Promises and pitfalls of neurocognitive biomarkers in CNS treatment research

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CNTRICS
Evaluating potential biomarkers of cognitive function

Baltimore, MD, USA

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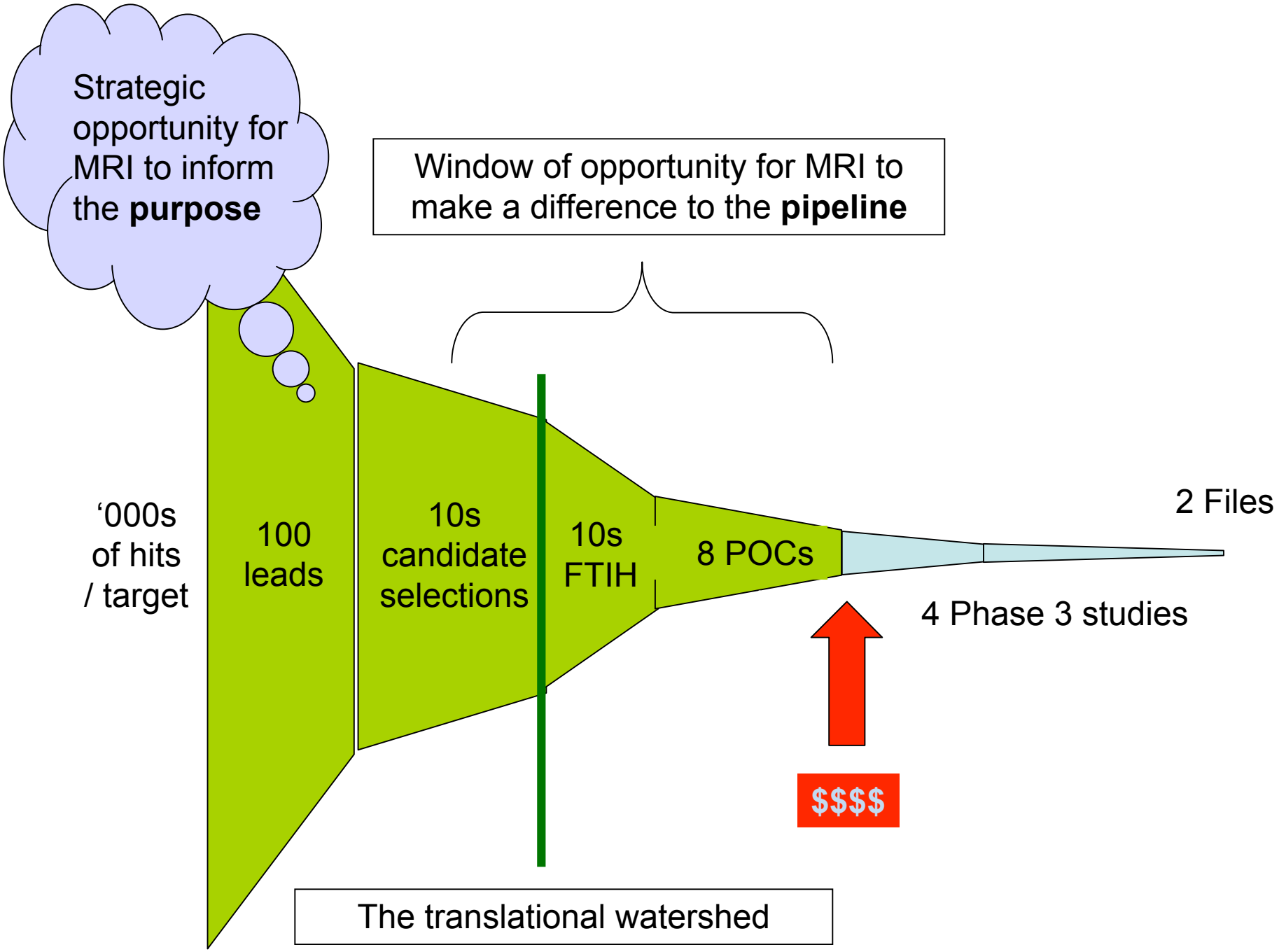
A few promises and pitfalls of biomarkers in drug discovery

- "Harder endpoints"
- Improved disease understanding and patient stratification
- Better prediction of clinical (phase 2) efficacy from phase 1 and preclinical studies

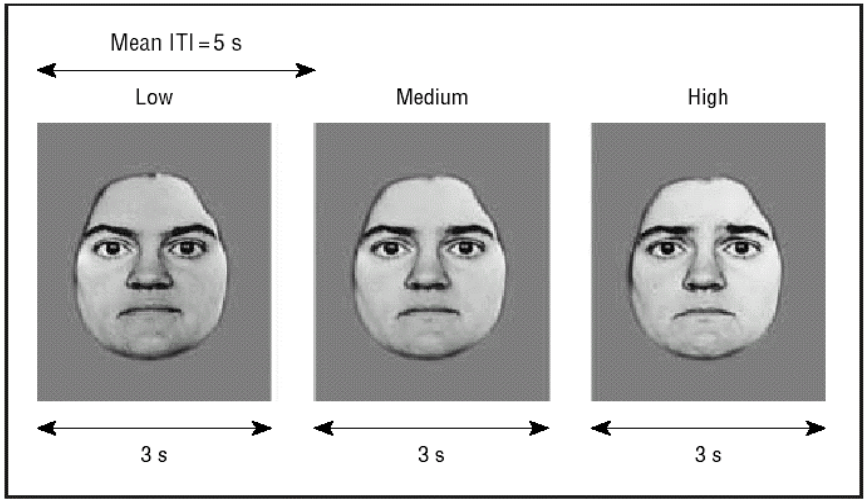
- Seductive glamour of new technology
- Non-trivial regulatory interface
- Interpretability of exotic signals or analyses
- Cost, scale, power


Strategic opportunity for MRI to inform the **purpose**
Window of opportunity for MRI to make a difference to the **pipeline**
'000s of hits / target
100 leads
10s candidate selections
10s FTIH
8 POCs
2 Files
4 Phase 3 studies
$$$$
The translational watershed

Pharma fMRI in a phase 2a trial of an antidepressant drug

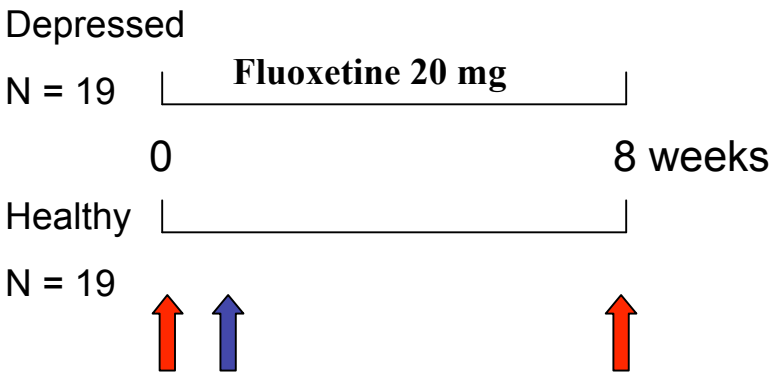
- **Parallel group, repeated-measures design**

- **Two groups:**
  - 19 people with major depressive disorder (DSMIV, unipolar)
    - Untreated for 6 weeks
    - HAM-D > 18
  - 19 healthy volunteers

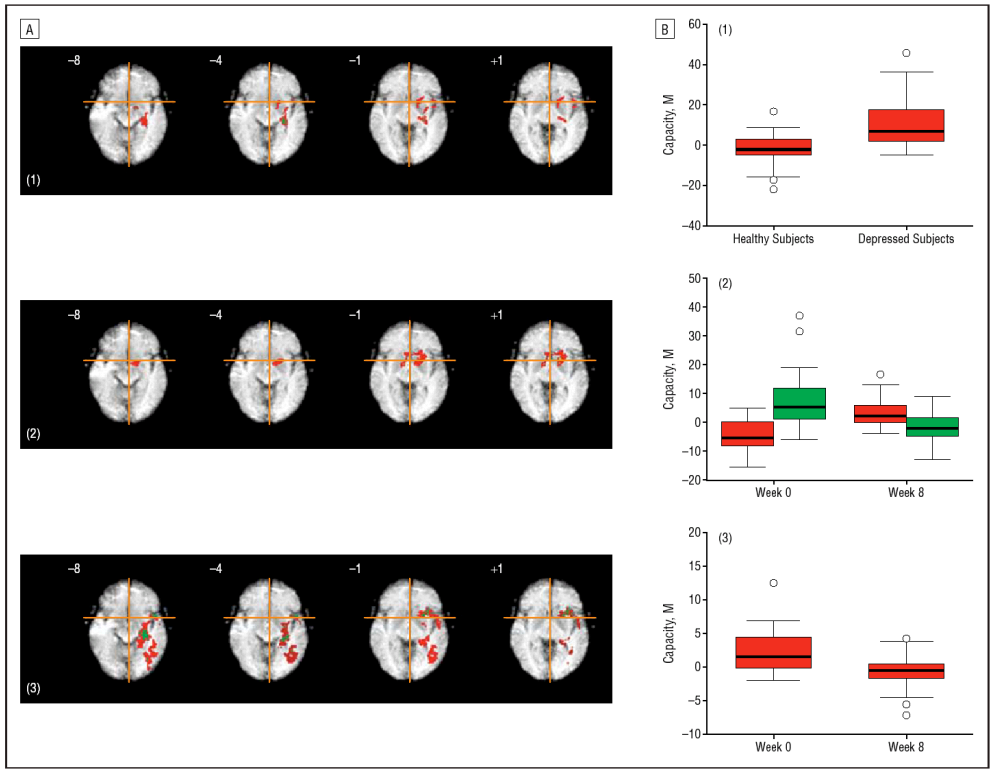


- **Each group scanned twice, at baseline and 8 weeks later**
  - Functional MRI at 1.5T
  - Sad facial affect processing task (explicit gender judgement)
  - Structural MRI at baseline only

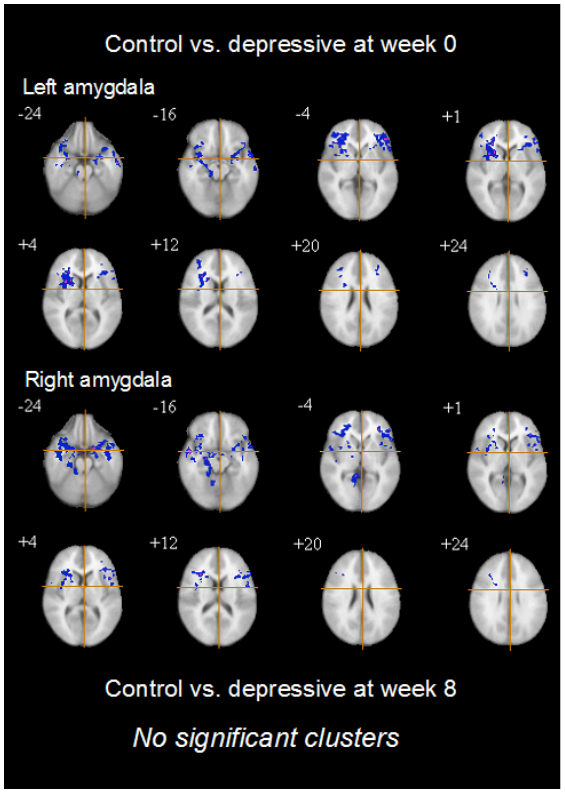
- **Depressed patients were treated with fluoxetine 20 mg/day after baseline scan**



SSRI treatment reduces amygdala activation and enhances amygdalo-frontal connectivity in depression

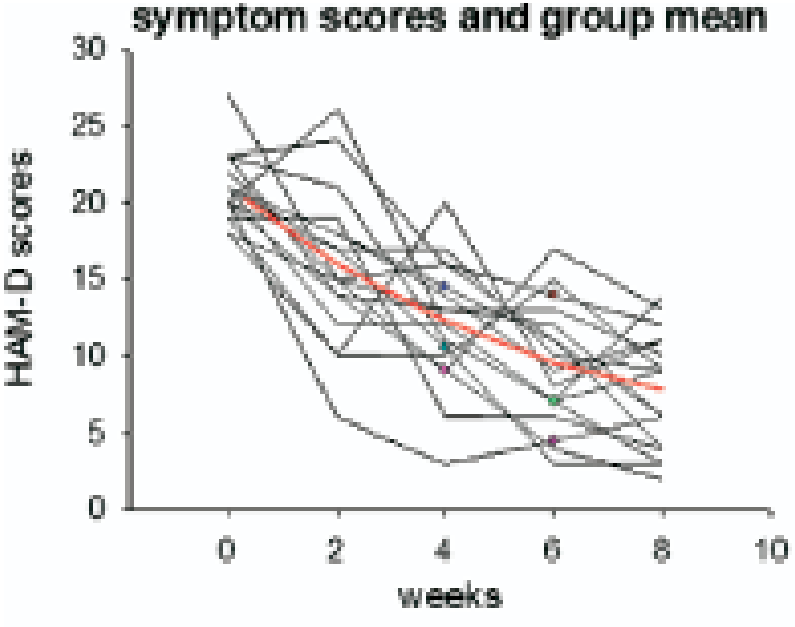


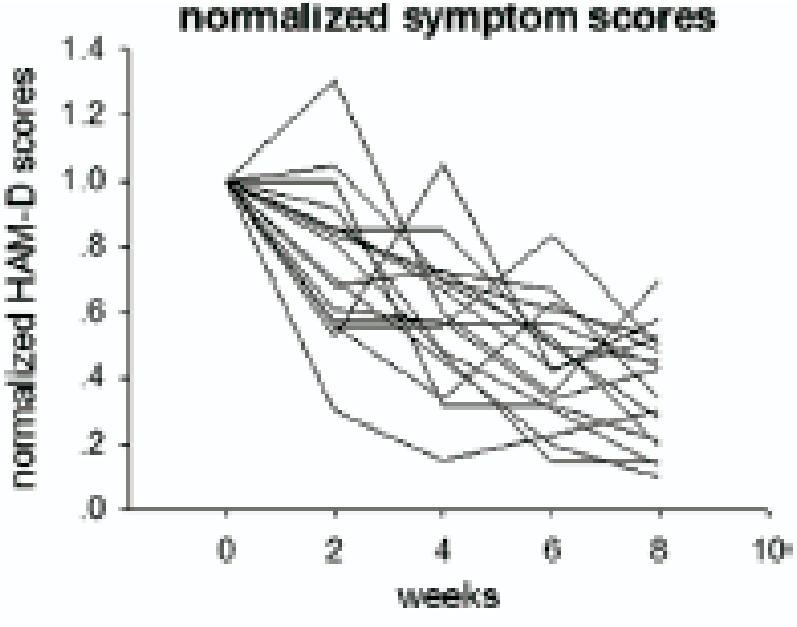
Fu et al (2004)
Arch Gen Psychiatry



Chen et al (2008)
Neuropsychopharmacology

Variability of symptomatic response to antidepressant treatment





Baseline HAM-D(0) = 20.9 (SD 2.2)

Final HAM-D(8) = 7.8 (SD 3.8)

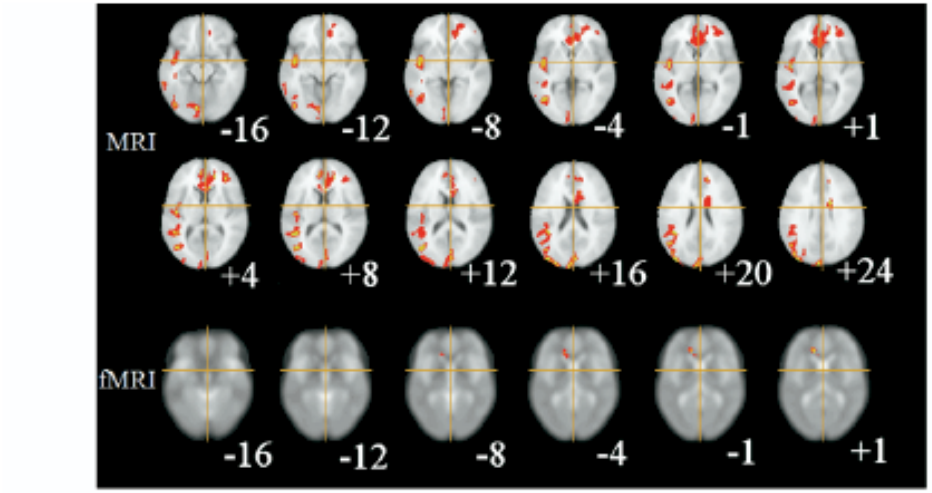
63% symptom improvement

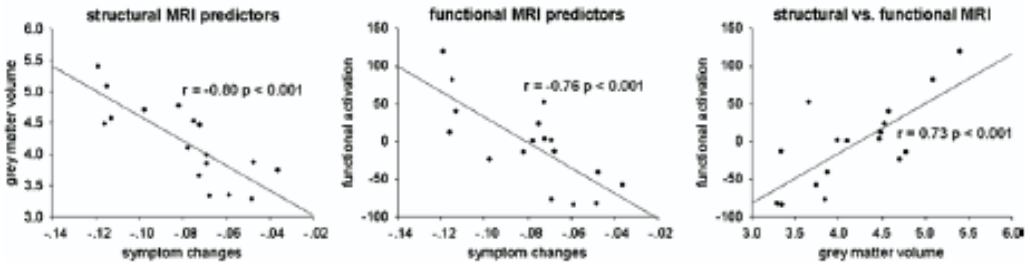
Normalized scores = HAM-D(t)/HAM-D(0)

Linear change coefficient B = 0.08 (SD 0.025)

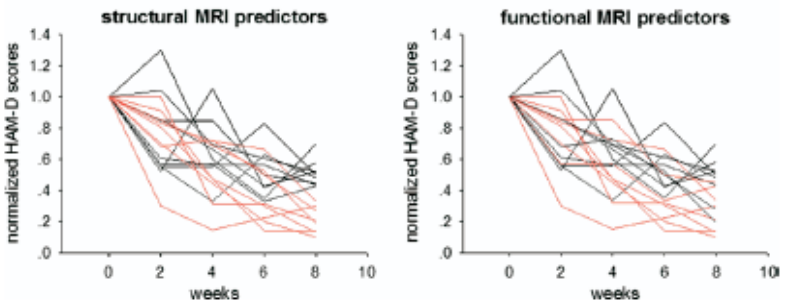
No correlation between B and HAM-D(0)

Structural and functional MRI at baseline predicts symptomatic response 8 weeks later





Chen et al (2007)
Biol Psychiatry



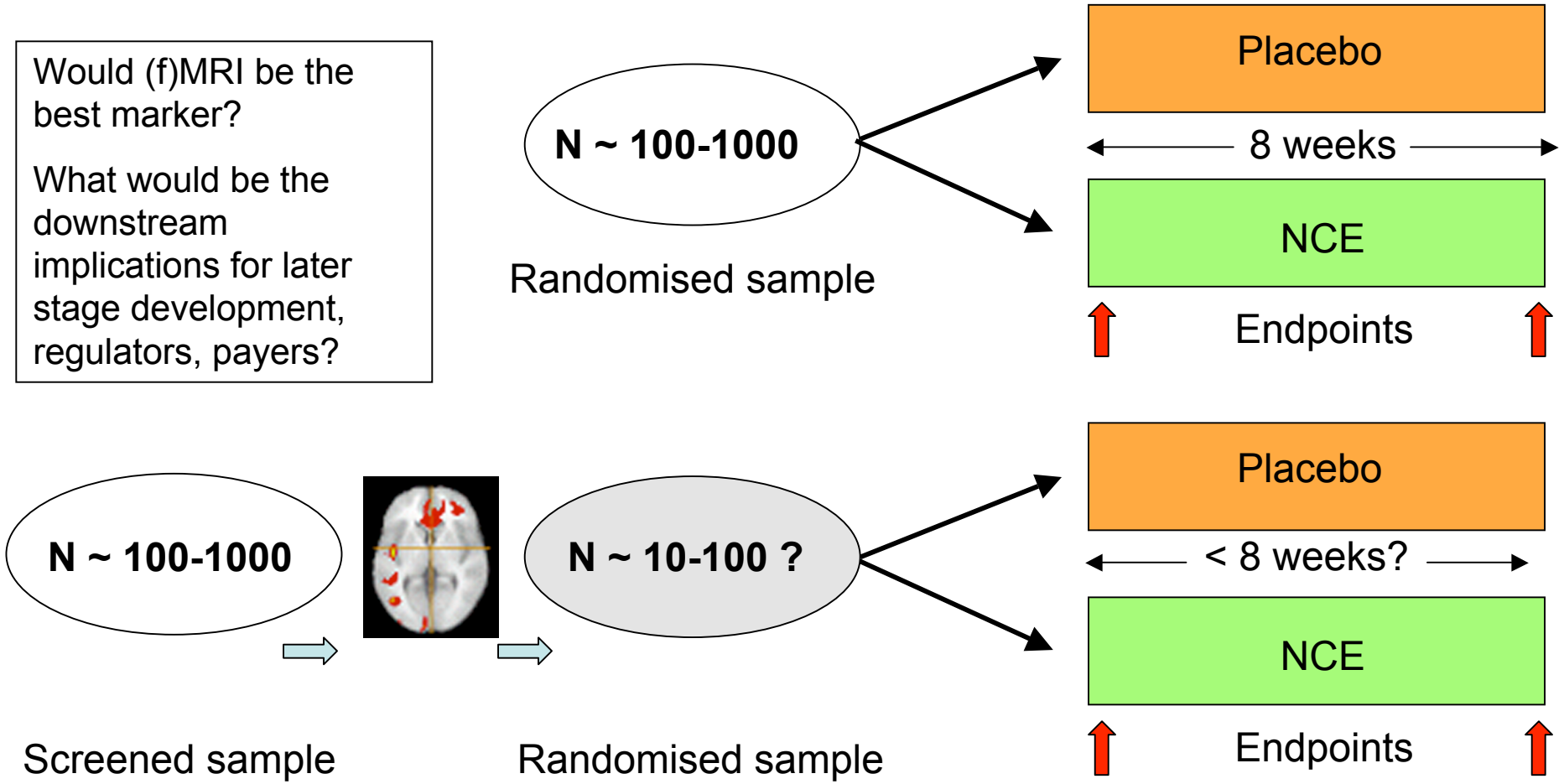
Greater than median grey matter volume in cingulo-parietal system predicts:

- faster symptom improvement
  -10%/week vs -6%/week
- less severe final symptom scores
  - 4.2 vs 10.9

Sample enrichment by cingulate screening for treatment response could enhance power of early phase 2 studies of depression

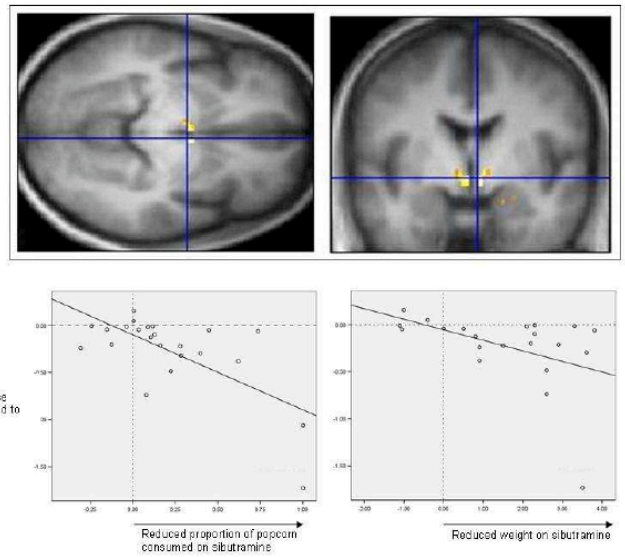
Would (f)MRI be the best marker?

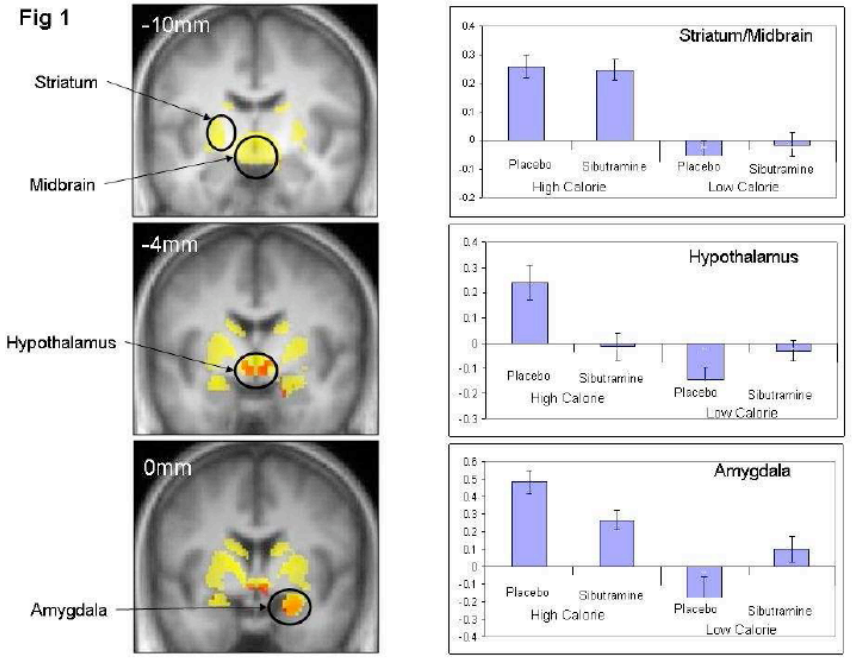
What would be the downstream implications for later stage development, regulators, payers?



FMRI predictors of weight reduction by centrally-acting drugs

- Obesity is mainly a *behavioural* disorder of over-eating
- To get a license for an obesity indication requires data on weight reduction in 1000s of patients over 1-2 years
- Can we use neurocognitive markers of acute response to centrally acting drugs to mitigate risk of definitive weight reduction trials?





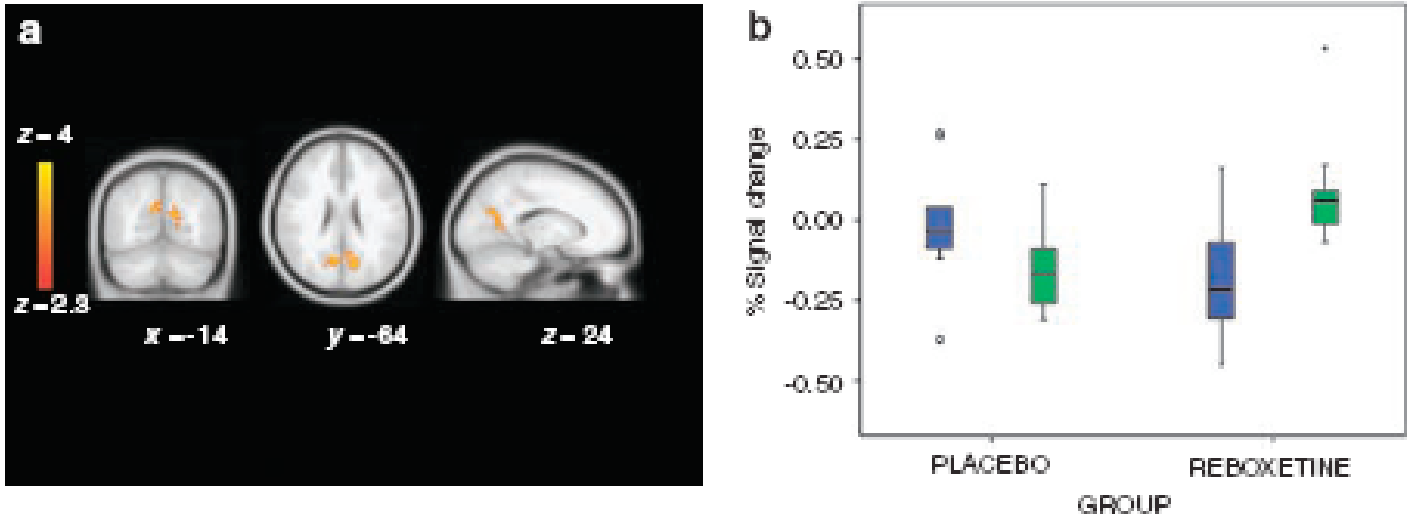
- 20 overweight/obese volunteers
- 2-way crossover design
  - 14 days placebo
  - 14 days sibutramine 10mg daily
- FMRI scanning at end of each treatment period
  - Visual presentation of high calorie foods (chocolate cake), low calorie foods (broccoli), non-food items

Fletcher et al (2009) in review

Neurocognitive markers in early clinical trials

- Functional MRI can corroborate, localise or explain at systems level a drug's effects on mood or cognitive function disturbance in patients
- Functional MRI seems unlikely to *replace* cognitive/behavioural endpoints in phase 2 any time soon
- Imaging *predictors* of therapeutic (or placebo) response could enhance power of phase 2 studies and/or mitigate financial risk of committing to later stage phase 3 development

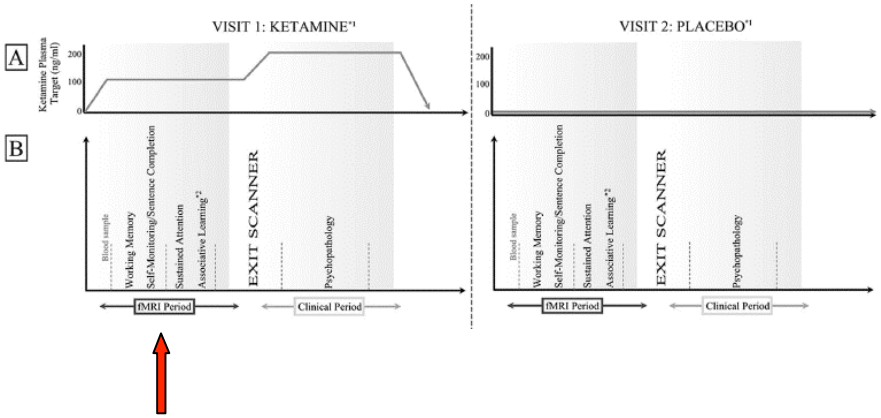
Predicting antidepressant efficacy in phase 1

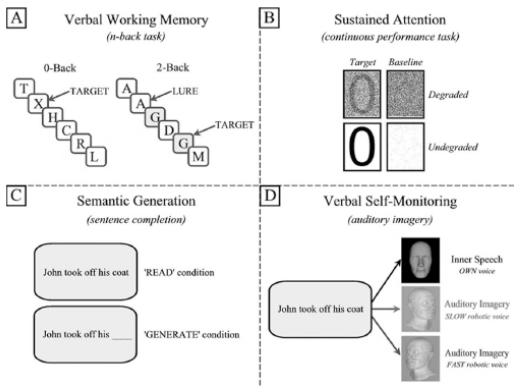


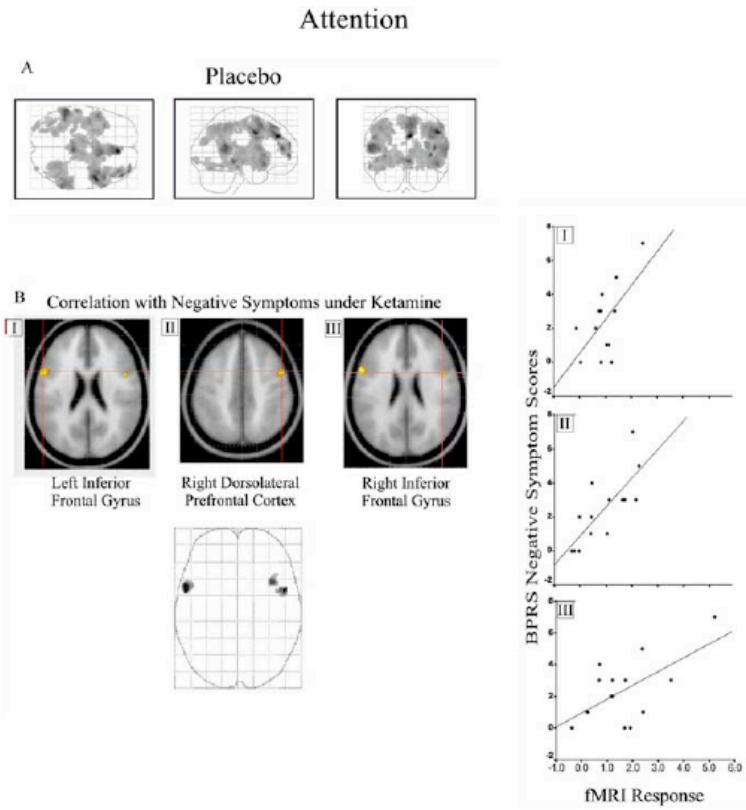
- 24 healthy volunteers were treated with reboxetine 4mg bd, or placebo, for 1 week each in a cross-over design
- Brain activation by categorization of words as personally likeable or dislikeable was modulated by reboxetine in a way that was considered consistent with its therapeutic effects on negative recall bias in patients with depression

Norbury et al (2008) *Mol Psychiatry*

Predicting adverse central effects: fMRI predictors of psychotogenic effects of ketamine

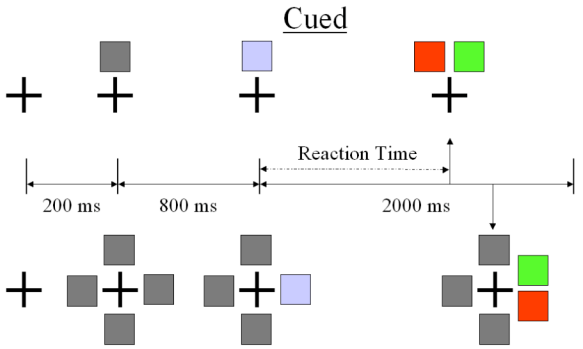


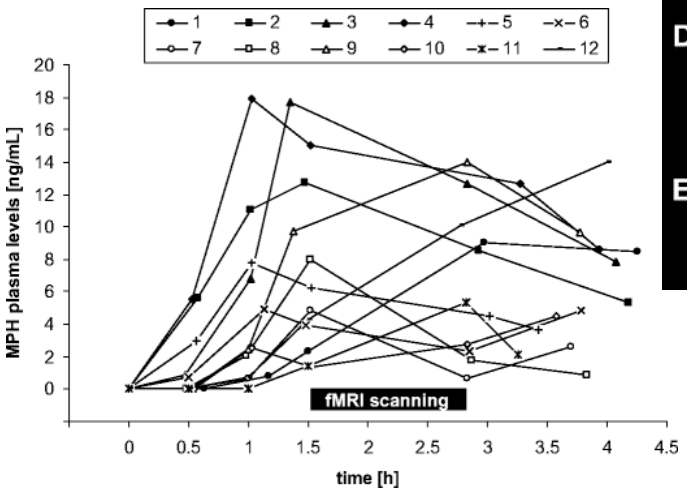


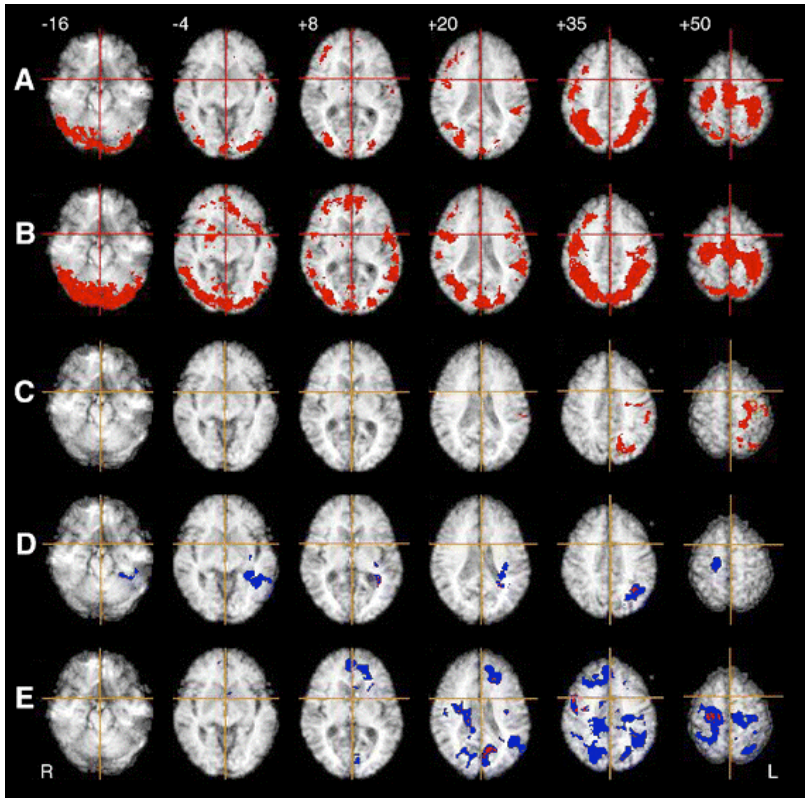


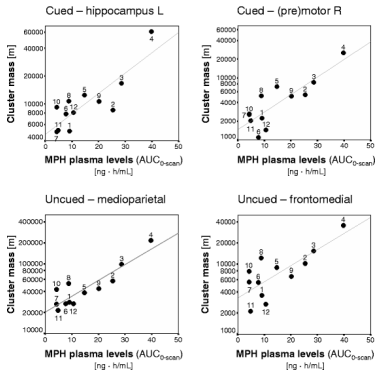
Honey et al (2008) *J Neurosci*

PK/PD studies using fMRI: pharmacological differentiation or dose finding in phase 1



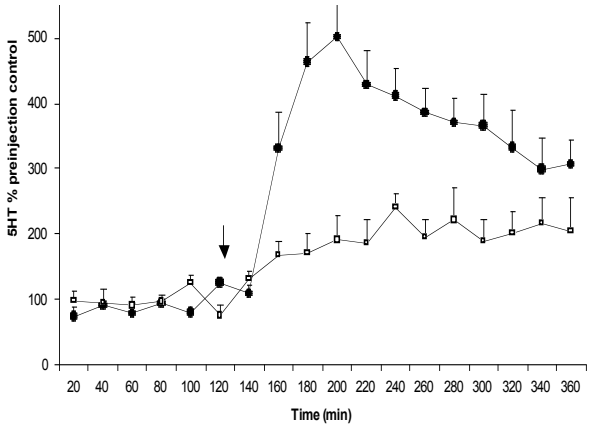




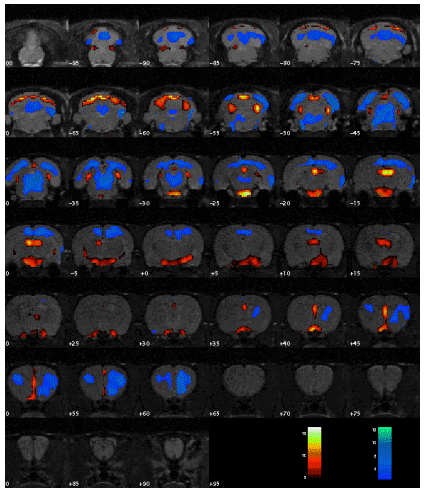


Müller et al (2005) *Psychopharmacology*

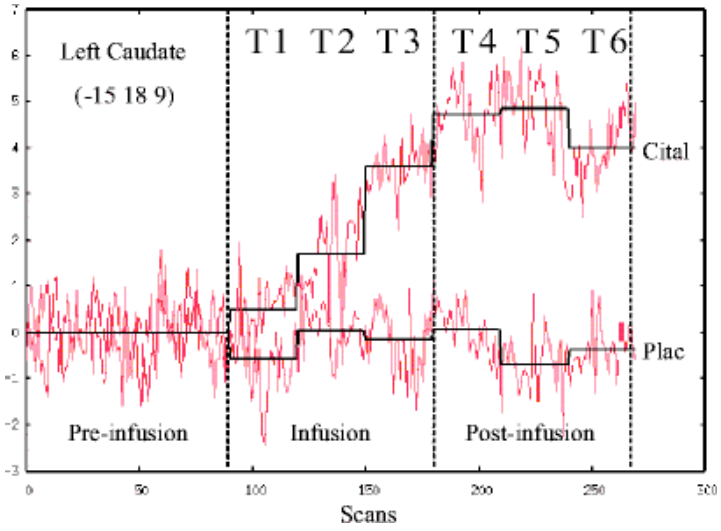
Pre-clinical to clinical translation: the potential of fMRI as a marker of endogenous brain dynamics



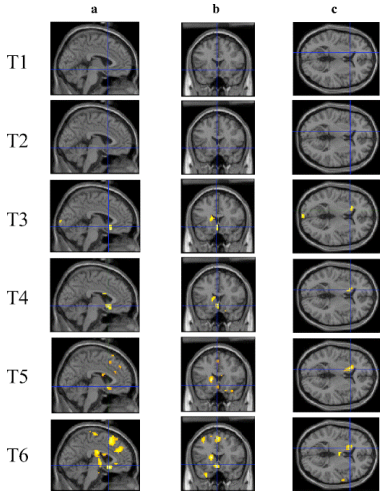
Williams et al (2006)



Rat – fluoxetine causes increased extracellular 5HT and correlated change in baseline BOLD signal

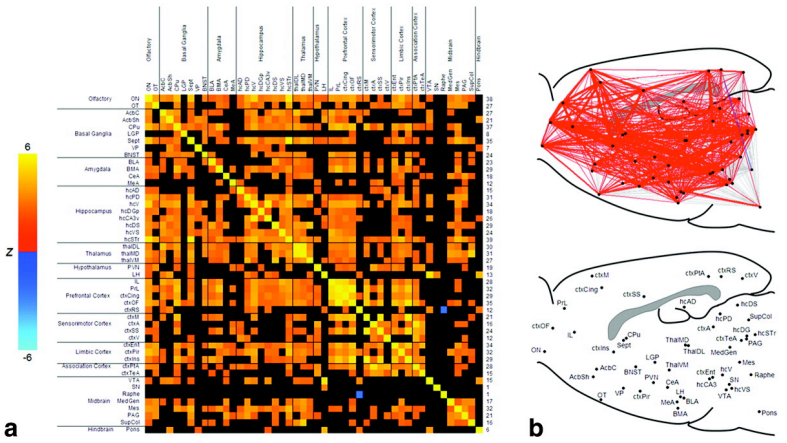


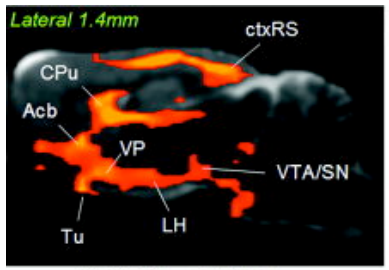
Deakin et al (2006)



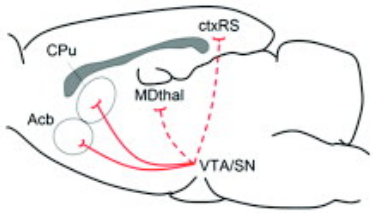
Human – citalopram infusion causes increased baseline BOLD signal in fMRI data recorded with the subject lying in the scanner “at rest”

Dopaminergic drug effects can be mapped to brain functional networks measured using fMRI

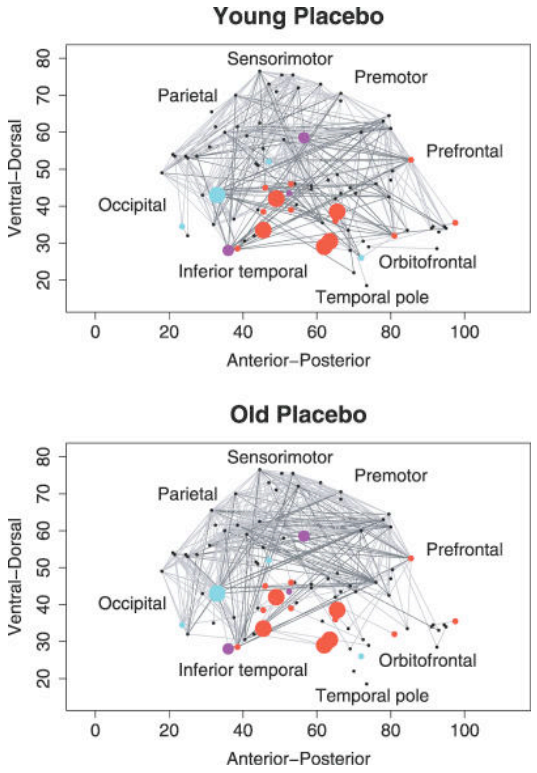




Cluster 1 – sagittal cut



Dopamine projections



Rat – amphetamine enhances functional connectivity between cortical regions sharing a strong dopaminergic input from midbrain.

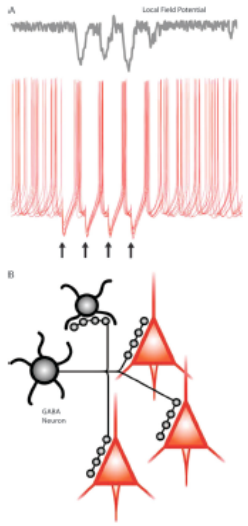
Schwarz, Bifone (2007) Magn Res Med

Human – sulpiride attenuates efficiency of network connections to cingulate and temporal cortex but not global “small world” parameters.

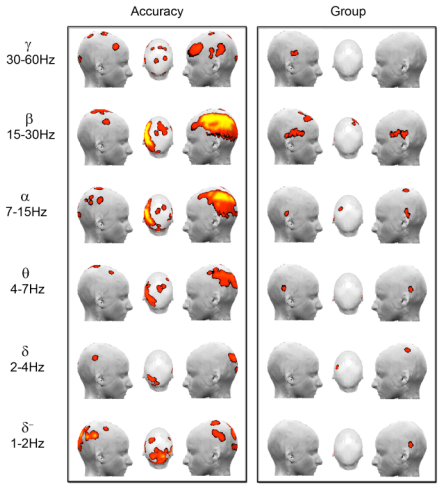
Achard, Bullmore (2007) PLoS Comput Biol

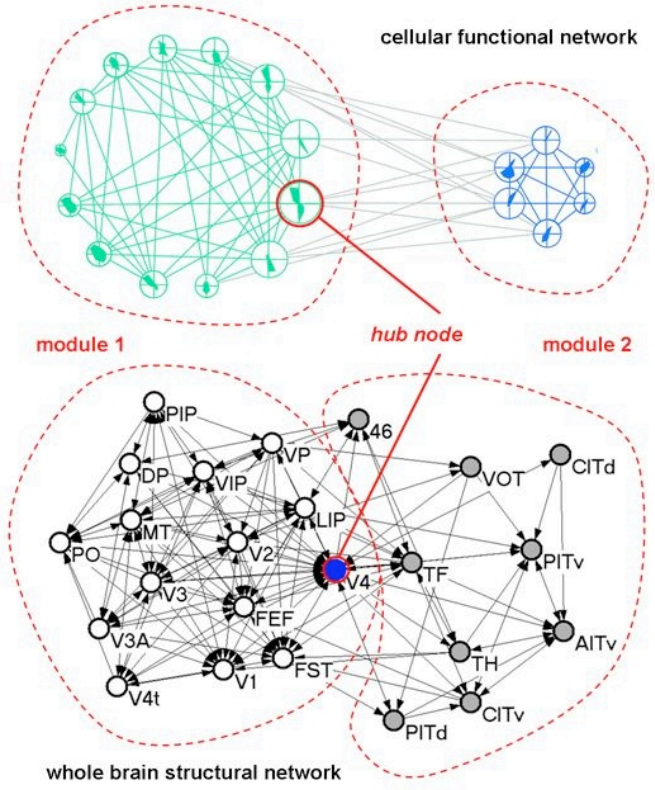
Scale invariance of complex network organization may support development of translational markers

Multielectrode studies of cellular networks generating beta rhythms



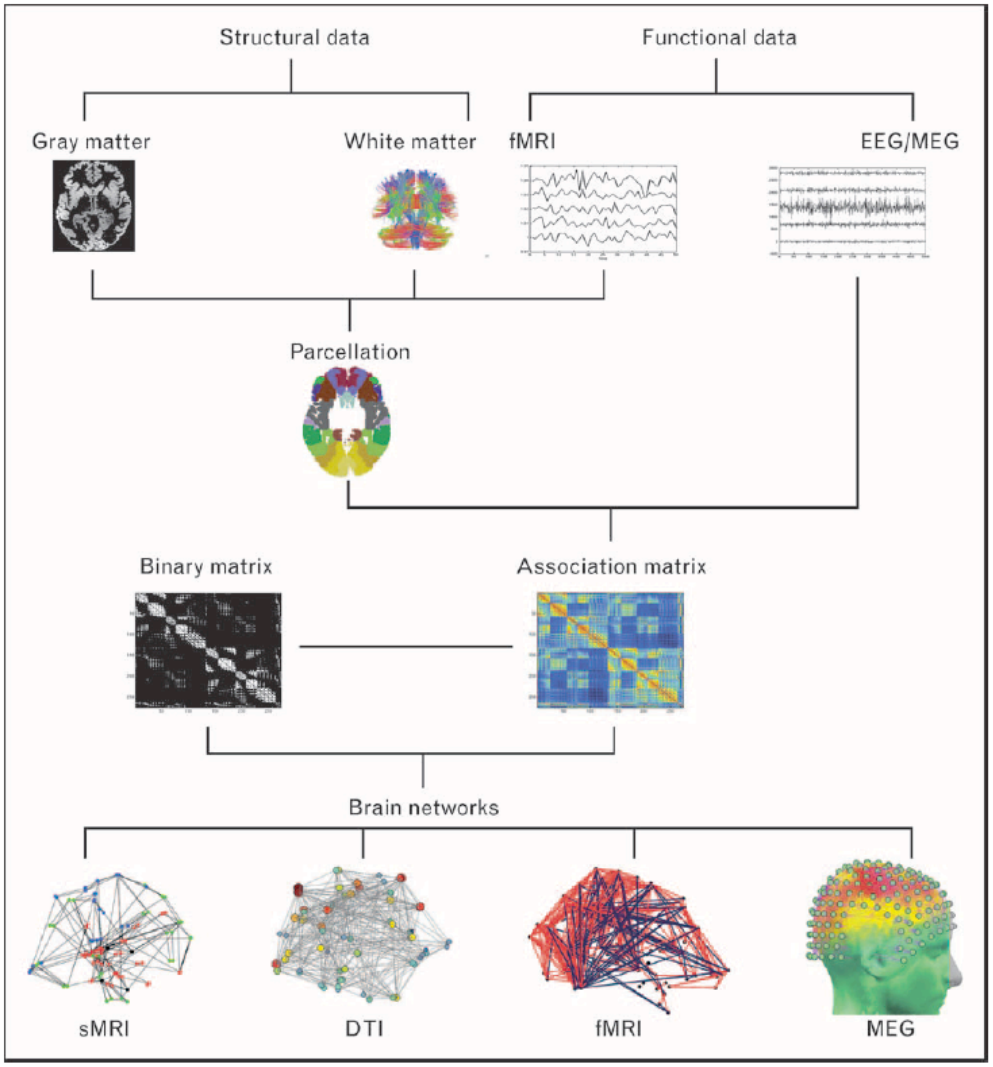
MEG studies of beta-band networks associated with cognitive impairment in schizophrenia





Bullmore & Sporns (2009) *Nat Rev Neurosci*

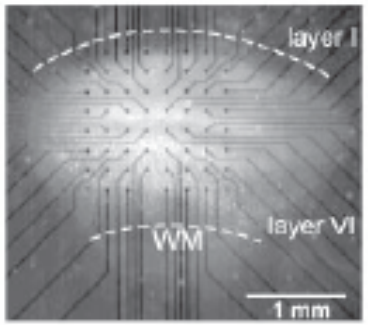
Modeling whole brain networks in multimodal human neuroimaging data

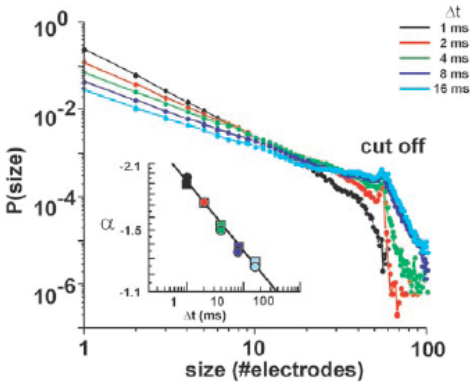


Bassett & Bullmore (2009) *Curr Op Neurol*

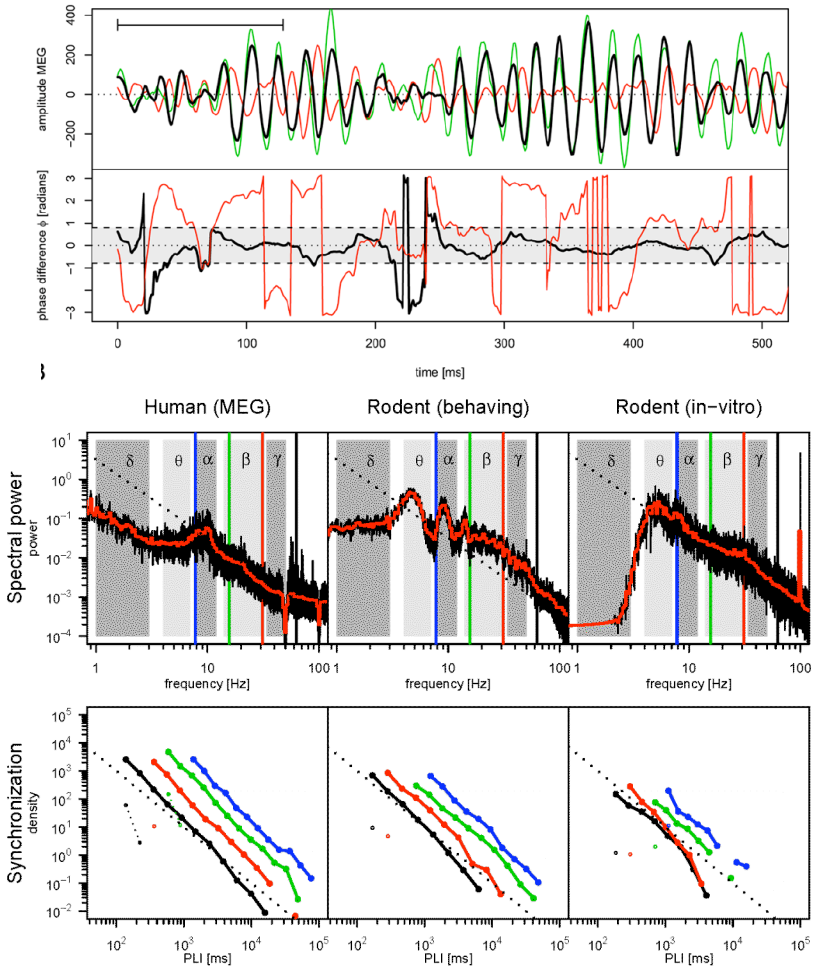
- Relatively simple tools for quantifying complex systems
- Applicable to all modalities of systems neuroscience data, from MRI to multielectrode arrays to gene expression
- Major current focus of activity in statistical physics with extensive applications

Functional brain networks can have critical dynamics over a range of spatial scales



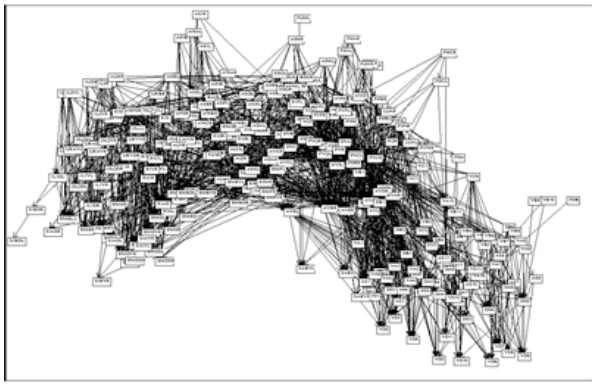


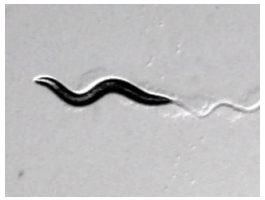
Beggs & Plenz (2003) *J Neurosci*

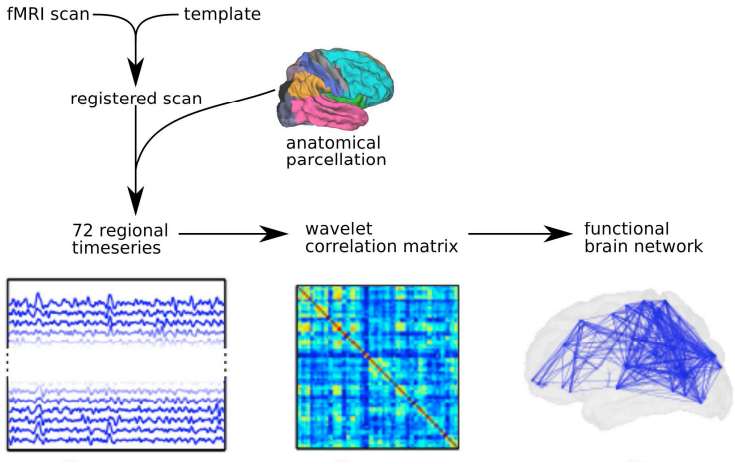


Kitzbichler et al (2009) *PLoS Comput Biol*

Cost efficiency of nervous systems

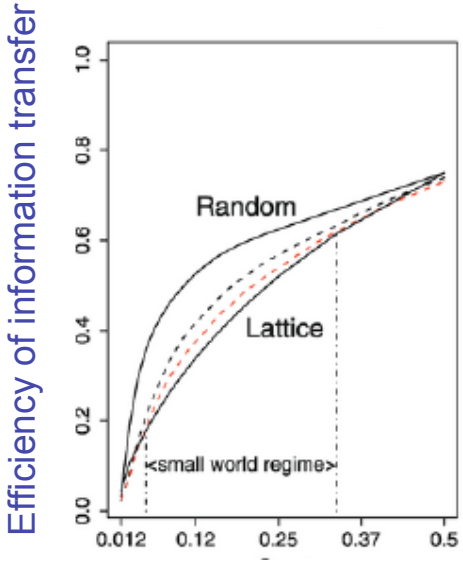


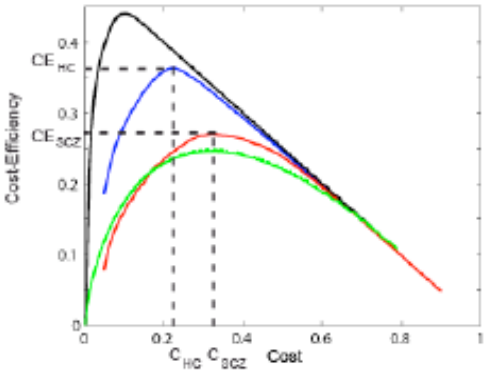




~300 neurons ~7000 synapses

- **Low cost**
  - Connection density ~ 3% of maximum
- **High efficiency of information transfer**
  - Global efficiency = 46% of maximum





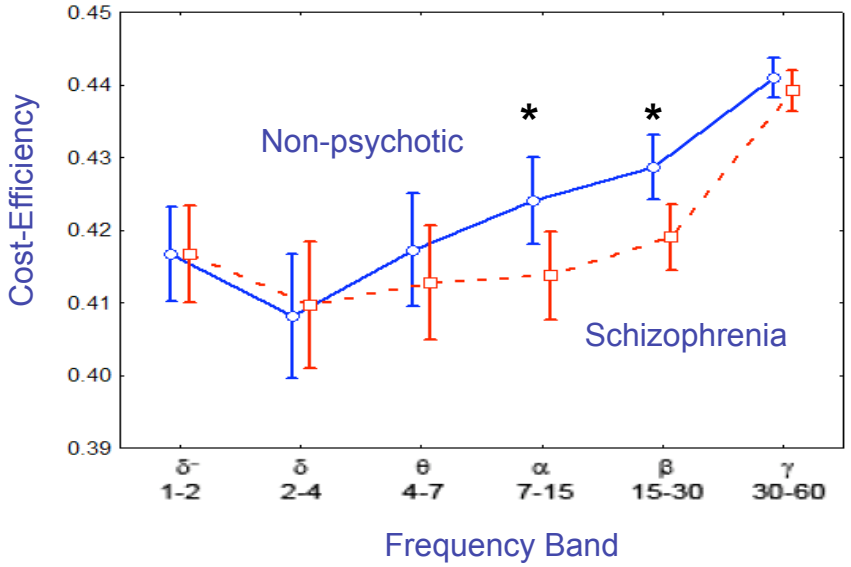
Watts & Strogatz (1998) *Nature*

Latora & Marchiori (2001) *Phys Rev Lett*

Achard & Bullmore (2007) *PLoS Comp Biol*

Cost-efficiency of human brain functional networks varies with frequency and schizophrenia

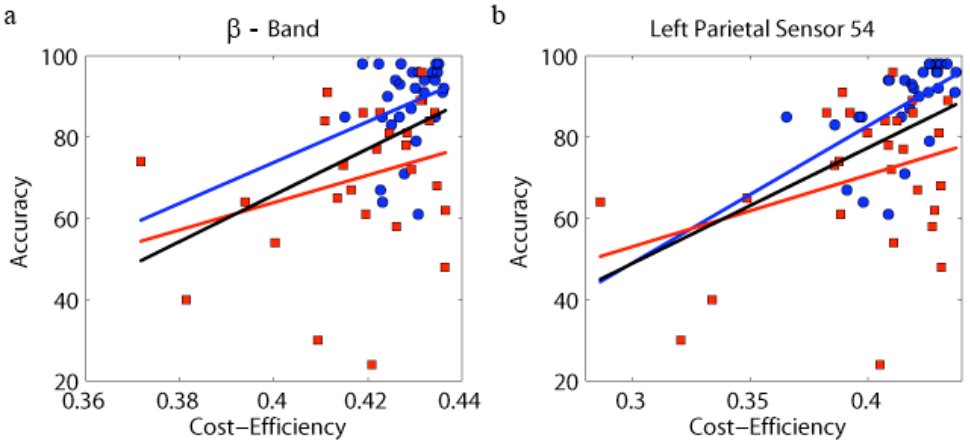
- Frequency-scale specific functional networks were constructed from MEG data recorded during performance of N-back working memory task (CBDB/NIMH)
  - 19 non-psychotic adults
  - 18 people with schizophrenia



• Network cost-efficiency is greatest at higher frequencies

• Cost-efficiency of alpha and beta networks is reduced in schizophrenia

•Cost-efficiency of beta networks is positively correlated with accuracy of working memory task performance



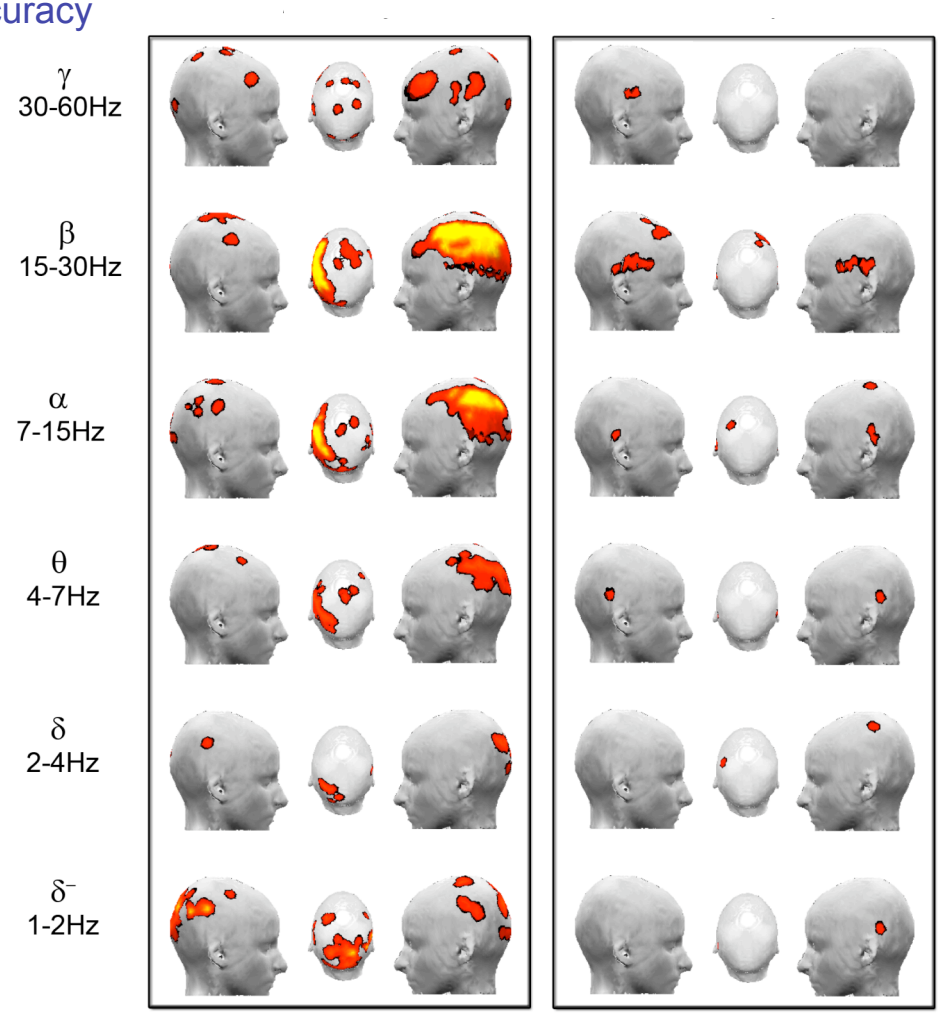
Bassett et al (2009) *Proc Natl Acad Sci (USA)*

Better cognitive performance is associated with greater cost-efficiency of high frequency functional networks

Bassett et al (2009) *Proc Natl Acad Sci (USA)*

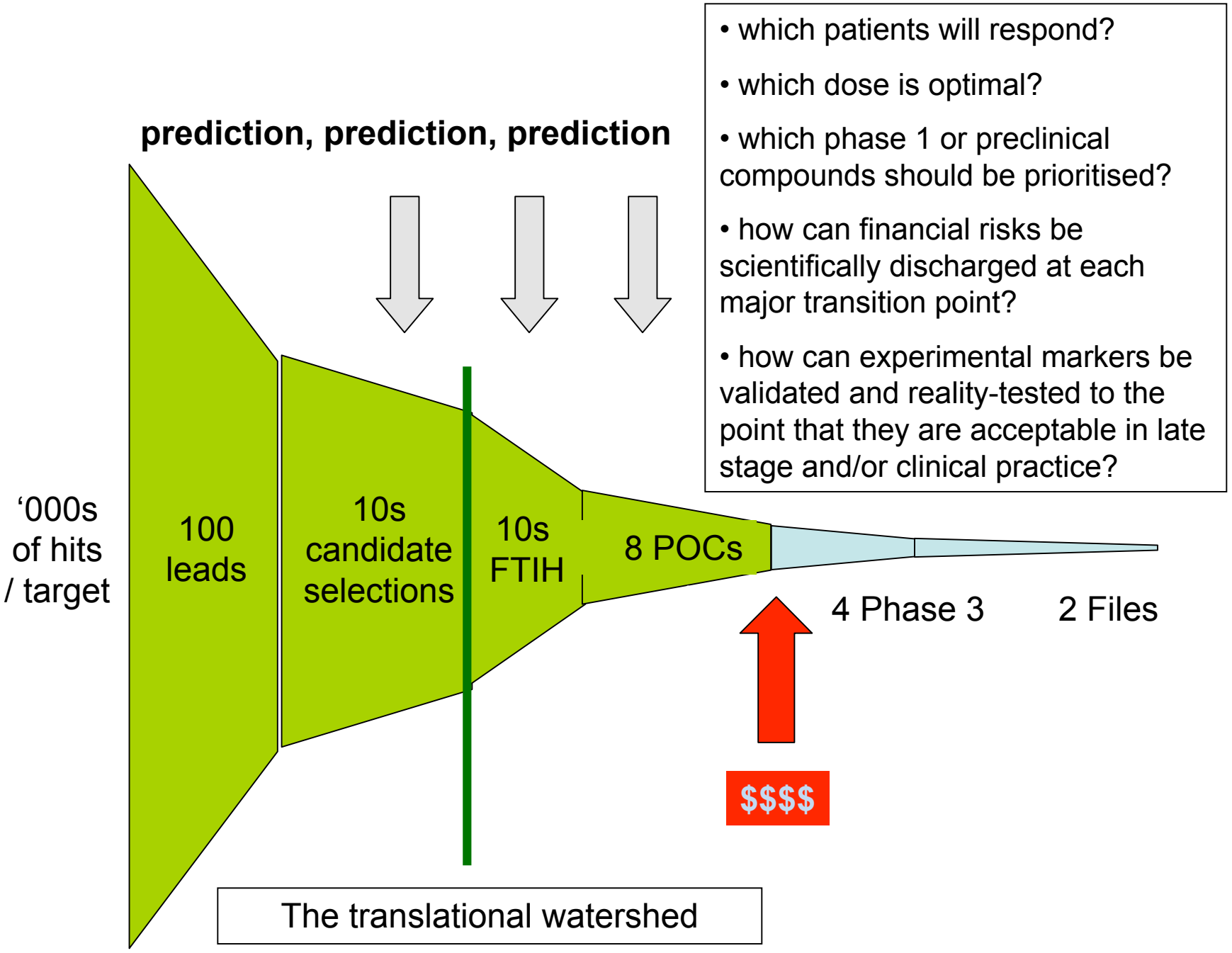
Working memory accuracy

Schizophrenia



Neurocognitive markers in phase 1 and pre-clinical development

- Functional MRI as a PD marker in PK/PD studies for pharmacological differentiation or dose finding
- Functional MRI as a predictor of therapeutic response or adverse effects in healthy volunteer models
- Brain network parameters – which seem often to be scale-invariant – could serve as translational PD markers, mitigating the risk of transition from pre-clinical to clinical development


prediction, prediction, prediction
• which patients will respond?
• which dose is optimal?
• which phase 1 or preclinical compounds should be prioritised?
• how can financial risks be scientifically discharged at each major transition point?
• how can experimental markers be validated and reality-tested to the point that they are acceptable in late stage and/or clinical practice?
'000s of hits / target
100 leads
10s candidate selections
10s FTIH
8 POCs
4 Phase 3
2 Files
$$$$
The translational watershed