Experimental medicine approaches using neuroimaging

Mitul Mehta

Support: Eli Lilly, European Commission (NEWMEDS), Wellcome Trust-EPSRC MEC
1. **Temporal modelling of drug effects – phMRI**
   I. Distribution of drug haemodynamics,
   II. Can be related to input functions

2. **Quantitative evaluation of drug effects – ASL**
   I. Distribution of drug haemodynamics
   II. Can be used for temporal modelling
   III. Great for session effects

3. **Cognitive activation studies of drug effects – fMRI**
   I. Distribution of context dependent effects
   II. Great to link with performance
The rise and rise of fMRI

Drug / Pharmacology Studies

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Box 3 | **Potential application of fMRI across drug development**

- **Drug discovery**
  - Target validation
  - Experimental assays
  - Disease models
  - Transgenics

- **Preclinical development**
  - Lead optimization
  - Off-target CNS effects
  - CNS ‘therapeutic window’

- **Clinical development**
  - Early proof of CNS activity
  - Early support for concept
  - Therapeutic index
  - Optimized dosing
  - Responder identification
  - Patient stratification

- **Life-cycle management**
  - Novel CNS indications
  - Expanded use

- **Approved drugs**
  - Novel uses for safe molecules
  - Recover development costs
  - Mechanistically unprecedented targets
  - Breakthrough neuroscience

The figure shows the classic progress of the components of drug development (ovals) and the potential applications of fMRI (boxes) at each point along this development line.
1. Defining deficits (glutamatergic abnormalities in schizophrenia)
2. Defining targets (working memory networks)
3. Defining neurobiology (disease models, patients)

1. Contrasting drugs (those producing clear MRI changes, reversing abnormalities)
2. Defining dose-response curves

1. Early indicators of efficacy
2. Support in human brain for concept (modulation of working memory networks)
3. Dose optimisation
4. Individual differences

1. Understanding systems-level mechanism of action
2. Dose-response relationships
3. Evidence for novel indications
4. Positive control / negative controls

The figure shows the classic progress of the components of drug development (ovals) and the potential applications of fMRI (boxes) at each point along this development line.
The fact that the drug uniformly intensified the primary symptoms of a small group of schizophrenic patients also suggests that it may act in a way fundamentally different from LSD or mescaline.

It also resulted in feelings which were more characteristic of the acute and earlier phases of the illness.

<table>
<thead>
<tr>
<th>Deviations</th>
<th>Percentages</th>
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<tbody>
<tr>
<td></td>
<td>Normals (N=9)</td>
<td>Patients (N=9)</td>
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<tr>
<td>Body-image changes</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Estrangement</td>
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<td>100</td>
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<tr>
<td>Disorganization of thought</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Negativism and hostility</td>
<td>67</td>
<td>67</td>
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<tr>
<td>Drowsiness and apathy</td>
<td>100</td>
<td>100</td>
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<td>Hypnagogic states</td>
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<td>Feelings of inebriation</td>
<td>78</td>
<td>22</td>
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<tr>
<td>Repetitive motor behavior</td>
<td>29</td>
<td>44</td>
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</table>
Ketamine: a model of schizophrenia?

Induces positive & negative symptoms similar to those seen in schizophrenia

Worsens already-present psychotic symptoms in schizophrenic patients

Induces cognitive deficits similar to those seen in schizophrenia (working memory, executive function, response inhibition)

Ketamine higher dose

Ketamine lower dose

NMDA Receptor Antagonists

(1) NMDA receptor hypofunction
(2) Reduced GABA
(3) Disrupted cortical activity
(4) Increased glutamate release

Rat

Ketamine / NMDAR antagonist models

- Ketamine/NMDA behavioral assays +/- drug

phMRI/2DG/O₂:

- ketamine response +/- compounds

Human

Healthy Volunteers, ketamine model

- fMRI: Cognition perturbed by ketamine +/- drug

- phMRI: ketamine response +/- drugs

Patients / HV

- fMRI: Cognition perturbed by disease +/- drug

Central Pharmacodynamic Biomarker
What do we want from a model?

1. Is it mechanistically viable?
2. Does it produce robust signal changes?
3. Does it produce reliable signal changes?
4. Is it dose sensitive?
5. Does it have translational potential?
Ketamine increases cortical glutamate levels


Ketamine and glutamate concentration

N=13, ketamine dose ~150ng/mL (Clements 250 model), PRESS sequence, water supressed and GM/WM/CSF corrected

Stone et al. (2011) Mol Psychiatry
Ketamine - PET studies

Langsjo et al. 2003 Anesthesiology
Holcomb et al. 2001 Neuropsychopharm.

Relative rCBF increases

A

Baseline vs. 300 ng/ml

6 min. - BL

16 min. - BL

26 min. - BL

A. Anterior Cingulate Cortex
(2, 38, 12)

Change from Baseline

KET

PBO

Langsjo et al. 2003 Anesthesiology
Holcomb et al. 2001 Neuropsychopharm.
Glutamate and the Neural Basis of the Subjective Effects of Ketamine

A Pharmaco–Magnetic Resonance Imaging Study

J. F. William Deakin, PhD, FRCPsych, FmedSci; Jane Lees, BSc, MSc; Shane McKie, MEng, MSc, PhD; Jaime E. C. Hallak, MD, PhD; Steve R. Williams, BA, MA, DPhil; Serdar M. Dursun, MD, PhD, FRCPC
**Aims**

**BOLD Modelling and optimisation**

Replicate ketamine phMRI effect (reproducibility)

Assess stability over 2 session (reliability)

Testing dose sensitivity

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10 healthy male volunteers scanned twice

- Doses chosen as those with minimal changes on BPRS.
- Infusion model chosen to maximise stability of plasma ketamine (Clements 250)

De Simoni et al. (2013) Neuroimage
Subjective effects

Reliability: 0.93 (0.03)    0.28 (0.18)
Ketamine produces a reliable BOLD phMRI response over two sessions
Replication of Deakin et al. (2008) Arch Gen Psych
(b)

**Dose - Response (BOLD signal)**

<table>
<thead>
<tr>
<th>ROI</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
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<th>2.5</th>
<th>3</th>
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Low dose

High dose

**Dose - Response (Effect size)**

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Low dose

High dose

**Brain Images**

50 ng/ml

75 ng/ml

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Ketamine phMRI – rat vs man

**Rat**

![Rat image with ACC, mPFC, and thalamus](image)

**Human**

![Human image with ACC, mPFC, and thalamus](image)

**Cingulate cortex (N=5)**

<table>
<thead>
<tr>
<th>rCBV</th>
<th>1mg/kg IV</th>
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<tr>
<td>time (min)</td>
<td>ket</td>
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<tr>
<td>-5</td>
<td>0.1</td>
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<td>5</td>
<td>0.1</td>
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<tr>
<td>10</td>
<td>0.1</td>
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**Anterior cingulate cortex (ACC)**

- ACC
- mPFC
- thalamus

1mg/kg IV Clements Model → 75ng/ml
Questions

1. Is it mechanistically viable? ✓
2. Does it produce robust signal changes? ✓
3. Does it produce reliable signal changes? ✓
4. Is it dose sensitive? ✓
5. Does it have translational potential? ✓
6. Can they be modulated?
7. How can we quantify the degree of modulation using all the available data?
Richard Joules

Lamotrigine (300mg)
Risperidone (2mg)
Placebo
Placebo

Ketamine
Ketamine
Ketamine
Saline

0 min 5 min 10 min 15 min

Baseline Steady State

Infusion

Pre-Treatment

Placebo
Placebo
Lamotrigine (300mg)
Risperidone (2mg)

Saline
Ketamine
Ketamine
Ketamine

0.12 mg/kg in first minute
0.31 mg/kg/h pseudo-continuous

X 16

Aged 20-37
Mean age = 25.8
TR = 2000ms

Baseline
Steady State Infusion

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Ketamine alone

Robust ketamine response

Presented at $P<0.05$ FWE corrected, voxelwise
Clear attenuation of ketamine response in paracingulate cortex by lamotrigine and risperidone
Train a binary classifier on the extremities:

PLA vs KET. Test the classifier on the PRE+KET.

Doyle et al, JPET, 2013
Comparison with PET approach

After Borsook et al. (2012) Drug Discov Today

Safety
Tolerability
Pharmacokinetics

PET
CNS penetration
Target engagement
Dose – occupancy relationship

Behavioural / patient studies

phMRI
CNS penetration via function
Dose – function relationship
Evidence for pharmacodynamic

Early decisions on dose in healthy and patients

Combine with paradigms in patients or healthy

Behavioural / patient studies
Application to novel compounds

Lilly
- 2 trials of mGlu2 agonists vs ketamine

MRC/AZ
- trial of tyr kinase inhibitor vs psilocybin

In discussion
- 4 studies in development/negotiation
Good imaging practice I

1. Good study oversight
2. Standardisation of procedures
3. Quality assurance and quality control
4. Data handling
5. Analysis and reporting of results to trial standards

Imaging and data acquisition
- Imaging equipment
- Scanner manufacturer, field strength and model
- Coil(s) to be used for the study
- Scanner software release
- Regular MRI QA assessment procedures
- Frequency and nature of regular scanner QA procedures (e.g. phantom scans)
- Documentation of results of same (e.g. plots of phantom SNR, drift, by week)
- Processes around upgrades and maintenance logs
- Date of last software upgrade
- Date of next scheduled software upgrade
- Frequency of preventative maintenance on scanner
- QA processes following upgrade or service intervention
- Records of QA and specification checks following upgrade or service intervention and document controls
- QA and maintenance processes for additional (non-imaging) equipment
- Stimulus presentation computer(s) and software
- Visual presentation and subject feedback equipment
- Physiological monitoring equipment
- SOPs for MRI operations

Data handling and backup
- Data routing, transfer, backup, retention and de-identification processes
- Diagram of site data flow
- Analysis pipelines and data QC procedures
- Description of study-relevant analysis procedures
- Vendor and/or product or validation records for software used for analysis
- Data and/or image QC procedures

Schwarz et al. (2011) Drug Discov Today
Good imaging practice II

Schwarz et al. (2011) Drug Discov Today
Experimental medicine approaches in neuroimaging can provide:

Robust and replicable outcomes
Reliable measurements
Relevant mechanistic indicators
Early indicators of efficacy

Pharmacological imaging is useful for:
Determining mechanisms of existing treatments
Validation of novel treatments
Translational approaches
Application or patient populations
Thanks for your attention!

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Volunteers & radiographers
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- Michel Bernanos
- James Stone
- Steven Williams

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Overview of uses

1. Evidence of functional target engagement
2. Evidence of pharmacological mechanism of action
3. Early indicators of efficacy (modulation of networks)
4. Dose response relationships (PK-PD modelling)
5. Off-target effects