Why isn’t fMRI more clinical?

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Neuro MRI Growth Trends

Incidence

Number of newly-diagnosed people per year. Corresponds to bubble sizes in growth chart.

- **Depression**... Huge (and growing) numbers suffer from mental illness
- **Stroke**... Increased focus on early detection, prevention of risk
- **Alzheimer’s Disease**... Phase III clinical trials on disease modifying drugs
- **Headache, numbness, etc.**... MRI used for diagnostic decisions – not always first line

Growth Potential

MRI Adoption

Research Early Adopters Early Majority Majority Full adoption

- Tumor
- PD
- MS
- Epilepsy
- TBI
- Depression
- AD
- Stroke

Spinal cord injury 50k Brain Tumor 190k Multiple Sclerosis 200k Parkinson’s 450k Alzheimer’s 2.2m Epilepsy 6.7m Trauma 9.7m Numbness 10m Headache 10m Stroke 15m Depression 29m

Corresponds to bubble sizes in growth chart.
Clinical Use of MRI

Large effect size
Radiologist can essentially look at a single unprocessed scan and make a diagnosis.
What can we see in an individual with fMRI?

- Activation (on or off)
- Modulations in activation
- Patterns of activation that are correlated with behavior, perception, conscious state, intrinsic state, intent, etc.
Clinically, Anatomic MRI has been extremely successful where fMRI has made almost no inroads.

Why?

• Several processing steps
• Small effect size to noise
• Many potential artifacts
MRI is exquisitely sensitive to individual traits

Comparisons of MRI-derived information vs. behavioral information
Cortical Magnification within Human Primary Visual Cortex Correlates with Acuity Thresholds

Robert O. Duncan and Geoffrey M. Boynton
Systems Neurobiology Laboratory B
The Salk Institute for Biological Studies
10010 North Torrey Pines Road
La Jolla, California 92037
Intelligence

BOLD magnitude in dorsal striatum predicts video game learning success

Predicting Individuals’ Learning Success from Patterns of Pre-Learning MRI Activity

Loan T. K. Vo¹,², Dirk B. Walther³, Arthur F. Kramer¹,⁴, Kirk I. Erickson⁵, Walter R. Boot⁶, Michelle W. Voss¹,⁴, Ruchika S. Prakash³, Hyunkyu Lee¹, Monica Fabiani¹,⁴, Gabriele Gratton¹,⁴, Daniel J. Simons¹,⁴, Bradley P. Sutton¹,⁷, Michelle Y. Wang¹,⁴,⁷,⁸

2011

A

<table>
<thead>
<tr>
<th>mean BOLD activity (a.u.)</th>
<th>measured score improvement</th>
</tr>
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<tbody>
<tr>
<td>1.6</td>
<td>2000</td>
</tr>
<tr>
<td>1.7</td>
<td>4000</td>
</tr>
<tr>
<td>1.8</td>
<td>6000</td>
</tr>
<tr>
<td>1.9</td>
<td>8000</td>
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</tbody>
</table>

$r = 0.47^{**}$

Dorsal striatum

mean-corrected BOLD activity

good > poor learners

good = poor learners

good < poor learners
Dorsolateral Prefrontal \( \gamma \)-Aminobutyric Acid in Men Predicts Individual Differences in Rash Impulsivity

Frederic Boy, C. John Evans, Richard A.E. Edden, Andrew D. Lawrence, Krish D. Singh, Masud Husain, and Petroc Sumner

Biol Psychiatry 2011: 70: 866-872
Dynamic States: Schizophrenia vs Controls

The structural basis of inter-individual differences in human behaviour and cognition

Ryota Kanai and Geraint Rees
Figure 4 | Brain structure correlates of higher cognitive functions. a | Grey matter (GM; left panel) and white matter (WM; right panel) correlates of general intelligence. Greater grey matter and white matter volumes in specific brain areas are associated with higher intelligence. b | Grey matter correlates of the Big Five traits. Grey matter volume in specific cortical areas correlates with scores on a specific trait. PFC, prefrontal cortex. Part a is reproduced, with permission, from REF. 125 © 2004 Elsevier. Part b is modified, with permission, from REF. 115 © 2010 Sage Publications.
Reaction Time

Response Conflict

Speed - Accuracy tradeoff ability

Figure 2 | Structural bases of inter-individual differences in action and decision making. a | The speed of reaction time in making a visual choice correlates with the fractional anisotropy (a measure of white matter integrity) of the right optic radiation (indicated by the white box). b | Grey matter density of the pre-supplementary motor area (pre-SMA) correlates with the degree of the response conflict effect. The scatter plot shows the correlation in the condition in which conflicting response tendencies were elicited consciously (because the conflicting stimuli were only weakly masked). c | Connection strength between the pre-SMA (upper green area in the left panel) and striatum (lower green area in the left panel) correlates with individuals' ability to adjust the speed-accuracy trade-off. Part a is modified, with permission, from REF. 33 © 2005 National Academy of Sciences. Part b is modified, with permission, from REF. 35 © 2011 MIT Press. Part c is modified, with permission, from REF. 42 © 2010 National Academy of Sciences.
Switching between competing percepts

Ability to see illusions

Metacognition

Figure 3 | Structural bases of inter-individual differences in conscious perception. a | Structural correlates of inter-individual differences in the duration of one percept in a perceptual rivalry task (in which a single visual input can have conflicting interpretations) (left panel). A larger posterior superior parietal lobe (pSPL) was associated with a slower rate of switching between competing interpretations of a visual input, whereas a larger anterior superior parietal lobe (aSPL) was associated with a faster switch rate. Data in the middle and right panels are from REF. 51 and REF. 52, respectively. b | The surface areas of visual cortical areas V1, V2 and V3 from two example participants (left panels). A larger V1 was associated with weaker Ebbinghaus and Ponzo illusions (right panels). c | A structural correlate of metacognitive ability (left panel). Statistical T-maps for positive (‘hot’ colour map: red, orange and yellow) correlations and negative (‘cool’ colour map: blue) correlations between grey matter volume and metacognitive ability are projected onto an inflated cortical surface. Better metacognitive abilities were associated with a larger Brodmann area 10 (BA10), an area in the rostral prefrontal cortex (right panel). The left panel of part a is reproduced, with permission, from REF. 52 © 2011 Cell Press. Part b is reproduced, with permission, from REF. 60 © 2011 Macmillan Publishers Ltd. All rights reserved. Part c is modified, with permission, from REF. 80 © 2010 American Association for the Advancement of Science.
Clinical functional magnetic resonance imaging.

Hart J Jr¹, Rao SM, Nuwer M.

Abstract

OBJECTIVE: To describe a new series of evaluation/procedural codes that were approved by the American Medical Association (AMA) CPT Editorial Panel for use in billing for these procedures by physicians or licensed clinical psychologists.

BACKGROUND: As of January of 2007, 3 distinct CPT codes for billing related to the functional magnetic resonance imaging (fMRI) procedure are available for use.

DESIGN: Description of CPT codes.

RESULTS: CPT code 70554: MRI, brain, fMRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration. CPT code 70555: MRI, brain, fMRI; requiring physician or psychologist administration. This is to be always reported with CPT code 96020: neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or psychologist, with review of test results and report.

CONCLUSIONS: These CPT codes will allow for billing of both the neurofunctional and imaging components of fMRI. Functional brain mapping will now be available as an activation study to aid in localizing neurofunctional abilities.
Current Clinical Applications of fMRI

- Presurgical mapping
- Wada test replacement (Epilepsy)

Issues:

- Hemodynamic coupling variability
- Veins as false-positives
- Motion / Patient motivation
- Registration and Landmarks
Potential Clinical Applications

• Disorder/Disease Biomarkers
• Perfusion deficit detection using resting state BOLD
• Neurofeedback
• Localization for Neuromodulation (TMS..)
• Assessment of Locked in Patients
• Brain Metabolism/Neurovascular Coupling/Blood Oxygenation Assessment
• Perfusion deficit detection using ASL
• Localization of seizure foci
• Clinical Importance of Basic Neuroscience
Biomarkers

Imaging Centre

Radiologist
The challenge of going from group studies to individual assessment

![Diagram of fMRI Measure vs Behavior Measure](image)
Typical fMRI Studies

Group 1

Group 2

Gold standard measures are not always clear: (i.e. DSM-IV?)
Group Differences: Yes
Individual classification >90% accuracy: Still working on it..

Neuronal, Psychiatric, Physiologic Trait:

- *Language Dominance*
- *Intelligence*
- *Gender*
- *Sensorimotor*
- *Personality*
- *Psychology*
- *Physiology*
- *Neurologic*
- *Developmental*
- *Degenerative*

A *biomarker* has been defined as a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”
The Challenges and Promise of Neuroimaging in Psychiatry

David E.J. Linden¹,*
¹MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, Cardiff University, Cardiff, UK
*Correspondence: lindend@cardiff.ac.uk
DOI 10.1016/j.neuron.2011.12.014
Start dataset – Imaging data from 2 (or more) diagnostic groups

G1: 1,...,n₁  G2: 1,...,n₂

Feature extraction:
- GM/WM density (VBM)
- Beta-/t-values (fMRI)
- FA values (DTI)

Feature selection:
- Pre-specified masks
- Data reduction (PCA)
- Feature elimination (RFE)

Classifier testing:
- Cross-validation (leave n out)
- Holdout test
- Yields sensitivity/specificity/prediction error for existing data set

Classifier training:
- Algorithm, e.g. SVM, to find optimal decision boundary
- Model selection (cross-validation)
- Permutation testing

Pragmatic testing:
- Diagnostic accuracy in new samples?
- Transfer across platforms/laboratories/populations?

Multidimensional Classification

healthy controls

Alzheimer's disease

Volume posterior hippocampus

Volume anterior hippocampus
Figure 2. A Highly Simplified Model of the Genetic Pathways in Polygenic Psychiatric Diseases, Using the Examples of Schizophrenia and Bipolar Disorder

The multiple genetic variants that can contribute to the clinical phenotype (Genes 1 ...) are likely to operate through a smaller number of intermediate biological pathways (a ...), and not all of them may need to be altered to affect the respective pathway. One gene can contribute to multiple pathways (as in the case of hypothetical gene 2), and both genes and pathways can contribute to more than one disorder, resulting in the genetic overlap between schizophrenia, schizoaffective disorder and bipolar disorder. Genes can interact with each other and with environmental factors. The effects of the altered biological pathways on brain structure and function result in neuroimaging phenotypes, which can reflect the underlying genetic/biological processes more sensitively and specifically than the clinical phenotypes. Only a subset of genetic variants would be present in each case of psychosis, and their number and effect strengths would determine individual genetic risk. The examples of the ZNF804A (Esslinger et al., 2009a) and CACNA1C (Erk et al., 2010) variants are discussed in the text.
Elements of a Classification Pipeline

1. Training Data Set.
   *Scan a very large number of well characterize subjects.*

2. Feature extraction from raw data and dimensionality reduction.
   *Find the most informative features from fMRI, genetics, physiology, and/or anatomy.*

3. Model training and optimization.
   *Teach an algorithm to use the information to allow differentiation.*

4. Application to test data.
   *Apply the learned rule to new data.*
Potential Clinical Applications

• Disorder/Disease Biomarkers
• Perfusion deficit detection using resting state BOLD
• Neurofeedback
• Localization for Neuromodulation (TMS..)
• Assessment of Locked in Patients
• Brain Metabolism/Neurovascular Coupling/Blood Oxygenation Assessment
• Perfusion deficit detection using ASL
• Localization of seizure foci
• Clinical Importance of Basic Neuroscience
Perfusion deficit detection using resting state BOLD

Published in final edited form as:

**Resting State BOLD MRI for Perfusion and Ischemia**

Hannes Kroll, MD¹, Greg Zaharchuk, MD, PhD¹, Thomas Christen, PhD², Jeremy Heit, MD, PhD¹, and Michael Iv, MD¹,²

¹Department of Radiology, Division of Neuroimaging & Neurointervention, Stanford University, Stanford, CA
²Richard M. Lucas Center for Imaging, Stanford University, Stanford, CA
## Neurofeedback

<table>
<thead>
<tr>
<th>Study</th>
<th>Disorder</th>
<th>Brain Region</th>
<th>Regulation Instructions</th>
<th>Control Condition</th>
<th>Outcome</th>
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<tr>
<td>Linden et al (2012)</td>
<td>MDD</td>
<td>Brain areas active while viewing positive pictures</td>
<td>Increase activity</td>
<td>Mental rehearsal outside of the scanner</td>
<td>Decreased depressive symptoms</td>
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<td>Amygdala</td>
<td>Increase activity</td>
<td>Alternate region of interest</td>
<td>Decreased state anxiety and increased state happiness</td>
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<td>Salience network</td>
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<td>ACC</td>
<td>Increase activity</td>
<td>Mental rehearsal inside of the scanner</td>
<td>Improved cognitive functioning</td>
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Neurofeedback for Depression

Targeting the affective brain—a randomized controlled trial of real-time fMRI neurofeedback in patients with depression

David M. A. Mehler, Moses O. Sokunbi, Isabelle Habes, Kali Barawi, Leena Subramanian, Maxence Range, John Evans, Kerenza Hood, Michael Lührs, Paul Keedwell, Rainer Goebel & David E. J. Linden

Neuropsychopharmacology 43, 2578–2585 (2018) | Download Citation

Whole-brain analysis. a Probability map (PM) of the localizer. b Activity of intervention groups, shown separately for NF-emotion and NF-scene group. c Group contrast. Key areas are labeled with numbers: (1) Insular cortex/ventrolateral prefrontal cortex, (2) parahippocampal Place area (PPA), (3) supplementary motor area, (4) lingual gyrus, (5) premotor cortex, (6) superior parietal lobule, and (7) ventrolateral prefrontal cortex. Statistical maps cluster-threshold corrected for multiple comparison (p < 0.001)
Epilepsy Localization

Communicating with Locked In Patients

What is needed for Clinical Implementation

- Streamlined clinical acquisition/processing pipeline
- More attention by vendors
- Just one major clinical application to get it started
- Agreed upon “biomarker” standards