Machine Learning for Pharmacological Imaging
Past, Present and Future

Mitul Mehta

Thanks to:
Andre, Marquand, Orla Doyle, Owen O‘Daly, Sara de Simoni, Richard Joules
Fernando Zelaya, Steven Williams
• **What have we been trying to measure**
  – Exemplar from dopaminergic functions
  – Monkey electrophysiology
  – Human neuroimaging
Electrophysiology

SN/VTA
Task modulations

Placebo

Dextroamphetamine

Methylphenidate

Pergolide (D1/D2 agonist)

• Dopaminergic drugs (including stimulants) modulate brain activity in dorsolateral prefrontal and posterior parietal brain regions during working memory tasks.
• Replicated findings in humans using univariate analyses
• Replicates and extends research in experimental animals
• However…. there are various lines of evidence that indicate a multivariate perspective is a useful one.
However….

1. Recording studies in experimental animals only examine limited regions

Wang et al. (2004)
However...

2. Human studies have also shown up other modulated regions.

Gibbs and D’Esposito (2006)
3. Up and down during working memory tasks

- “Deactivations” have been associated with
- stimulus independent thought
- unconstrained thought processes
- Monitoring of external environment
4. The anatomy of the dopaminergic system suggests distributed rather than delimited, localised effects
Dopamine striatal projections can modulate distinct processing pathways

DA modulation of striatal structures influences information flow within the cortico-striato-thalamic system

After Alexander et al. (1986) Ann Rev Neurosci
• Recording studies in experimental animals only examine limited regions

• Human studies have also shown up multiple modulated regions

• Activations and deactivations may be affects by drugs

• The anatomy of the modulatory drug systems suggest distributed rather than delimited, localised effects

• The effects on dopamine in one region can influence the dopaminergic effects in another region
  – Roberts et al. (1994) J Neurosci

• Many drugs of interest bind to receptors across more than one transmitter system
• These findings and features lead to the hypothesis that for drugs that modulate the dopaminergic system distributed effects are predicted.

• In addition, prior group studies show considerable overlap in signals, thus the use of univariate-based discrimination or diagnostics would be limited by poor sensitivity and specificity – example from schizophrenia.
Increased F-DOPA uptake in schizophrenia

Bose et al. (2008) Schiz Res
Present

![Graphs showing uptake constant for FOPA and laterality quotients for ROIs.](image-url)

- Normal
- Patient with Schizophrenia

Bose et al. (2008) Schiz Res
• Using an ANN approach good discrimination can be achieved relative to GDA

• Feed forward multilayer perceptron

Table 1
Summary of results for the four models applied to the striatal [18F] DOPA uptake input data in schizophrenia patient and normal subjects showing 95% confidence intervals (CI) for sensitivity and specificity

<table>
<thead>
<tr>
<th>Variable used (ROIs)</th>
<th>Model used</th>
<th>Classification rate (%)</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal subject</td>
<td>Schizophrenia</td>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 bilateral*</td>
<td>ANN</td>
<td>74</td>
<td>84</td>
<td>78</td>
<td>84 (59.5–95.8)</td>
<td>74 (55.0–87.4)</td>
</tr>
<tr>
<td>12 bilateral*</td>
<td>General discriminant analysis (GDA)</td>
<td>77</td>
<td>74</td>
<td>76</td>
<td>74 (48.5–89.8)</td>
<td>77 (58.4–89.7)</td>
</tr>
<tr>
<td>6 laterality quotients (left/right)*</td>
<td>ANN</td>
<td>94</td>
<td>89</td>
<td>91</td>
<td>89 (65.4–98.1)</td>
<td>94 (77.1–98.8)</td>
</tr>
<tr>
<td>6 laterality quotients (left/right)</td>
<td>General discriminant analysis (GDA)</td>
<td>58</td>
<td>63</td>
<td>60</td>
<td>63 (38.6–82.7)</td>
<td>58 (39.2–74.9)</td>
</tr>
</tbody>
</table>

*Significant classification using likelihood ratio: \( \chi^2 = 17.3, df = 1, P < 0.001 \); \( \chi^2 = 13.0, P < 0.001 \); \( \chi^2 = 38.8, P < 0.001 \); \( \chi^2 = 2.1, P = 0.14 \).
Major objectives in MVPA applied to psychopharmacological studies: part I

- Improved sensitivity and specificity in discrimination of drug responses from placebo response and drug responses from each other
- A distributed representation of drug effects across the whole brain, or across predefined brain regions, or within predefined brain regions
- Contribution to new knowledge of the understanding of systems level drug effects
- Sophisticated outcome measures that represent patterns of change across the brain, rather than single regions or voxels
Pattern Classification of Working Memory Networks Reveals Differential Effects of Methylphenidate, Atomoxetine, and Placebo in Healthy Volunteers

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The effects of stimulant medication during WM tasks

Encoding

Delay

Retrieval

Task vs. Baseline
(Placebo condition, control trials)

Task
BL
Default Mode Network (TRDs)
Rewarded working memory
Machine learning schema

labeled training examples -> Gaussian Process Classifier

machine learning algorithm -> prediction rule

new example -> predicted classification
Pattern recognition approach: Multivariate Analysis

Input

| Volumes from group 1 |
| Volumes from group 2 |
| New example |

Classifier - training

Map: Discriminating regions between group 1 and group 2

Classifier - test

Prediction: group 1 or group 2

Classical approach: Mass-univariate Analysis

Input

1. Voxel time series
2. Experimental Design

Intensity
BOLD signal

Time

e.g. GLM

Map: Activated regions between group 1 and group 2

Andre Marquand
- 15 subjects received oral 30mg MPH, 60mg ATX or a placebo (PLC)
- Perfusion imaging 90-135 min post-dose (multi-shot continuous arterial spin labelling)
- fMRI of ‘delayed match to location’ spatial working memory (WM) task.

Marquand et al. (2011) NPP; Marquand et al. (2012) Neuroimage
### Table 1 Summary of Classification Results

<table>
<thead>
<tr>
<th>Contrast</th>
<th>WM components exceeding chance</th>
<th>Neuronal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reward vs control</td>
<td>Encoding, delay and retrieval for all drug contrasts, except for encoding on MPH</td>
<td>Reward increased activity in WM networks and suppressed TRDs</td>
</tr>
<tr>
<td>ATX vs PLC (rewarded trials)</td>
<td>Encoding, delay and retrieval</td>
<td>ATX decreased activity in WM networks and enhanced TRDs</td>
</tr>
<tr>
<td>ATX vs PLC (non-rewarded trials)</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>MPH vs PLC (rewarded trials)</td>
<td>Encoding, delay and retrieval</td>
<td>MPH decreased activity in WM networks and enhanced TRDs</td>
</tr>
<tr>
<td>MPH vs PLC (non-rewarded trials)</td>
<td>Encoding only</td>
<td>MPH increased activity in WM networks and suppressed TRDs</td>
</tr>
<tr>
<td>MPH vs ATX (rewarded trials)</td>
<td>Delay only</td>
<td>MPH had greater activity in WM regions relative to ATX and ATX resulted in greater TRDs</td>
</tr>
<tr>
<td>MPH vs ATX (non-rewarded trials)</td>
<td>None</td>
<td>—</td>
</tr>
</tbody>
</table>
Also includes:
- Premotor cortex
- SMA
- Occipital lobe
- Medial PFC
- Posterior cingulate
- Inferior parietal lobe
- Temporal lobe
- Midbrain

DLPFC

Post parietal lobe

A

Encoding

B

Delay

C

Retrieval
Rewarded working memory

Activation network

Deactivation network

Placebo  Methylphenidate

Non-rewarded working memory

Activation network

Deactivation network

Placebo  Methylphenidate
Major objectives in MVPA applied to psychopharmacological studies: part II

- Improved sensitivity and specificity in discrimination of drug responses from placebo response and drug responses from each other
- A distributed representation of drug effects across the whole brain, or across predefined brain regions, or within predefined brain regions
- Contribution to new knowledge of the understanding of systems level drug effects
- Sophisticated outcome measures that represent patterns of change across the brain, rather than single regions or voxels
First application of multi-class ML classifiers to pharmacological MRI

• Has broad application in preclinical & early phase drug development when discrimination between more that two drugs is required, e.g. placebo, positive control/market leader, novel compound.

• Demonstration of excellent discrimination between ADHD treatments atomoxetine and methylphenidate.

• Insight into mechanisms of action of these compounds (right)

• Demonstration that accuracy of classifier increases with more scans – pragmatic value (below)

‘Pharmacological subtraction’ and ‘pharmacological blockade’ designs

• If methylphenidate enhances working memory and acts through the dopamine and noradrenaline systems can we use a dopamine blocker to test the hypothesis that the dopaminergic effects underpin the working memory improvement?

• If scopolamine (cholinergic antagonist) reduces blood flow can we reverse this with donepezil (blocks acetylcholinesterase)
First application of ML classifiers to phMRI

- Has broad application in preclinical & early phase drug development.
- Method developed for dealing with crossover designs;
  - Important in Clin Pharm context.
- Demonstration on ketamine phMRI and its modulation by single doses of:
  - Lamotrigine (300mg);
  - Risperidone (2mg).
- ML affords a single variable which quantifies (over the whole brain) the attenuation of the ketamine effect, enabling effective benchmarking of compounds.
- Current application to novel compounds

**Classification scenario**
- Probabilistic classification and ordinal regression

**Saline-Ketamine Continuum**

- Probability of belonging to the ketamine class or definition of intermediate class.

Doyle O, de Simoni S et al. (2013) Neuroimage; Doyle O, de Simoni et al. (2013) JPET
Utilisation of dynamic information

- Robust data-driven approaches to model the phMRI timeseries which alleviates the need for a pre-defined model (defining peak response(s))
- Variation in effects over time
- PK/PD modelling of mutivariate drug effects
- Integration of physiological data to control for non-neuronal effects
- Principled and model-driven integration of multimodal data
- Data libraries for interpretation

Thanks

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