

Imaging for Translational Medicine

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Clinical Imaging Centre



GlaxoSmithKline

The GSK Clinical Imaging Centre: an experiment for translational medicine

- A facility operating at the academic-industry interface
- A mission to pursue advanced human imaging studies in the service of drug development and progression
- Facilities
 - *~4000 m² clinical, laboratory and office space*
 - *3T MRI, 2 PET/CT, 2 cyclotrons radiochemistry and biology laboratories (supported by microPET)*
 - *Dedicated specialist IT environment*
- People
 - *65 FTE including radiochemists, biologists, physicians, clinical scientists, physicists, nurses, radiographers, data analysts and operations staff*
 - *Seconded staff from GSK business partners*
 - *Academic collaborators, fellows and students*



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What is translational medicine?

- **Biologically-driven therapeutics development involving hypothesis-led research performed across levels of biological complexity (e.g., cells to tissue preparation) or across species e.g., mouse to man)**
 - Accelerated testing of laboratory hypotheses in the clinic



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 - Accelerated testing of laboratory hypotheses in the clinic
- **Outcomes are defined as clear answers from precise questions**
 - This is not a search for a “clinically predictive” marker



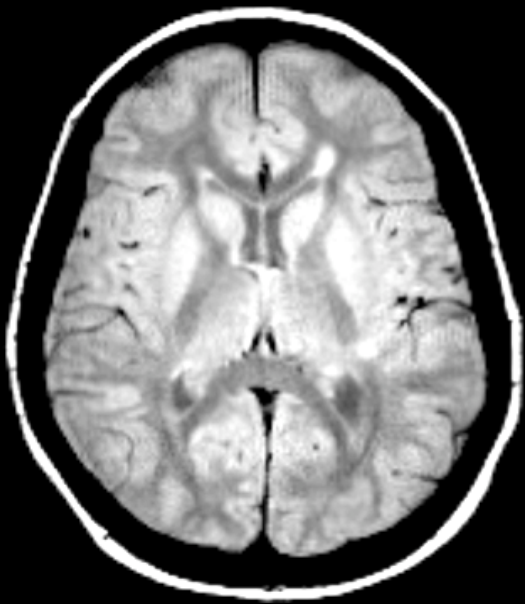
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 - Accelerated testing of laboratory hypotheses in the clinic
- **Outcomes are defined as clear answers from precise questions**
 - This is not a search for a “clinically predictive” marker
- **Bench-to-bedside and back again**
 - Development and application of new technologies in a patient-focused environment
 - Testing of new concepts

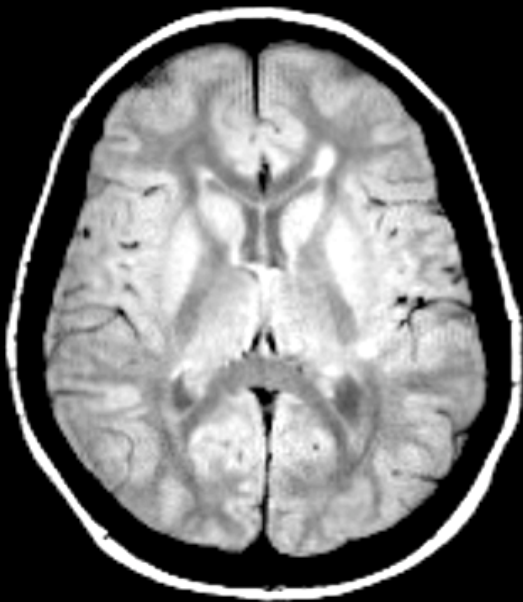


Imaging for Translational Medicine should be contrasted with Diagnostic Imaging

- **Diagnostic imaging is testing a general null hypothesis: is the image “normal”?**
 - General principles
 - Validated approaches: evidence-based
 - Qualitative/categorical



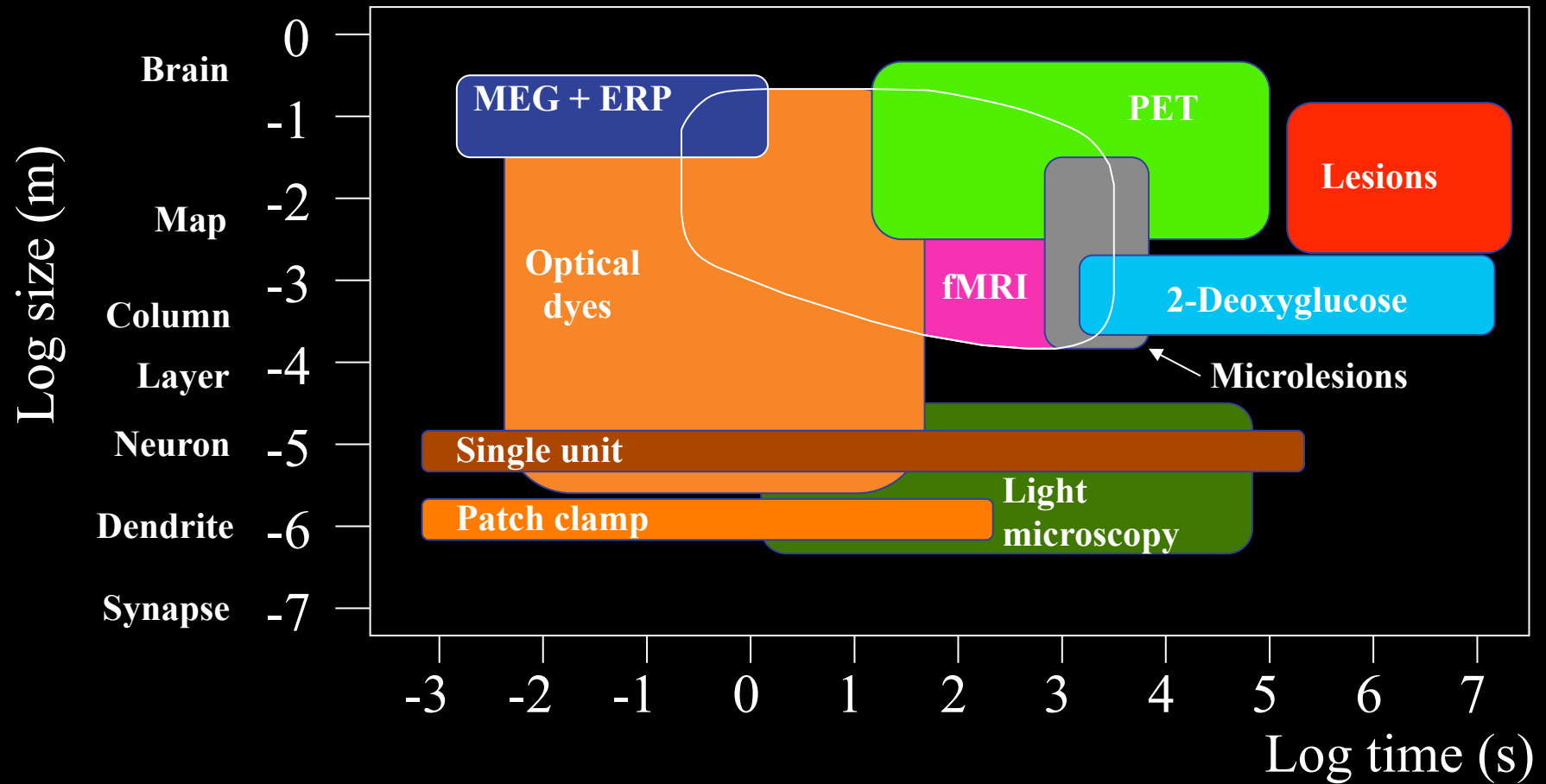
Imaging for Translational Medicine should be contrasted with Diagnostic Imaging



- **Diagnostic imaging is testing a general null hypothesis: is the image “normal”?**
 - General principles
 - Validated approaches: evidence-based
 - Qualitative/categorical
- **Imaging for translational medicine will test a *specific hypothesis*-physiological or pharmacological**
 - Context-specific
 - Qualifying: building an evidence-base
 - Quantitative



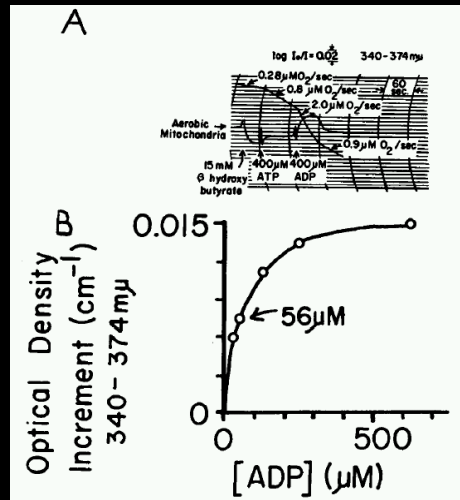
Exploiting spatial and temporal scales for imaging



Non-Invasive
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Invasive

Direct translation of hypotheses

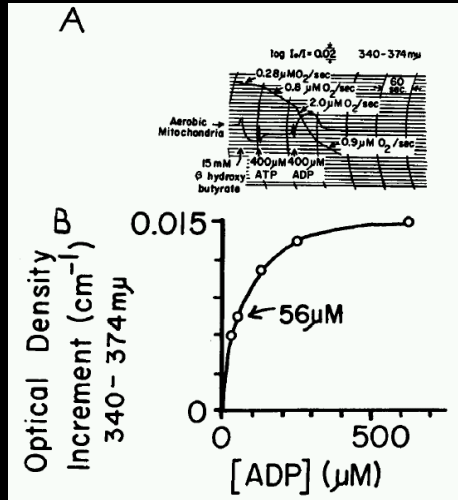


Chance and Williams, 1956

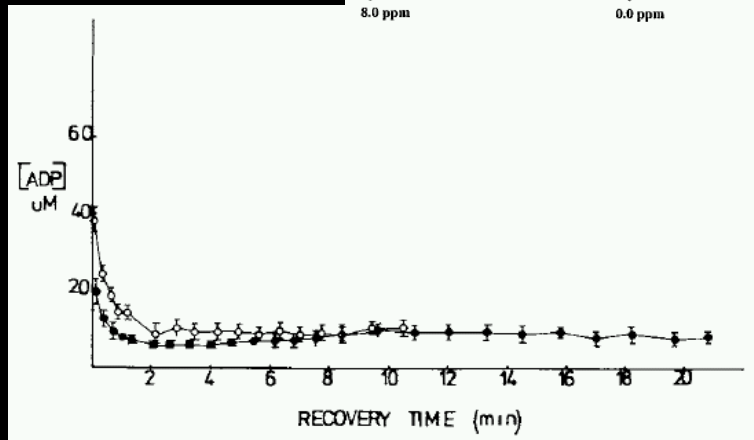


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Direct translation of hypotheses



Chance and Williams, 1956

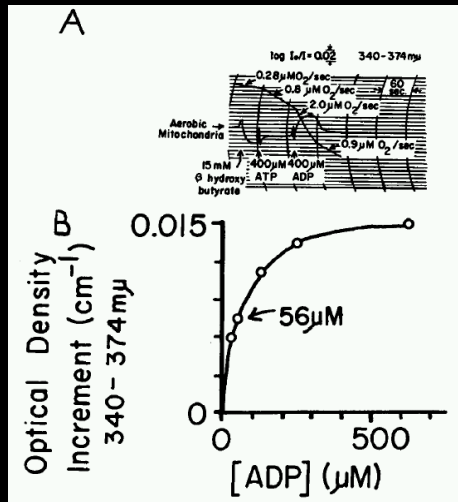


Arnold et al. 1981

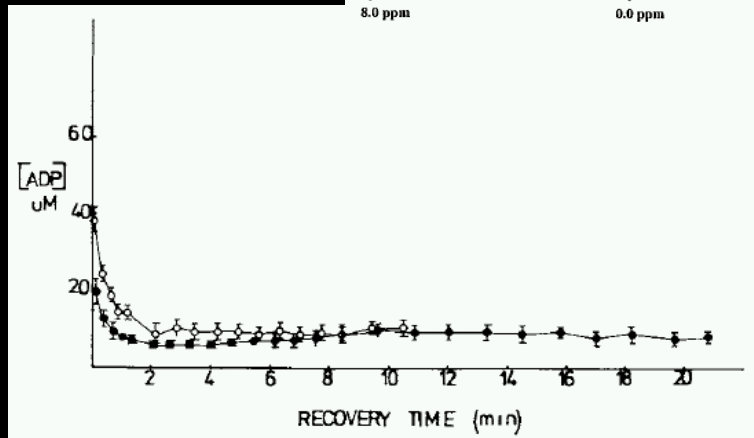
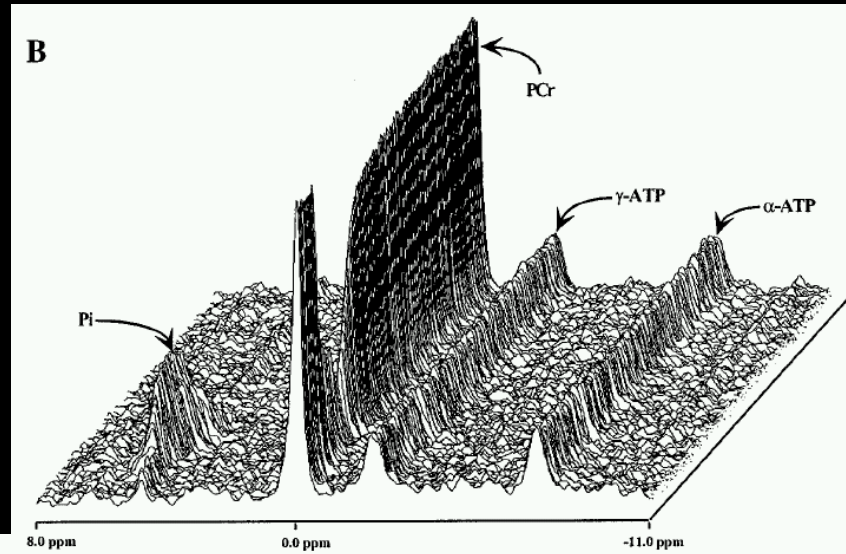


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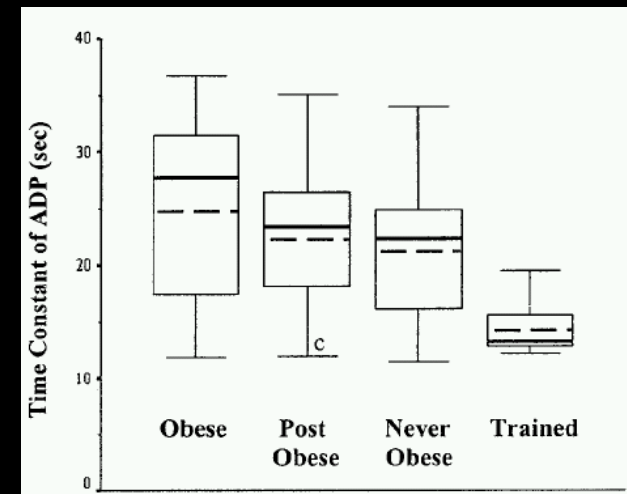
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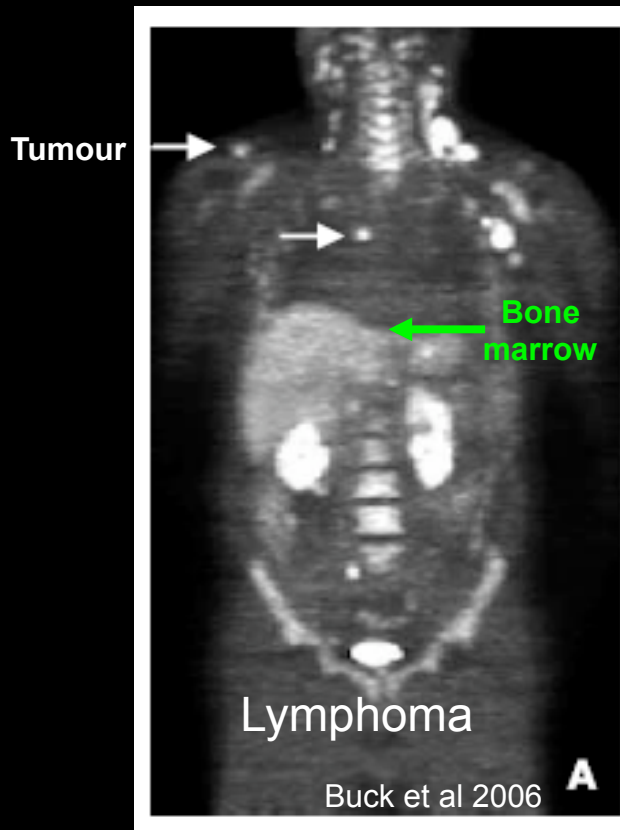
Larson-Meyer et al. Am J Physiol end Metab 278: E153-E161

How can these approaches fundamentally change the way we can *think* about clinical trials?

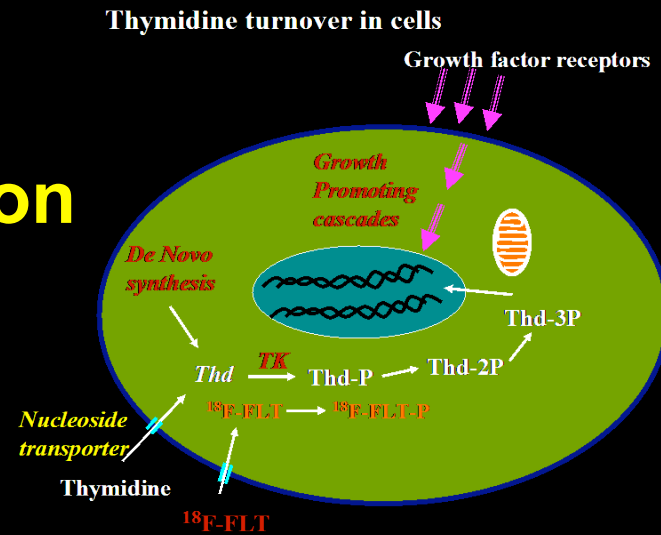
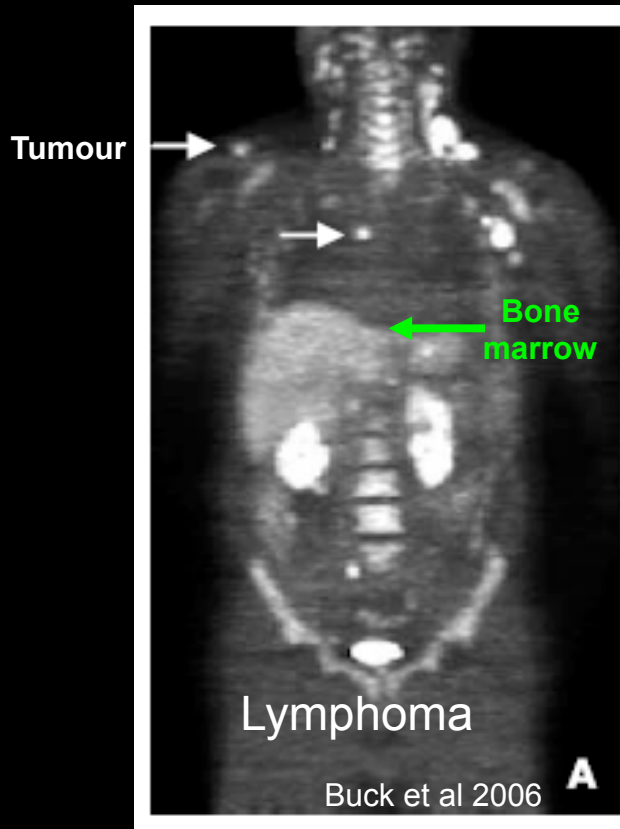
- The large effect size of many imaging markers can shift us away from the need for conventional population-based approaches
- Individual responses can be expressed with respect to Bayesian priors that model specific hypotheses
- Hypotheses can be tested by “falsifiability” or “futility” criteria on the basis of models and confidence intervals
- We can move away from the “tyranny of the p-value”



^{18}F -fluoro-thymidine for oncology: probing malignant cell proliferation



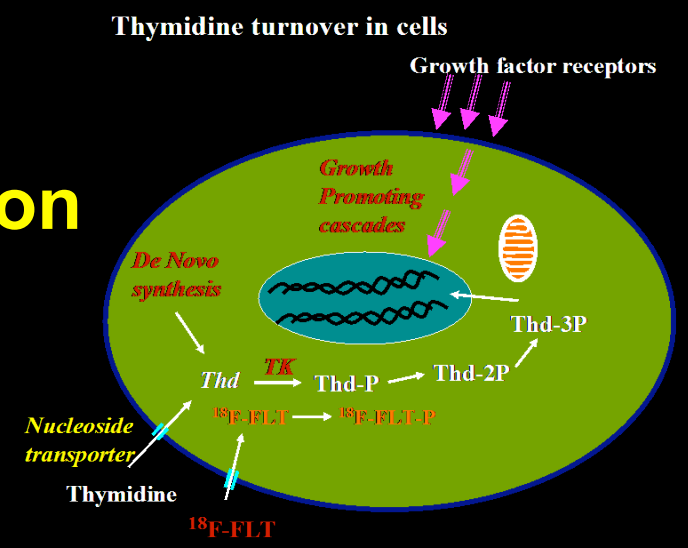
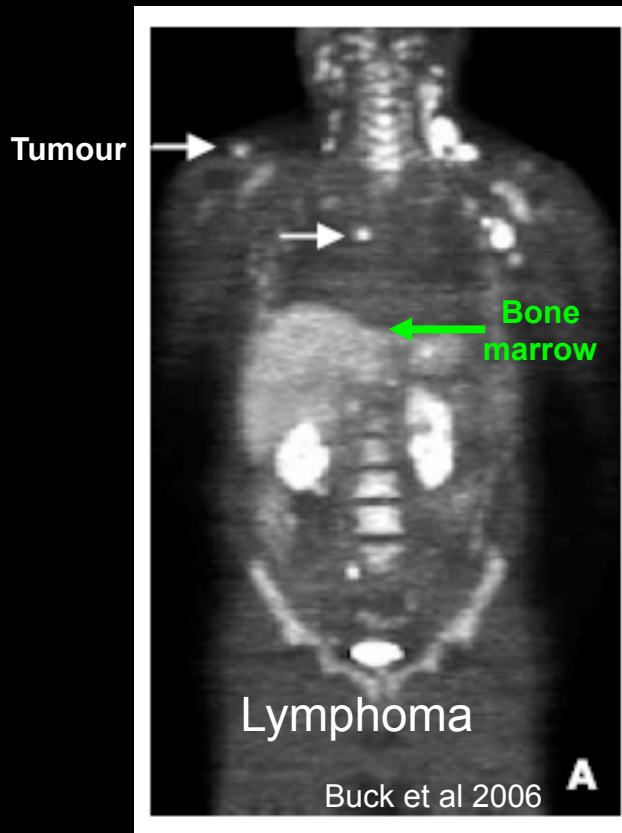
¹⁸F-fluoro-thymidine for oncology: probing malignant cell proliferation



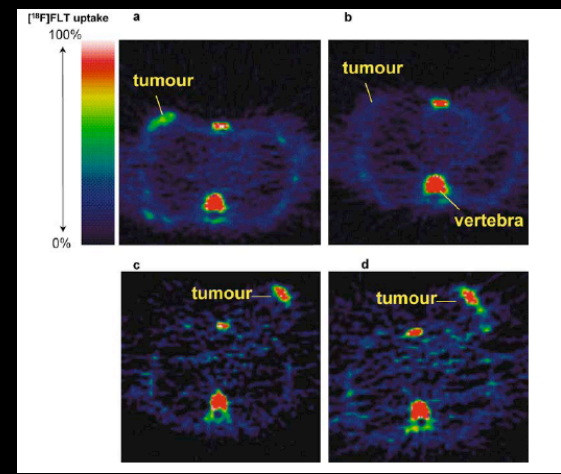
FLT trapping is an index of thymidine kinase activity: increased in S-phase



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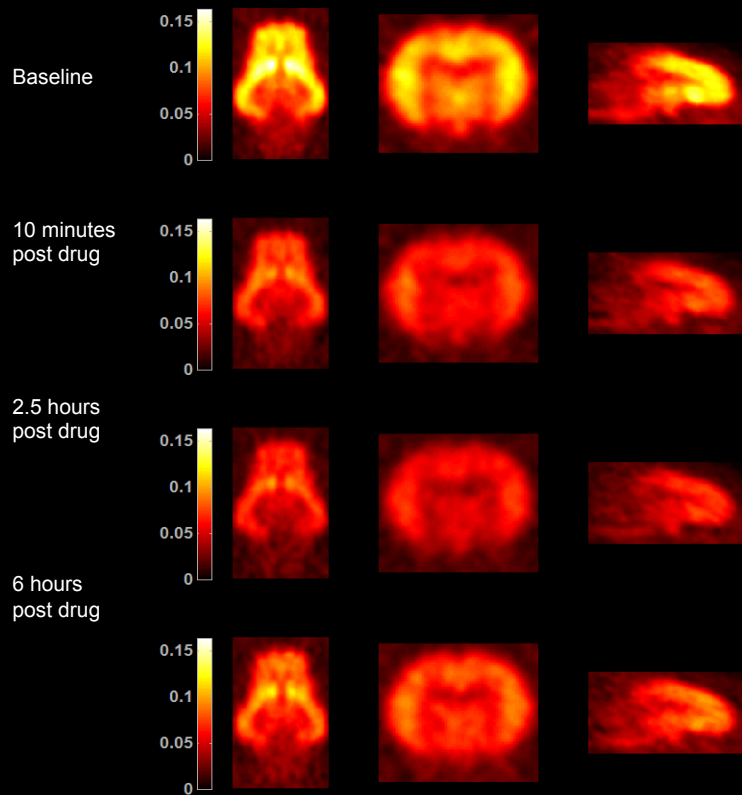
Stratification:

Responder

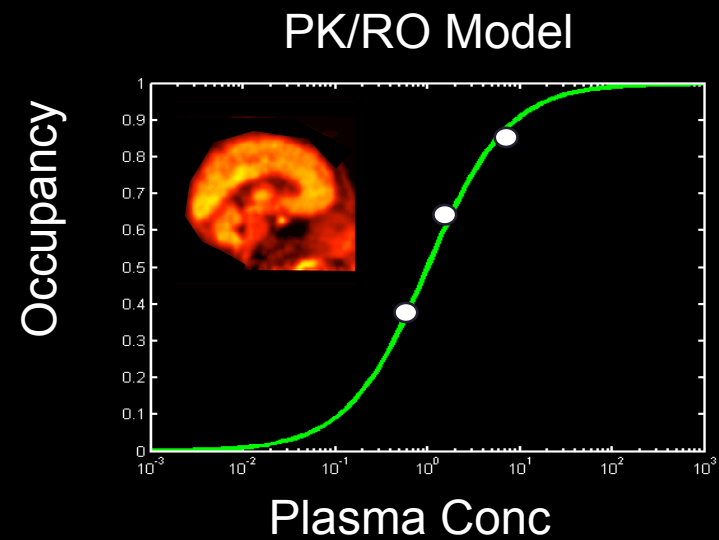
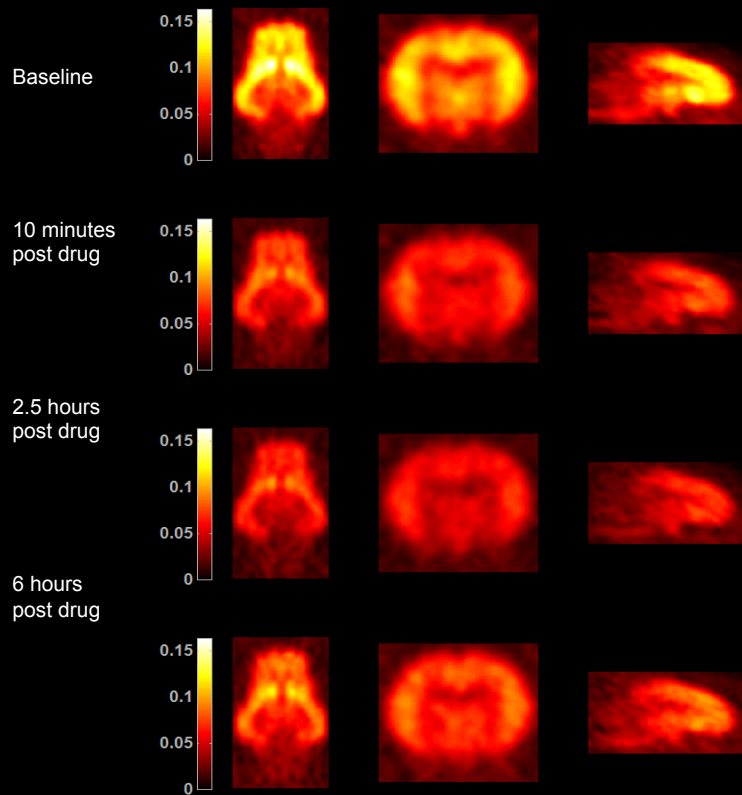
Non-responder

Kenny et al 2007

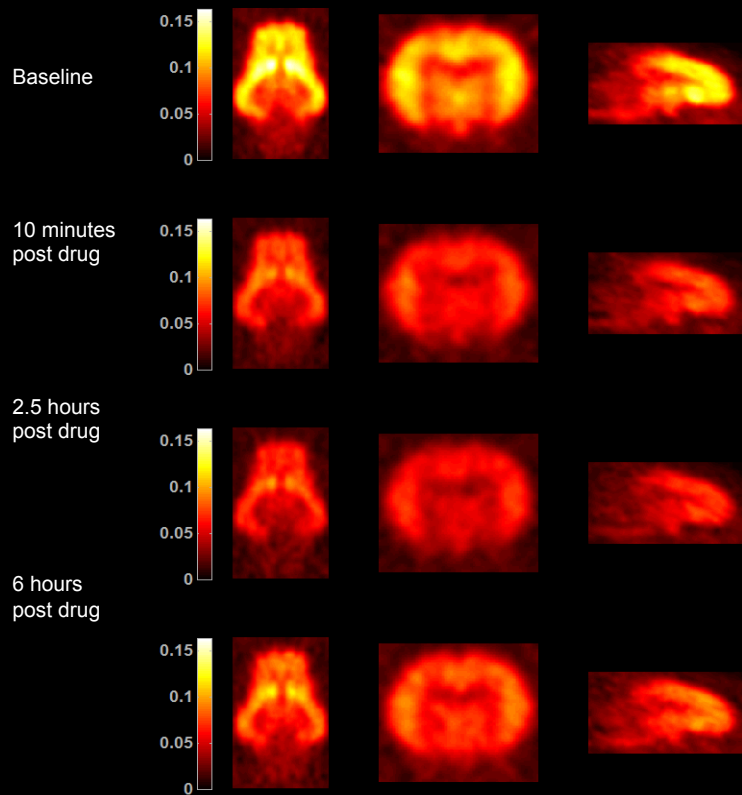
Pharmacology *in vivo*: translating across species



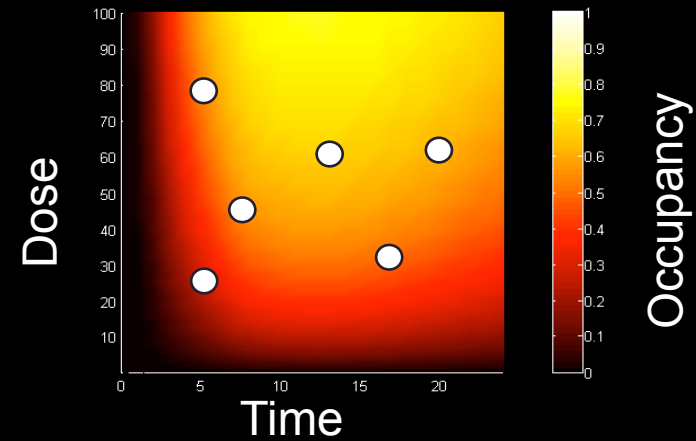
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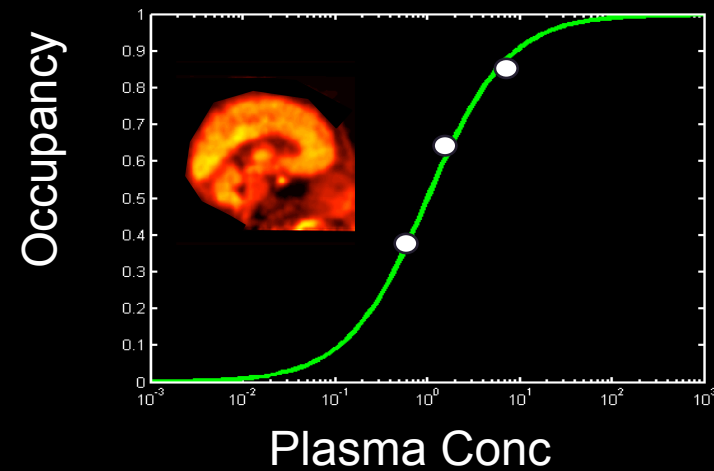
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The challenge

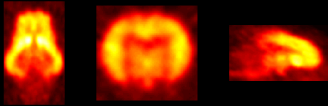


PK/RO Model

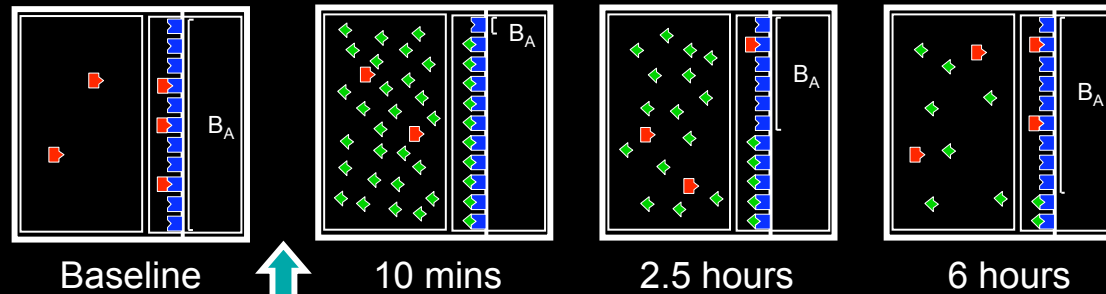


Exploiting the potential for understanding dynamics offered by non-invasive physiology

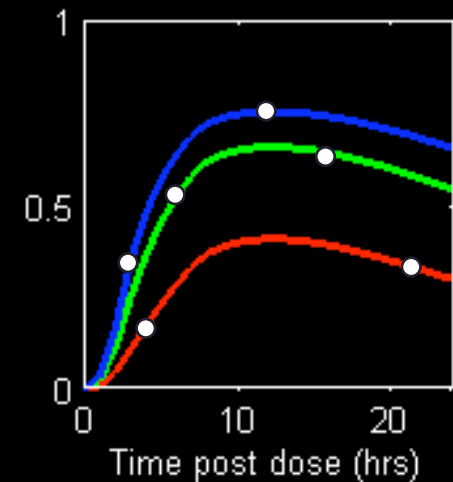
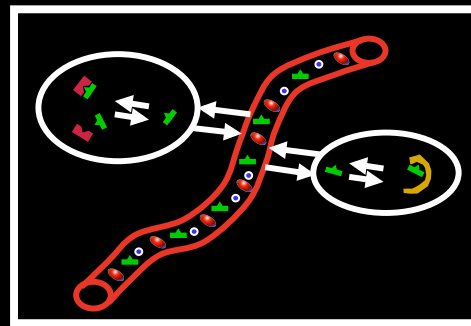
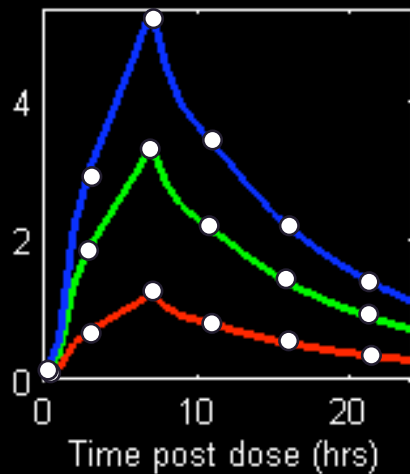
Radiotracer binding



Landrace Pig



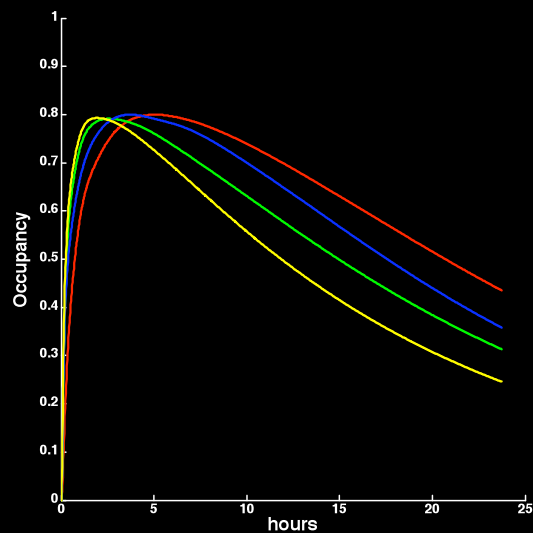
Drug Candidate



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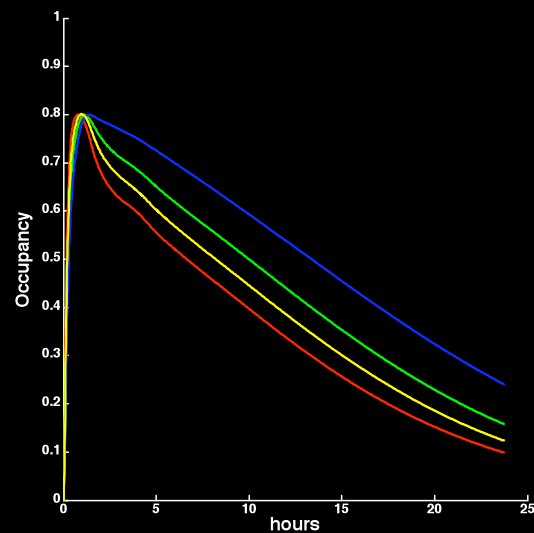
Hypothesis-led models to transform data into information

Impact of Plasma Kinetics



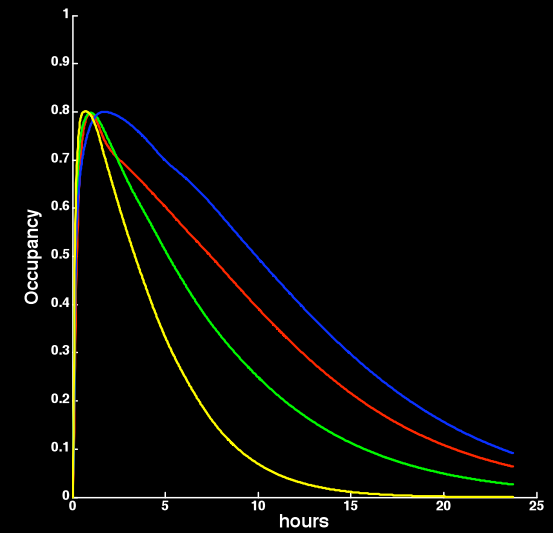
- Individual Plasma
- Homogeneous Tissue Kinetics

Impact of Tissue Kinetics



- Homogeneous Plasma
- Individual Tissue Kinetics

Combined Kinetics



- Individual Plasma
- Individual Tissue Kinetics

All normalized to 80% peak occupancy



The challenge of developing PET molecular imaging probes: new partnerships, new tools

Serotonergic

- 5-HT1A
- 5-HT2A
- SERT

Dopaminergic

- D1
- D2
- DAT

Opioids

- μ -selective
- non-selective
- Sigma 1

Cannabinoids

- CB1

Histaminergic

- H1

Adrenergic

- β -adrenoceptor
- NET

Adenosine

- A1A
- A2A

Nicotinergic

- $\alpha 4\beta 2$

Cholinergic

- BuChE

Muscarinic

- M2
- non-selective

Gabaergic

- GABA(A)

Inflammation/function

- PBR (TSPO)
- MAO-A
- MAO-B

Degeneration

- amyloid plaques

Transporters

- P-gp
- VMAT



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Industry-led partnerships

Serotonergic

- 5-HT1B (Pfizer)
- 5-HT4 (GSK)
- 5-HT6 (GSK)

Dopaminergic

- D3 ('GSK')

Glutamatergic

- mGluR5 (Merck)
- GlyT1 (GSK/Merck)

Histaminergic

- H3 (GSK)

Neurokinergic

- NK1 (GSK/Merck)

Inflammation/function

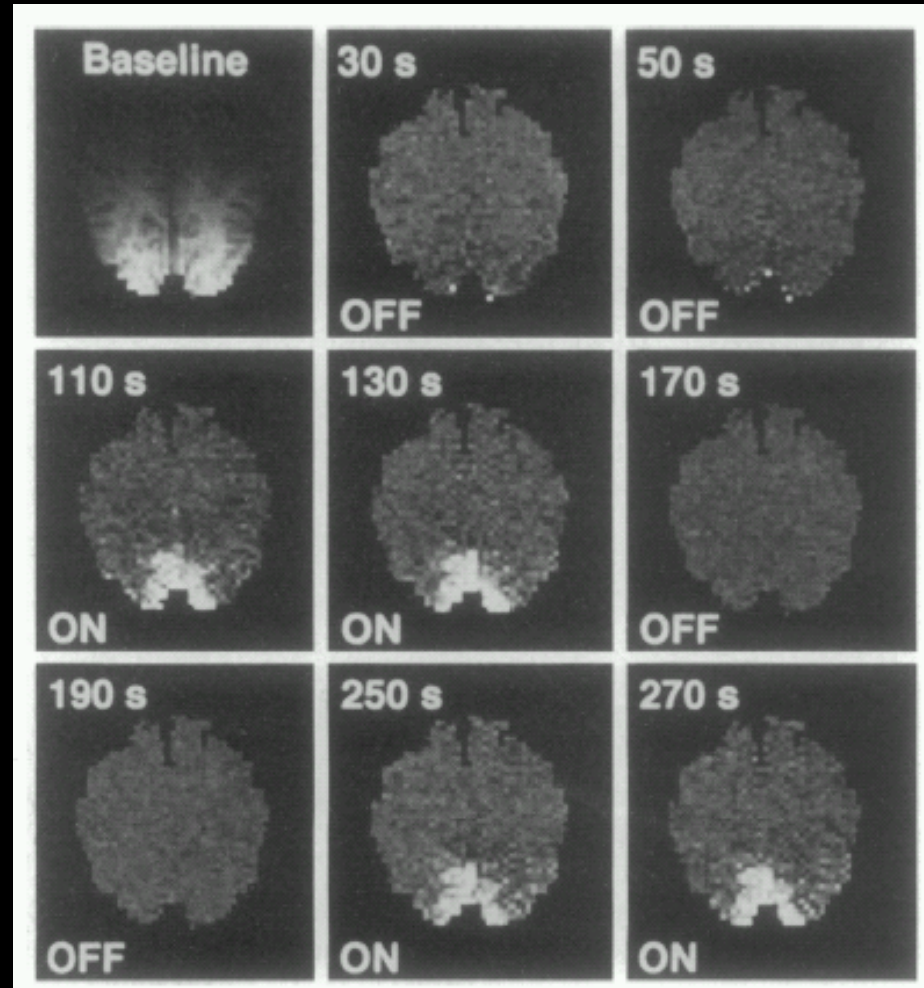
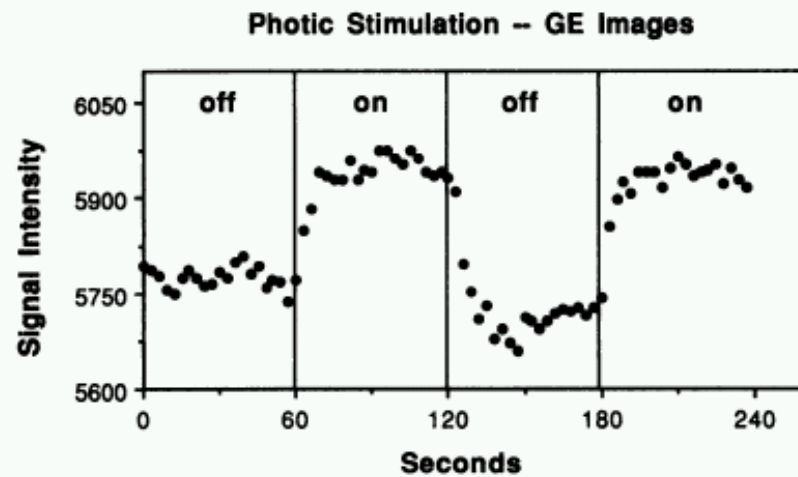
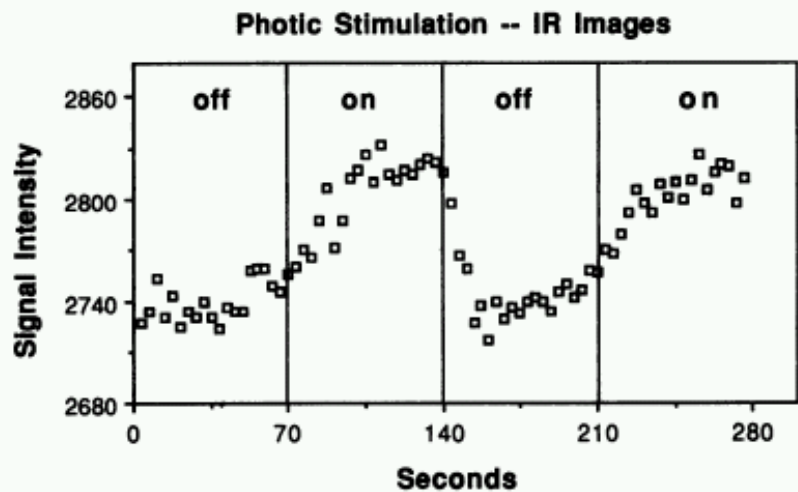
- PDEIV ('GSK')

Future tools

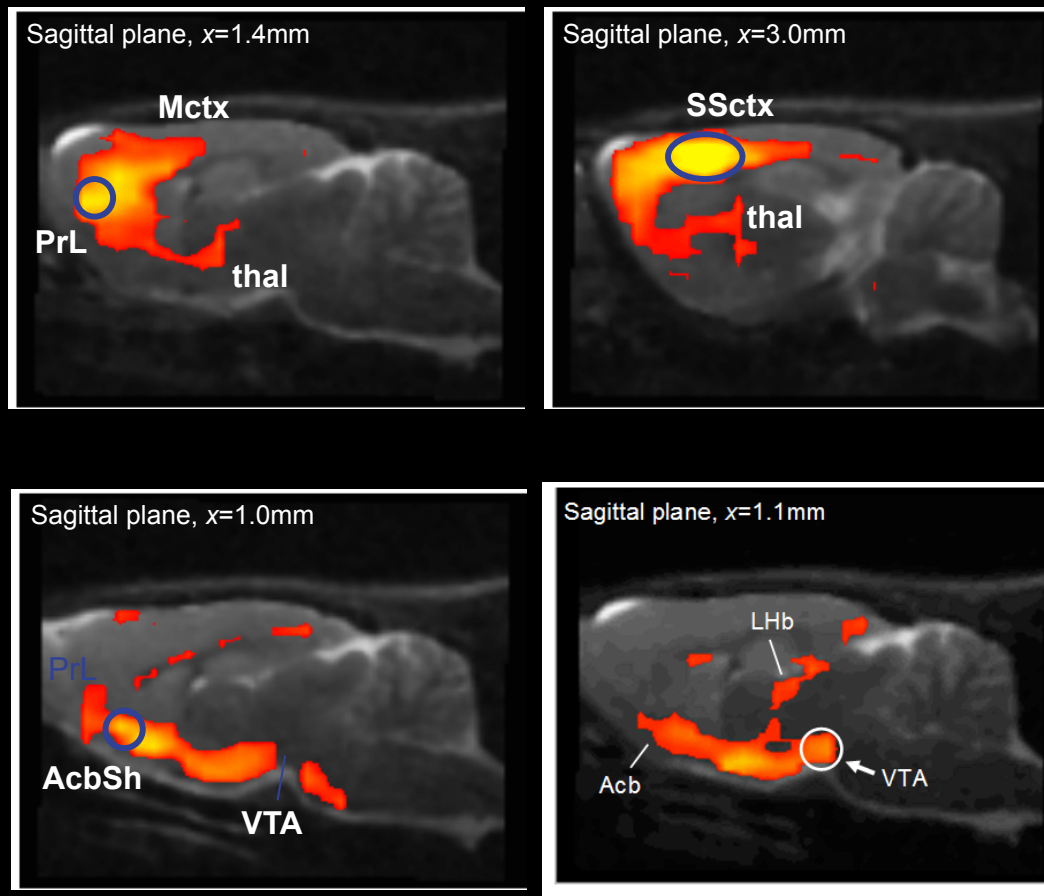
- "Click chemistry"
- Microfluidics
- Biologicals



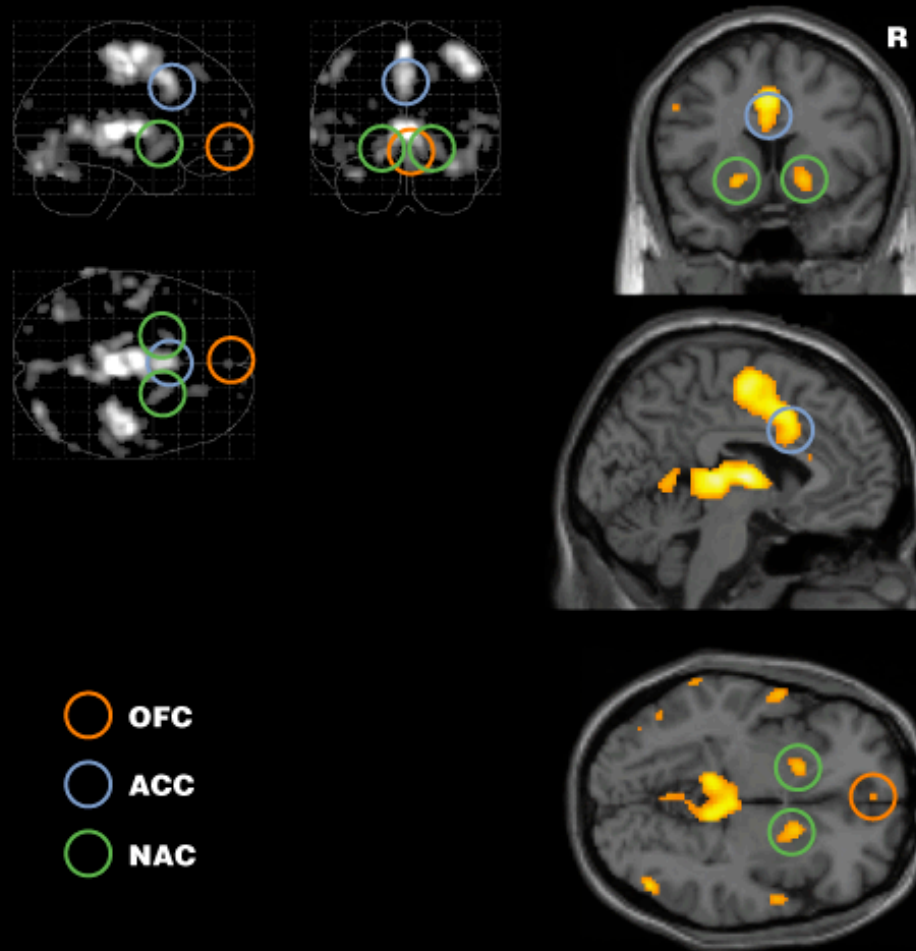
Bedside to bench and “the power of one”



Systems level analysis of brain modulation with a pharmacological challenge: a new translational medicine paradigm



Direct translation of the paradigm to humans

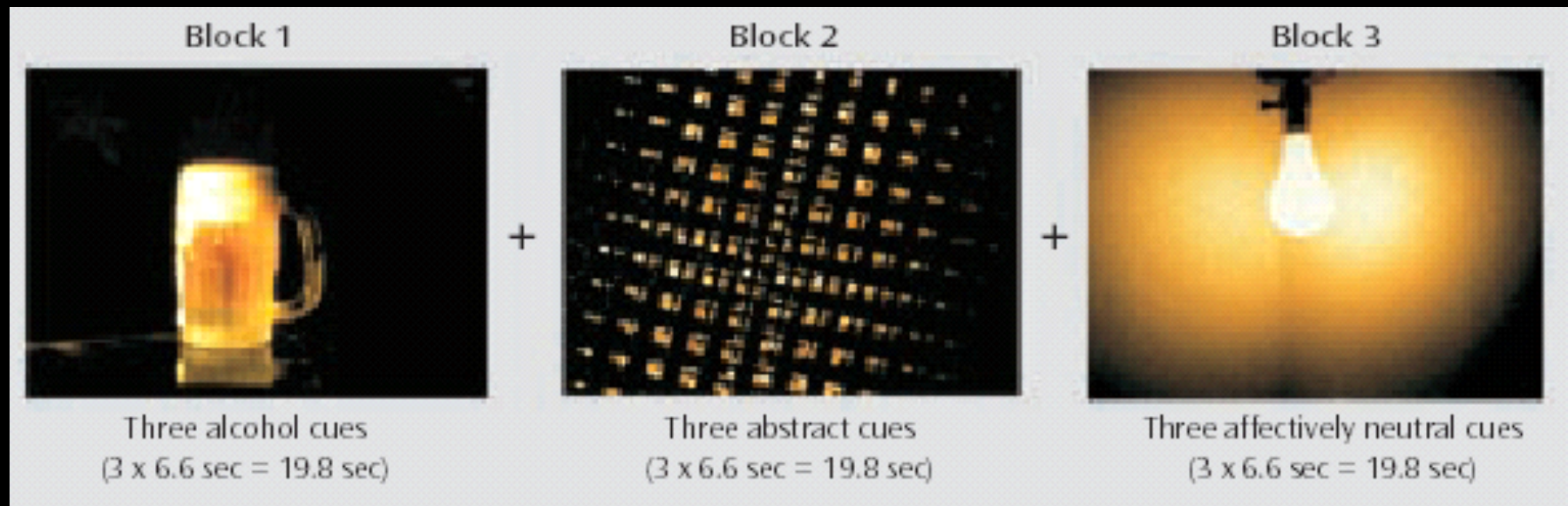


Vollm et al., 2005



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Using “real time” physiology to relate physiology to behaviour

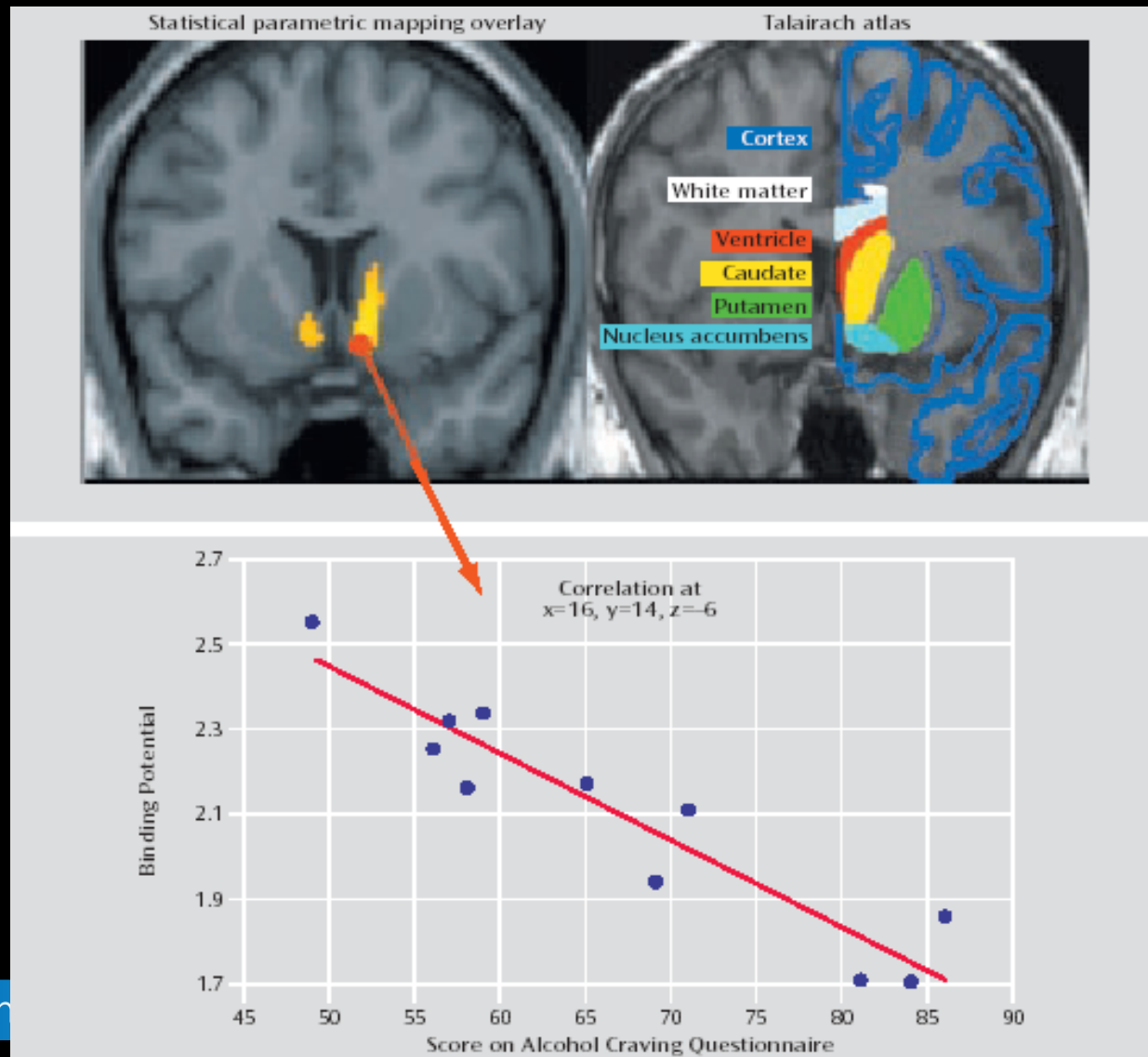


Heinz et al. Am J Psych 161 (2004) 1783

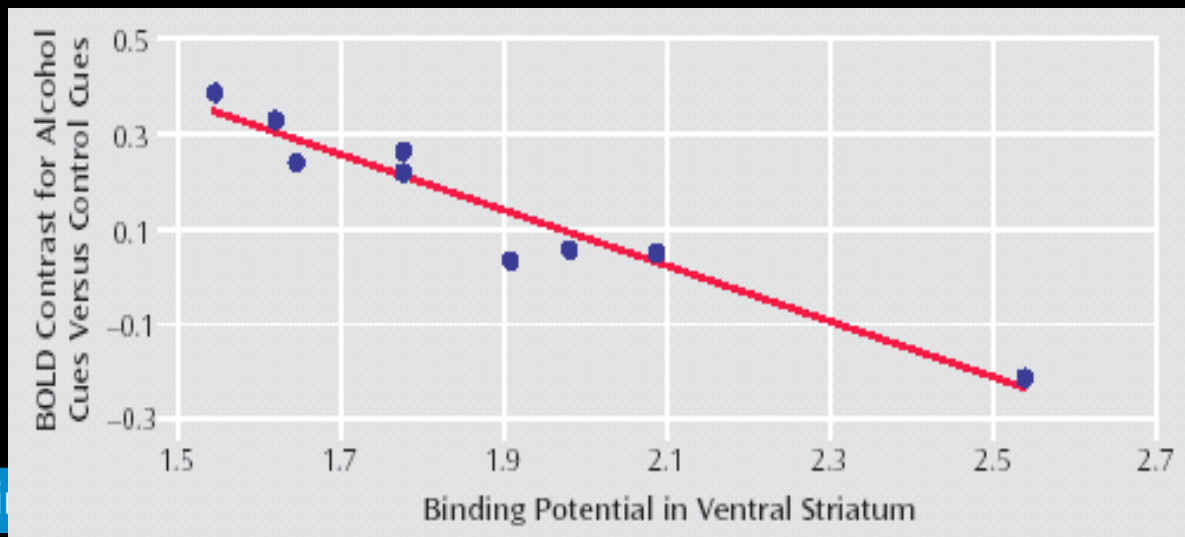
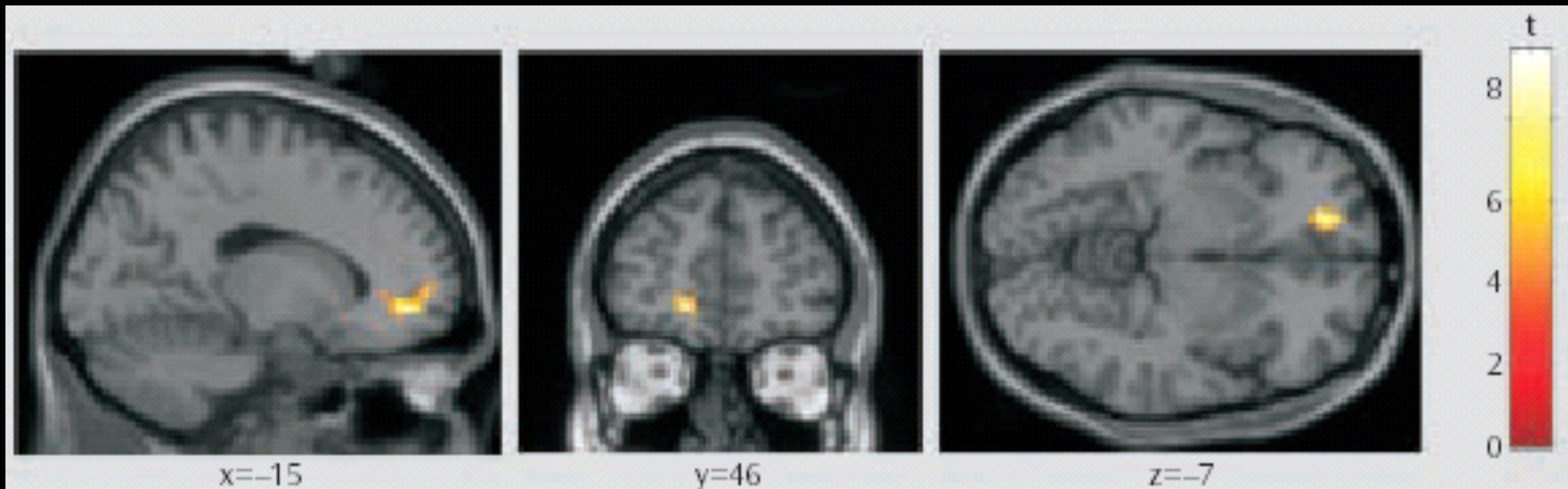


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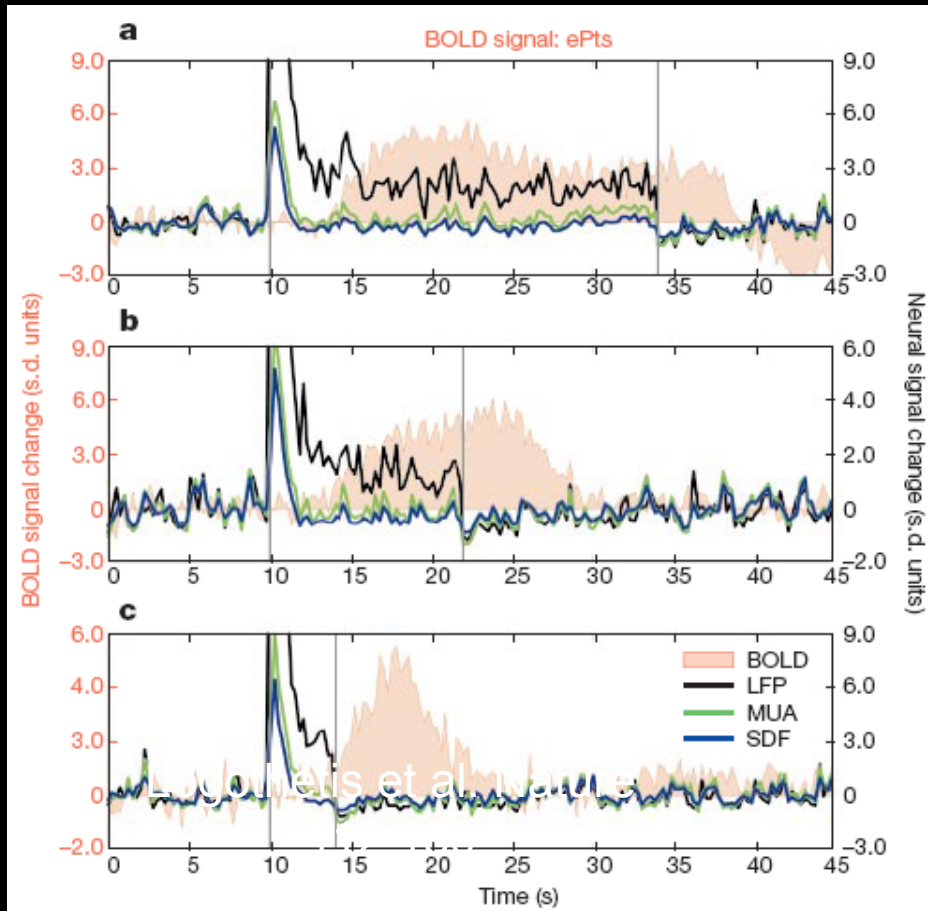
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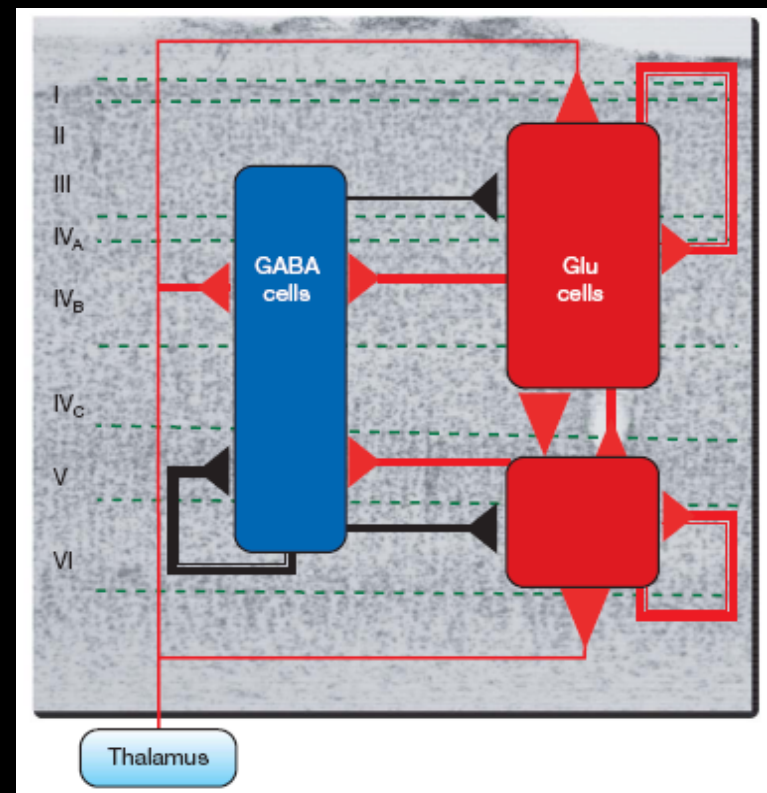
Relating drug target interactions to systems-level response



Back to the bench: BOLD signal correlates with local field potential (LFP)- reflecting presynaptic changes



Logothetis Nature 453:869



BOLD as an integrated measure of information transfer



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**The scope of imaging should free the
“translational medic “to ask questions *first* -
and then find the tools**



Imaging for Translational Medicine: *in vivo* physiology and pharmacology

- **Direct measures of biodistribution, target interaction**
- **Physiological hypothesis-based measures of PD**
- **Moving from PD to stratification**
 - Susceptibility markers
 - Short-term markers related to response
- **Developing new measures of response: enhancing precision, sensitivity**
 - But moving away resolutely from a focus on “surrogates”



Challenges for Imaging in Translational Medicine

- **Training**
 - Emphasis on integration: thinking about molecules and systems
 - Moving from *observational awe* to *hypothesis-testing*
- **Careers**
 - Supporting (and advancing) scientists outside of traditional discipline focus
 - Encouraging intelligent “discipline hopping”
 - Transforming the model for science: effective work in collaborative groups
 - Advancement and tenure need to recognise *contributions* and break from old concepts of *independence*
 - Not just not reducing the penalties for this, but *incentivising*
- **Funding**
 - Moving out of a comfort zone: it is easier to fund science accountably if it has clear borders
 - Striking a portfolio balance
- **Evolution of the community that drives science**
 - New partnerships between academia and industry
 - Making health research a central concern of healthcare

