What has biological psychiatry ever done for us?

Imaging the mind-brain in psychiatry

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Director of the Scottish Mental Health Research Network
Director of the Medical Research Foundation & Medical Research Council
Clinical Research Training Fellowship Programme for Mental Health for the UK (aka 'PsySTAR')
Plan

• PsySTAR!
• New imaging methods
• Dementia
• (‘functional’) Psychosis
• Depression
• (Developmental disorders)
• Conclusions
MRF/MRC Mental Health Research Training Fellowship Programme for the UK

Psychiatry - Scottish Training in Academic Research (PsySTAR) scheme

“Standard” Post MMC NHS Specialist Training
Funded NHS etc.

PsySTAR Advertised. Subject to successful entry to specialist Psychiatry training, appointees join PsySTAR, typically beginning ST4

PhD selection 20% Research
Full time PhD
Further Research and Clinical training

Checkpoints: Year 1 report PhD Graduation etc

“Graduation” from PsySTAR with Clinical Academic Training and CCT or Further Training as required

Encouraged to take substantive period of Post Doc training via Intermediate Fellowship

PsySTAR training programme
Funded by NHS Education for Scotland through ST posts and SCREDS Lectureships with MRF/MRC-funded PhD

PsySTAR1 (ST4)
PsySTAR 2-4 PhD; (Out of Programme Experience)

PsySTAR training programme
Funded by NHS Education for Scotland through ST posts and SCREDS Lectureships with MRF/MRC-funded PhD

PsySTAR5 (ST5)
PsySTAR6 (ST6)

Checkpoints: Year 1 report PhD Graduation etc
Amazing PhD supervisors & Unique PhD opportunities

• We want PsySTAR trainees to identify the research project that most interests, excites and suits them and to work with the supervisors most suited to their project.

• Examples of possible supervisors and topics include:
  - Adrian Bird FRS: Epigenetics
  - Ian Deary: Cognitive epidemiology
  - Ian Ford: Record linkage
  - Nick Hastie FRS: Psychiatric genetics
  - Jerry Lambert: GABA receptor neurobiology
  - Dame Sally Macintyre: The social determinants of mental well-being and ill health
  - Richard Morris FRS: Hippocampal biology
  - Gordon Murray: Clinical trials
  - Sir Ian Wilmut FRS: Stem cell biology
The first PsySTAR Annual Summer School in Mental Health Research
Royal Society of Edinburgh, 21 – 22 September

The School is aimed at clinical trainees (FY1-ST4) interested in an introduction to cutting edge research relevant to psychiatric disorders. The topics to be introduced include epidemiology, clinical trials, neuroimaging, molecular biology, stem cell research and genetics.

Via lectures, workshops and informal discussion participants will gain an appreciation of a range of exciting approaches to mental health research and the opportunities available to pursue a career in academic psychiatry. Participation is limited to 50 attendees and places will be allocated competitively. If you are successfully awarded a place there will be no attendance fee and required accommodation will also be paid for, as a result of generous funding from the MRF and MRC.

For further information visit: http://www.ed.ac.uk/schools-departments/psychiatry/psystar

To apply for the summer school please send a copy of your CV (maximum 2 pages) and a covering letter saying why you would like to attend the course to: psystar@ed.ac.uk

The deadline for applications is 5pm on Monday 30th July 2012 and successful candidates will be notified by mid August.

PsySTAR is funded by the Medical Research Foundation and the Medical Research Council
Novel approaches to neuroimaging

DATA ACQUISITION
More ‘precise’

• Resting state fMRI

• Arterial spin labelling (‘tagging’) MRI

DATA ANALYSIS
Using more of the info

• Connectomics:
  - e.g. Small world networks

• Pattern classification:
  - e.g. Support vector machines
SCANNING THE CONNECTOME

The Human Connectome Project aims to trace the brain’s long-range communication network using two main techniques, both of which rely on magnetic resonance imaging (MRI) to obtain data from living people.

**Mapping structure**
Diffusion spectrum imaging detects the movement of water molecules that flow along nerve fibres in the brain. The result is a map of the brain’s neuronal network.

**Mapping function**
Resting-state functional MRI maps resting brain activity, then looks for correlations between one area and another. Highly correlated areas are thought to have some kind of functional link.

The brain has many areas specialized for specific functions, some of which are shown here.

Data on structure and function can be combined and analysed using tools such as network theory.

The connectome ties these areas together, allowing the brain to function as a coherent whole. The project’s goal is to understand how the connectome works.

Neuroscience: Making connections

Is a project to map the brain’s full communications network worth the money?

- **Jon Bardin** (21 March 2012)
  Nature 2012; 483: Pp 394–396

- Technical issues:
  WM terminations in Cx & BOLD signal components
Support vector machines
Linden, Neuron 2012

### Table 3. Classification Accuracies of Selected Structural Brain Imaging Studies Employing Multivariate Analyses to Classify Patient Groups

<table>
<thead>
<tr>
<th>Group Discrimination</th>
<th>Imaging Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD versus normal aging</td>
<td>Whole-brain gray matter morphometry</td>
<td>60.6–100</td>
<td>80–95</td>
<td>81.1–96.4*</td>
<td>Klöppel et al., 2008</td>
</tr>
<tr>
<td>AD versus FTD</td>
<td>Whole-brain gray matter morphometry</td>
<td>83.3</td>
<td>94.7</td>
<td>89.2</td>
<td>Klöppel et al., 2008</td>
</tr>
<tr>
<td>MCI versus normal aging</td>
<td>Shape of hippocampus</td>
<td>83%</td>
<td>84%</td>
<td>83%</td>
<td>Gerardin et al., 2009</td>
</tr>
<tr>
<td>SZ versus HC</td>
<td>Whole brain morphometry</td>
<td>73.9%</td>
<td>87.3%</td>
<td>81.1%</td>
<td>Davatzikos et al., 2005</td>
</tr>
<tr>
<td>Adults with ASD versus HC</td>
<td>Whole-brain gray matter morphometry</td>
<td>60% (RH) /</td>
<td>70% (RH) /</td>
<td>65% (RH) /</td>
<td>Ecker et al., 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90% (LH)</td>
<td>80% (LH)</td>
<td>85% (LH)</td>
<td></td>
</tr>
<tr>
<td>FXS versus controls</td>
<td>Whole-brain gray matter morphometry</td>
<td>96.1%</td>
<td>89.6%</td>
<td>92.9%</td>
<td>Hoefft et al., 2008</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; ASD: autism spectrum disorder; FTD: frontotemporal dementia; FXS: fragile-X syndrome; HC: healthy controls; LH: left hemisphere; MCI: mild cognitive impairment; RH: right hemisphere; SZ: schizophrenia. *For analyses of different subgroups.
## Diagnosing dementia with imaging

<table>
<thead>
<tr>
<th></th>
<th>Alz</th>
<th>Vascular</th>
<th>Lewy</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT/sMRI</strong></td>
<td>Atrophy (*)MTL</td>
<td>HIS’s Lacunae</td>
<td>General atrophy</td>
<td>Anterior atrophy</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>slow</td>
<td>slow</td>
<td>very slow</td>
<td>normal</td>
</tr>
<tr>
<td><strong>SPE(C)T (rCBF)</strong></td>
<td>Global (*)posterior</td>
<td>Multifocal</td>
<td>Posterior</td>
<td>Anterior</td>
</tr>
<tr>
<td><strong>PET (lig) binding</strong></td>
<td>increased PiB uptake</td>
<td>-</td>
<td>low DAT uptake</td>
<td>-</td>
</tr>
</tbody>
</table>

The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease (McKhann et al, Alzheimer & Dementia 2011)

### Table 1: AD dementia criteria incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td></td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>(atypical clinical presentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Brain imaging in psychosis could already be cost-effective!

- Structural neuroimaging in psychosis: a systematic review and economic evaluation.
- Source: Department of Public Health and Epidemiology, University of Birmingham, UK.

The evidence to date suggests that if screening with structural neuroimaging was implemented in all patients presenting with psychotic symptoms, little would be found to affect clinical management in addition to that suspected by a full clinical history and neurological examination. From an economic perspective, the outcome is not clear. The strategy of neuroimaging for all is either cost-incuring or cost-saving (dependent upon whether MRI or CT is used) if the prevalence of organic causes is around 1%. However, these values are nested within a number of assumptions, and so have to be interpreted with caution. The main research priorities are to monitor the current use of structural neuroimaging in psychosis in the NHS to identify clinical triggers to its current use and subsequent outcomes; to undertake well-conducted diagnostic before-and-after studies on representative populations to determine the clinical utility of structural neuroimaging in this patient group, and to determine whether the most appropriate structural imaging modality in psychosis should be CT or MRI.
Sch Vs BPD sMRI meta-analyses

- Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM (Br J Psych 2009) - 36 ROI studies, 1823 BPD, 670 Sz, and 1940 healthy controls. Participants with BPD had whole brain and PFC reductions; increases in globus pallidus and LVs. **Compared to schizophrenia, BPD is associated with smaller LVs and enlarged amygdala.** Heterogeneity was widespread, partly explained by age, illness duration & mood stabilisers.

- Yu K, Cheung C, Leung M, Li Q, Chua S, McAlonan G. Front Hum Neurosci. 2010 Oct 26;4:189 - VBM ALE method. 19 Sz studies (651 pts, 693 cls) matched to 19 BPD studies (540 pts, 745 cls). Substantial overlaps in the regions affected, but schizophrenia was almost exclusively associated with additional GM deficits (left insula and amygdala) in the left hemisphere.

- Ellison-Wright & Bullmore (Sz Res 2010) VBM ALE of 42 Sz studies (2058 pts, 2131 con), compared with 14 BPD studies (366 pts, 497 con). GM deficits in neoCx, limbic and paralimbic regions in Sz; only paralimbic in BPD (ACC & bilat. insula).

- **Bora E, Fornito A, Yücel M, Pantelis C. Psychol Med. 2011 Aug 11:1-13** When sex matched, GM reductions were restricted to dorsal anterior cingulate cortex (ACC) and DLPFC in schizophrenia and ACC and bilateral fronto-insular cortex in bipolar disorder.

In total, 21 studies were identified including patients (n = 729) and healthy subjects (n = 465). Relative over-activation in the medial temporal lobe and associated structures was found in BD versus SCZ in tasks involving emotion or memory. Evidence of differences between the disorders in prefrontal regions was less consistent.
Functional MRI imaging in Sz vs BPD

• Sixteen patients with Sz, 16 with BPD and 16 controls performed a face-name pair memory task during functional MRI.
• During encoding patients with Sz showed decreased anterior hippocampal activation c.f. BPD; while during encoding and retrieval patients with Sz showed greater DLFPC activation.
• The model that best differentiated the patient groups included the hippocampal (c1) and DLPFC clusters from the early encoding period (c2) and the early retrieval period (c3). This model correctly classified 100% of patients with schizophrenia and 93% of patients with bipolar disorder.

Hall et al 2010 Psychological Medicine
Data extracted from these clusters showed differences in activation between schizophrenia (red) and bipolar (green) groups on DFA.
Extracting morphological networks from individual grey matter MRI scans in healthy subjects and people at high risk for schizophrenia

1. Extract grey matter from structural MRI
2. Divide in to equal cubes
3. Determine the similarity between each cube: maximise for rotation and reflection
4. Threshold similarity matrix
5. Create random version, that keeps degree intact.
### Predicting schizophrenia with individualised small world network analysis of sMRI data

#### Prediction accuracy

<table>
<thead>
<tr>
<th>Group</th>
<th>Selected area</th>
<th>Mean accuracy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>class 1</td>
</tr>
<tr>
<td>HC vs HR</td>
<td>l angular gyrus + r MTG</td>
<td>0.59 (0.50, 0.69)</td>
</tr>
<tr>
<td>HR-sym vs HRill</td>
<td>global + r angular gyrus</td>
<td>0.75 (0.71, 0.80)</td>
</tr>
<tr>
<td>HR+sym vs HRill</td>
<td>global</td>
<td>0.67 (0.61, 0.74)</td>
</tr>
</tbody>
</table>

*HC* is healthy control, *HR* is high risk, *HR-sym* is high risk without symptoms, *HR+sym* is high risk with symptoms, *HRill* is high risk ill.

Exploratory analyses:
step 1. automated variable selection with Random Forest (Breiman, 2001).
step 2. Logistic model, best fit with top ranked variables
step 3. Prediction accuracy with bootstrap validation (i.e., assess accuracy with data not used for model-fitting)
Predicting response to antidepressants
Conclusions

• Brain imaging is one means of moving towards objective diagnosis in psychiatry, but we should do so with an eye on treatment.
• Brain imaging is recommended in the evaluation of dementia, and now figures in diagnostic criteria, more because it has been used than because of accuracy (or even recognised pathology).
• sMRI could be more used in FEP and TRS, with some caution.
• sMRI and fMRI (& ASL) might be able to distinguish schizophrenia from bipolar disorder, perhaps especially with SWN and SVM approaches, but these are as yet group differences and rarely include psychotic bipolar disorder.
• (If you are young, come to the PsySTAR Summer School! Google Edinburgh Psychiatry or email s.lawrie@ed.ac.uk)