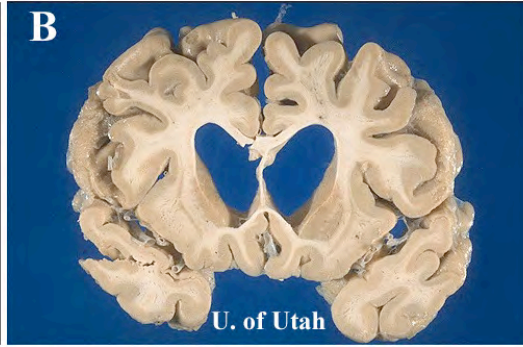
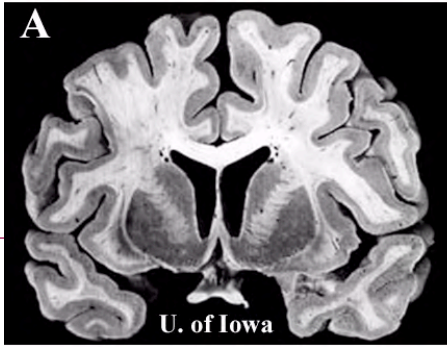
Better animal welfare means better science

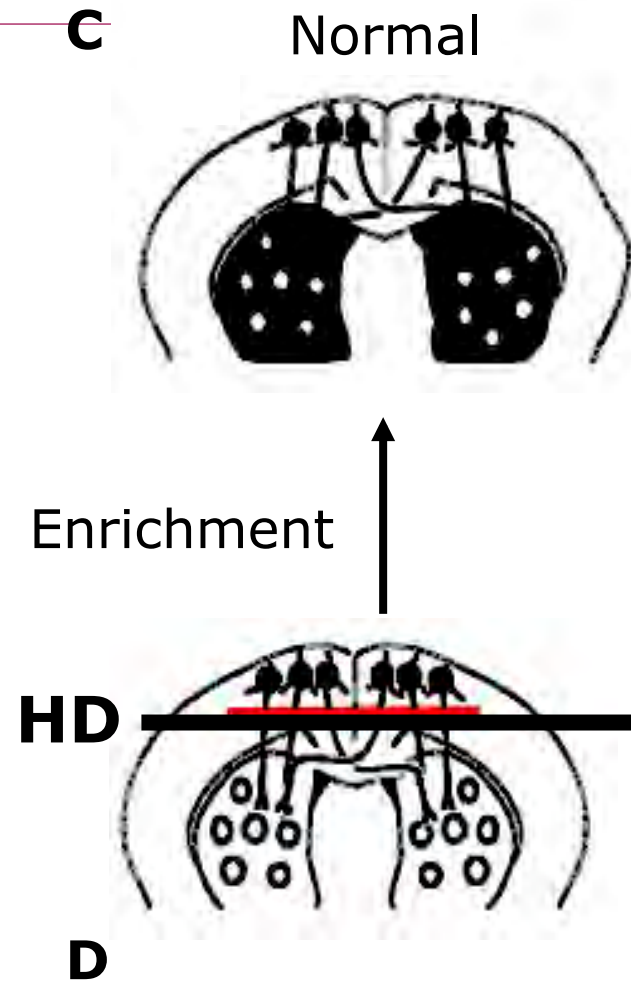
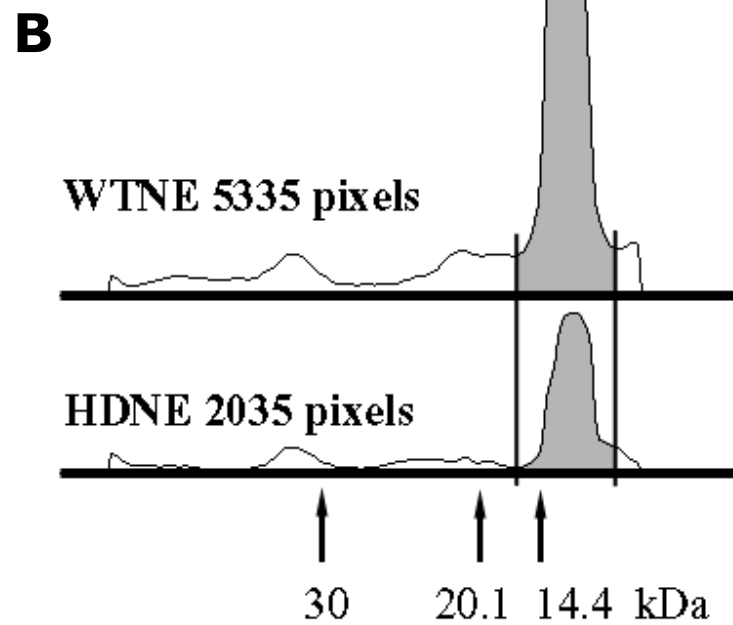
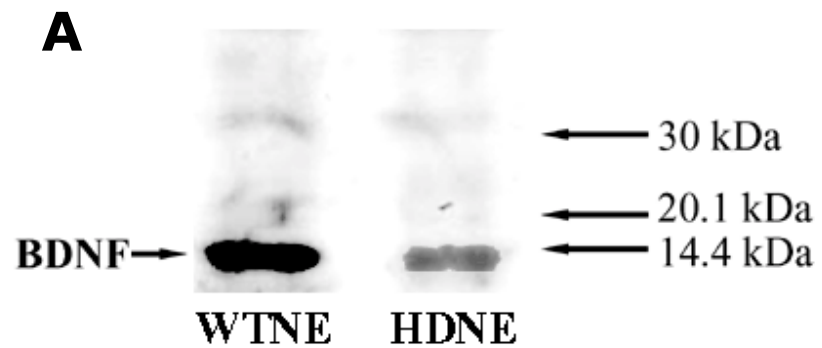
Models of Huntington's disease



Complex environment slows disease progression in Huntington's disease mice – may actually mimic human disease more accurately

Hockly *et al.* (2002). *Ann Neurol*, 51






Boyd Group

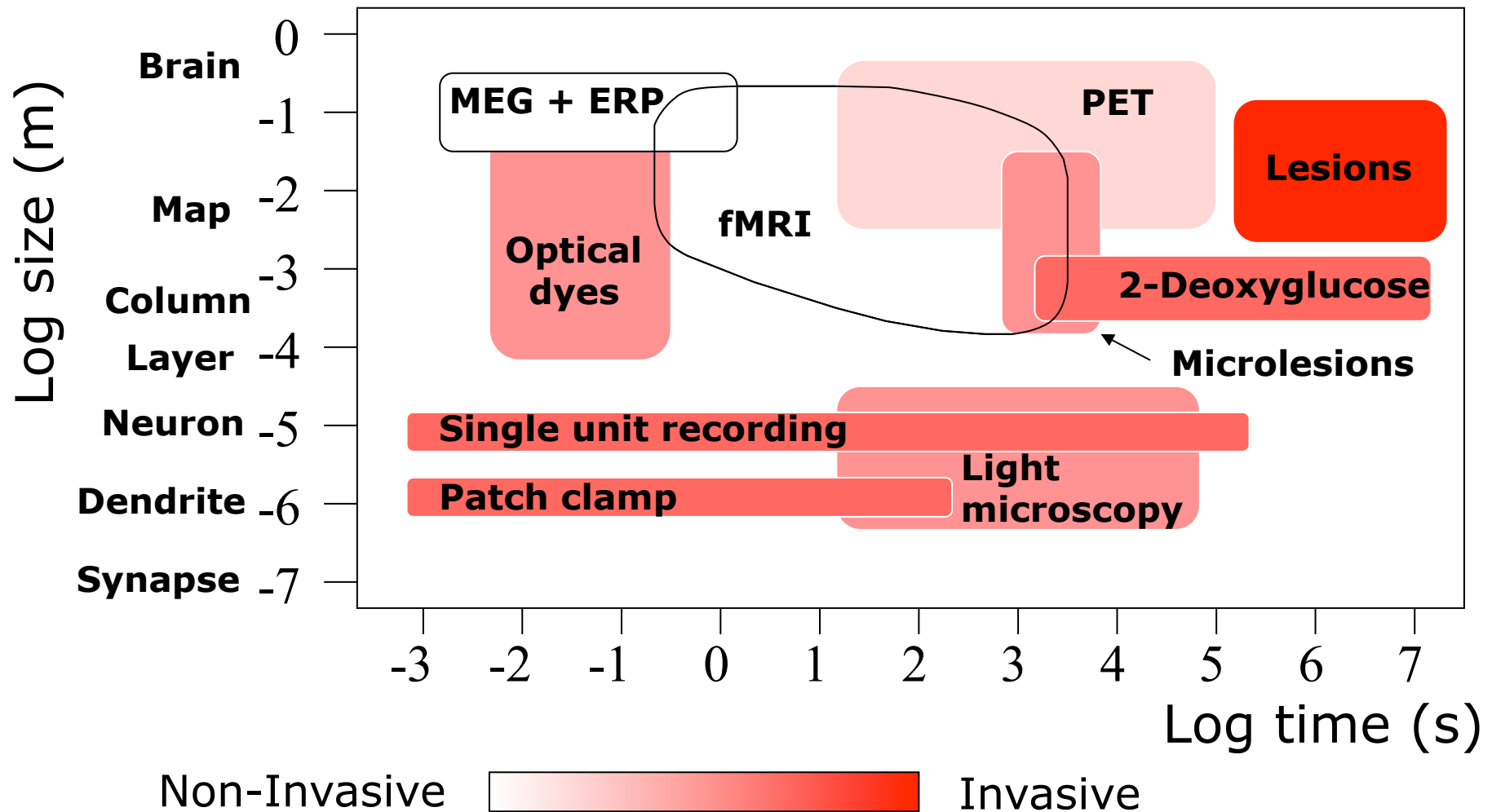


- **a UK-based forum for open exchange of views on issues of concern related to the use of animals in science**
- **brings together those with the full spectrum of views on the use of animal in research to discuss areas of concern in an open environment**
- **due to its diverse membership, the Boyd Group commands a lot of respect**
- **the MRC is a major funder**

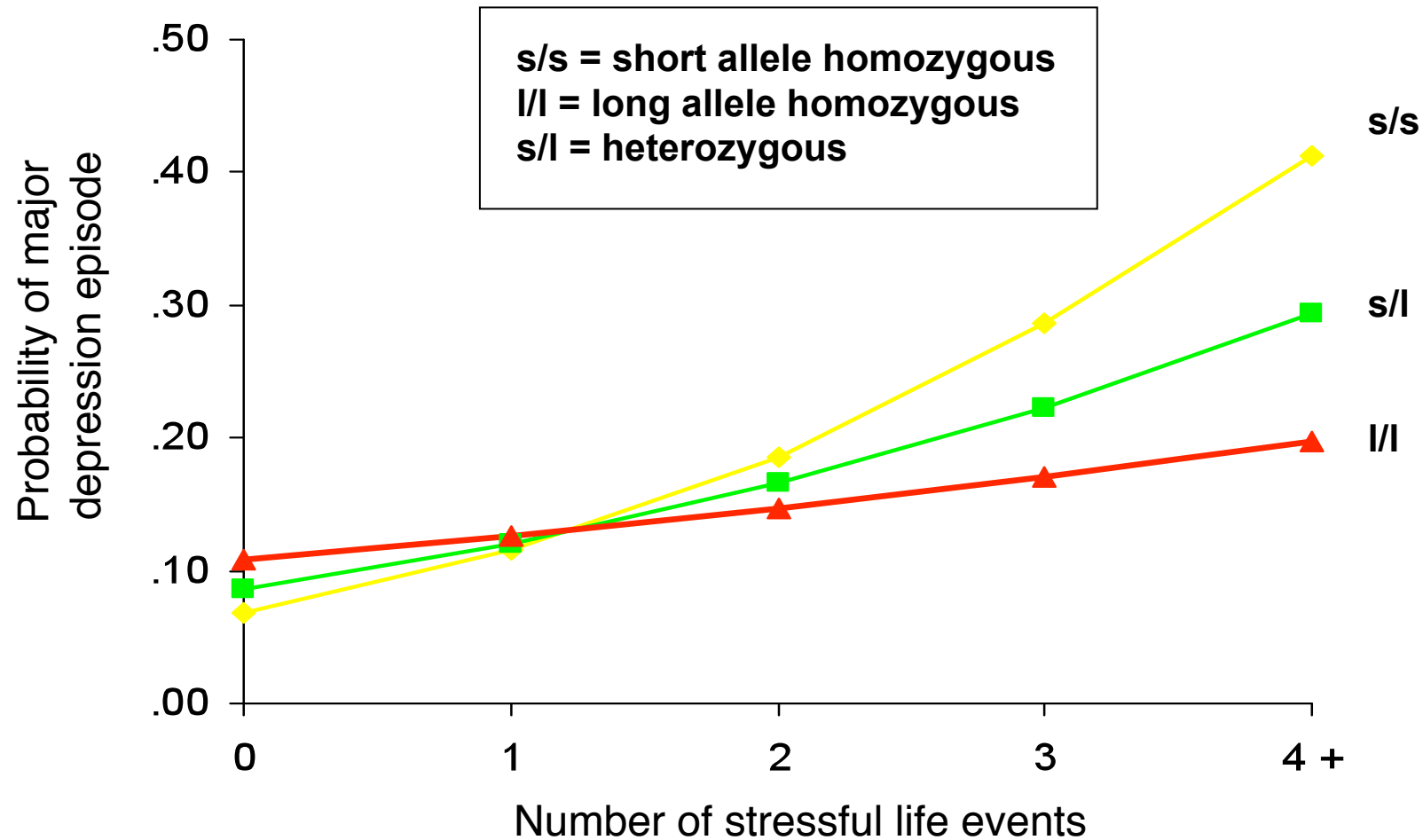
Current activities

- **reviewing the classification of the severity bands used to categorise levels of suffering experienced by animals**
 - **considering the feasibility of setting targets to replace animal use**
- 

Imaging structure and function: integrating information over space and time



Effects of life stress on incidence of depression moderated by one allele of the 5-HTT gene



Caspi et al., (2003)

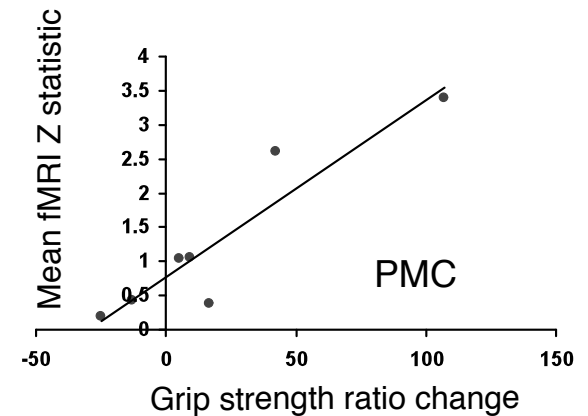
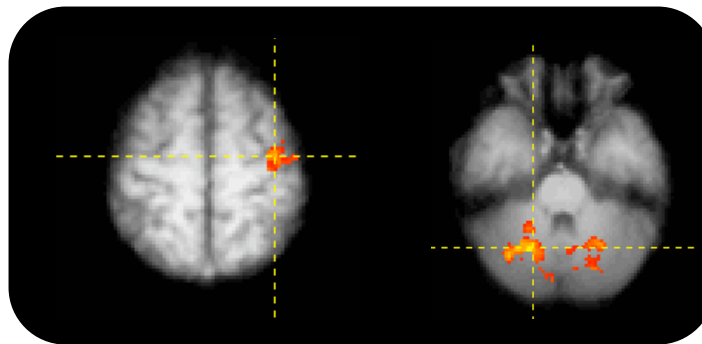
Changes in the brain with therapy



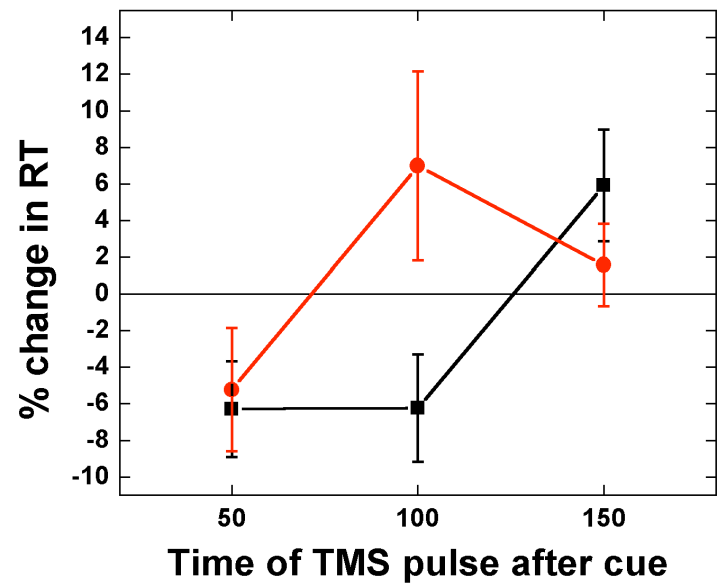
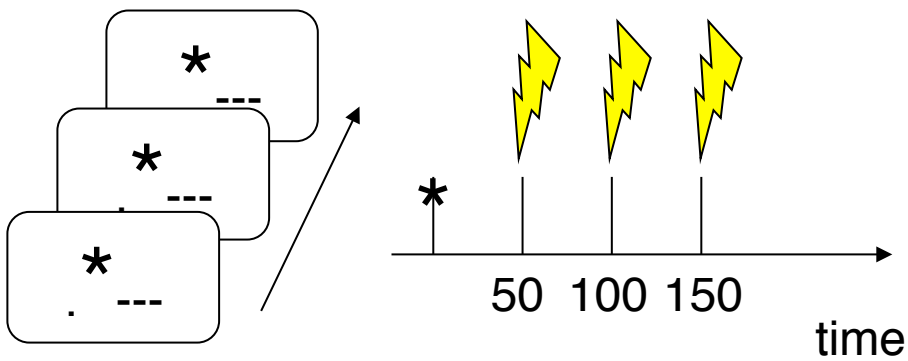
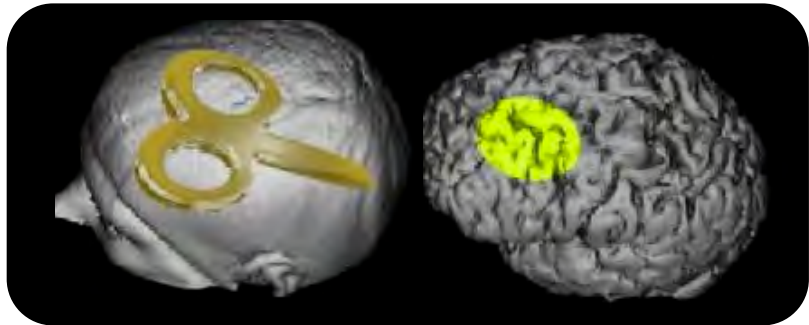
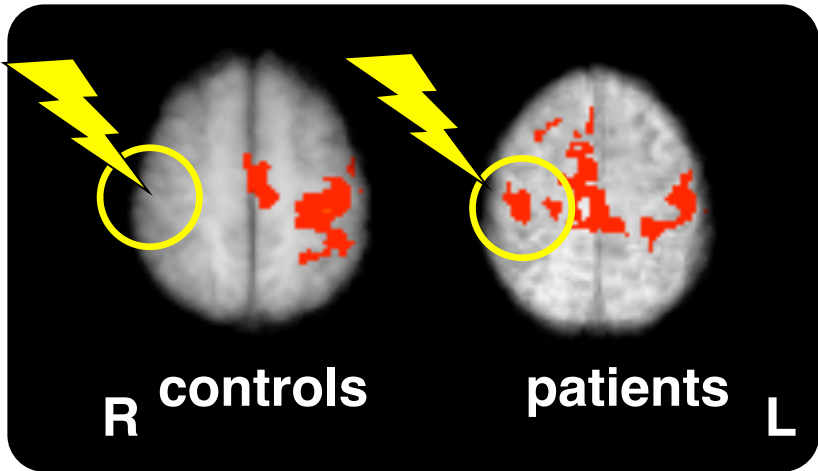
Single subject: responder



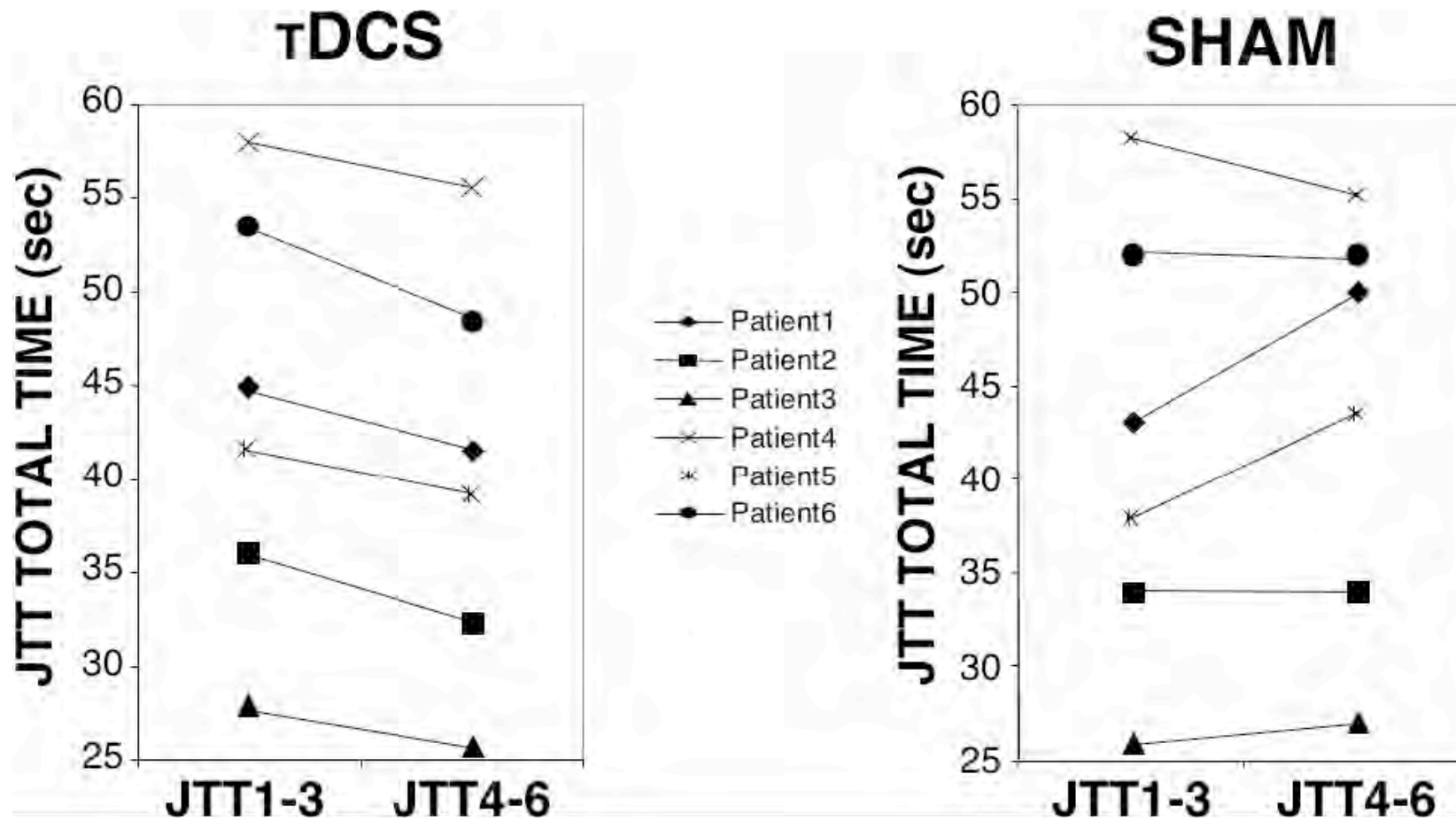
Group: Correlations with improvement



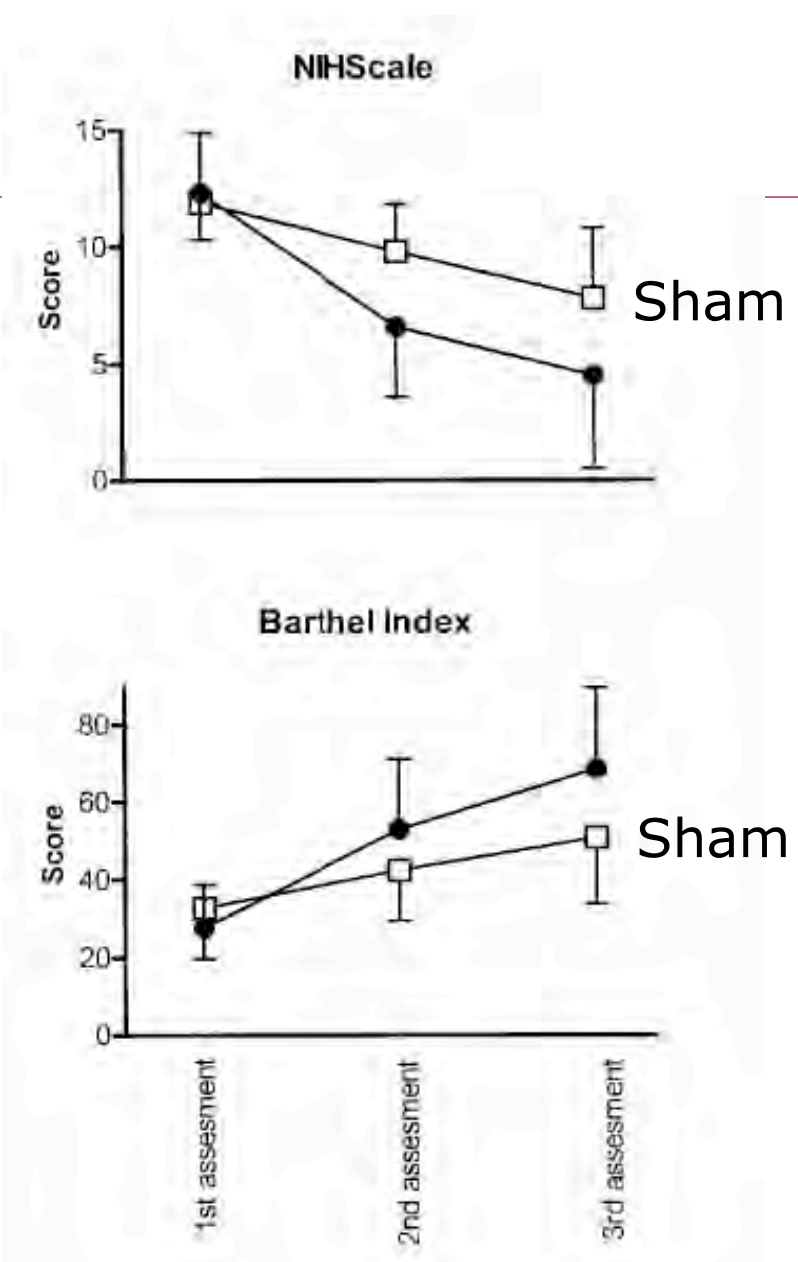
TMS of region of increased activity in ipsilateral motor cortex impairs performance after recovery from stroke



Transcranial direct current stimulation of motor cortex improves hand control in subcortical stroke



Hummel et al. *Brain* 2005



rTMS of stroke-affected motor cortex (daily for 10 days during normal treatment) improves motor performance

Khedr et al. *Neurology* 2005