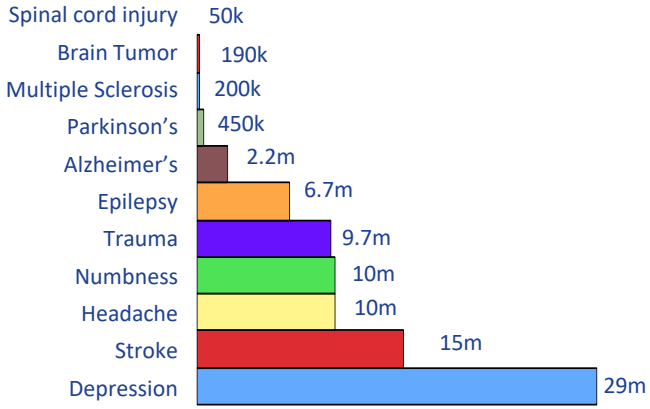
Why isn't fMRI more clinical?

Peter A. Bandettini, Ph.D.

Section on Functional Imaging Methods,
Laboratory of Brain and Cognition, NIMH
&
Functional MRI Facility, NIMH/NINDS

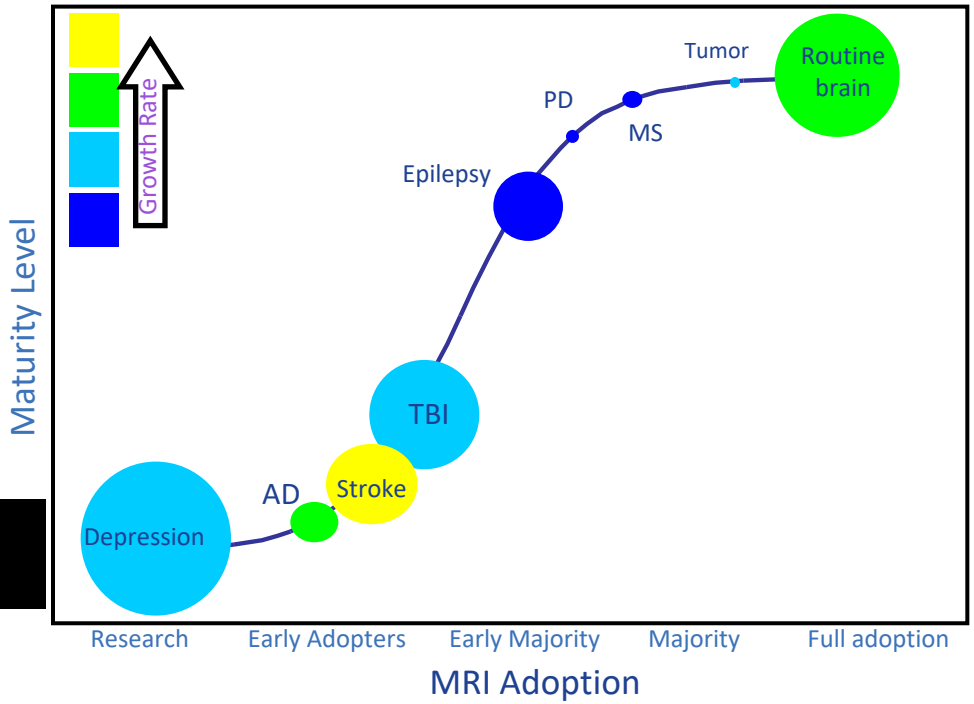
Neuro MRI Growth Trends

Incidence



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

Growth Potential



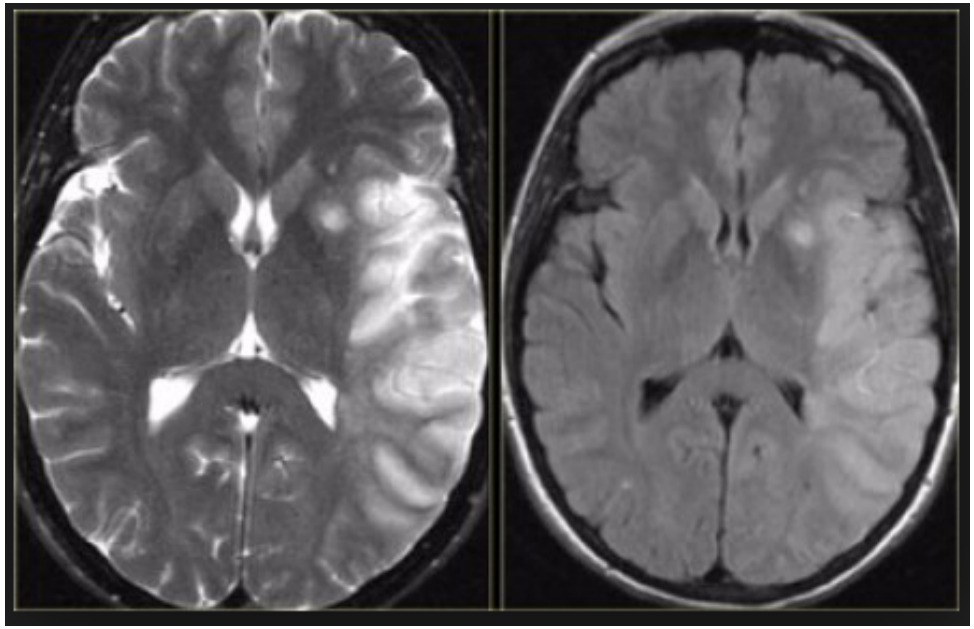
- **Depression…** Huge (and growing) numbers suffer from mental illness
- **Stroke…** Increased focus on early detection, prevention of risk
- **Alzheimer's Disease…** Phase III clinical trials on disease modifying drugs
- **Headache, numbness, etc. …** MRI used for diagnostic decisions – not always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

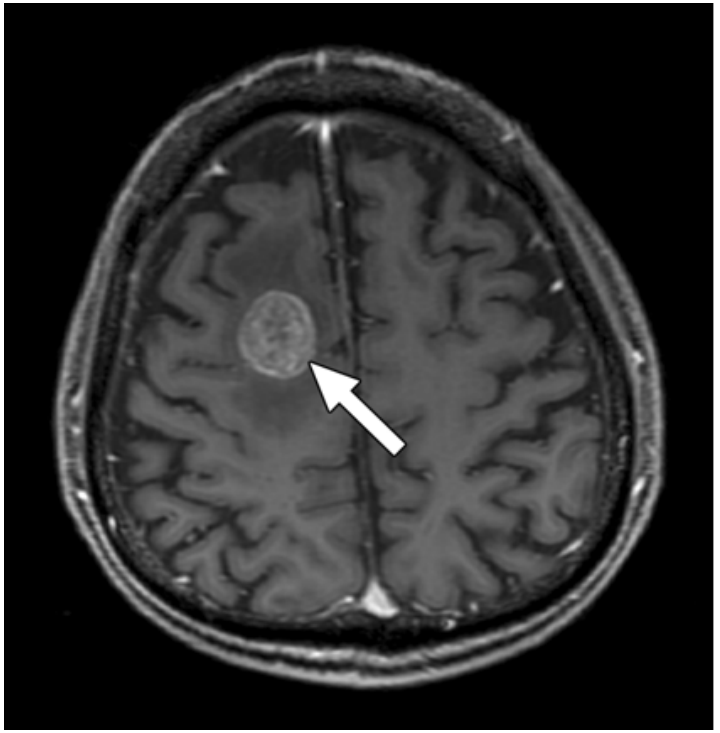
Courtesy: Scott Hinks (GE Medical Systems)

Clinical Use of MRI

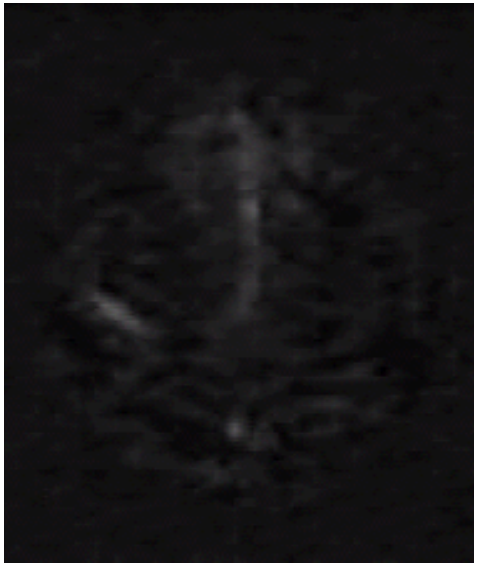
Large effect size

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 activatic
- 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**

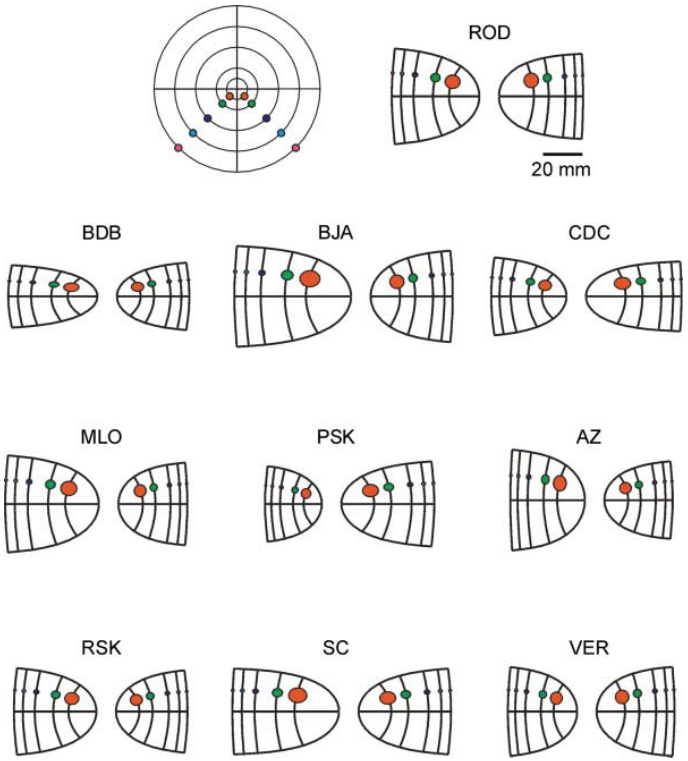
MRI is exquisitely sensitive to individual traits

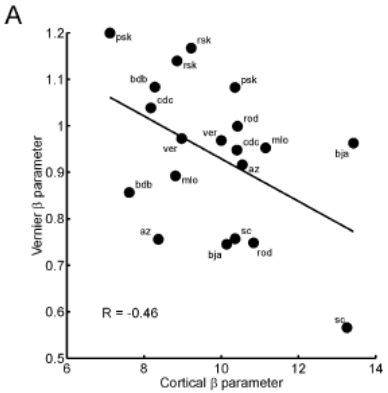
Comparisons of MRI-derived information vs. behavioral information

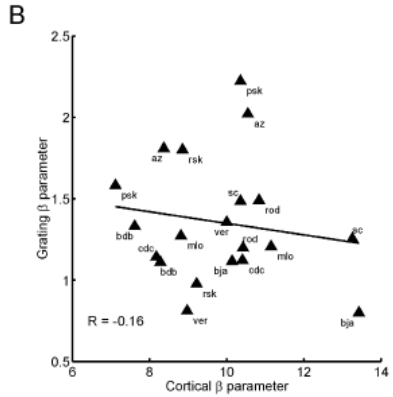
Neuron, Vol. 38, 659–671, May 22, 2003, Copyright ©2003 by Cell Press

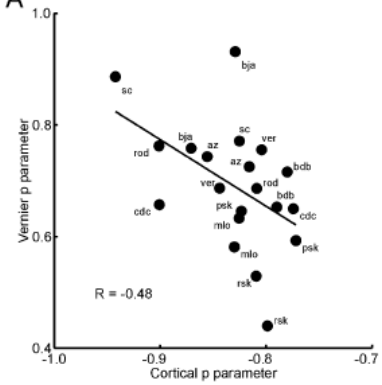
Cortical Magnification within Human Primary Visual Cortex Correlates with Acuity Thresholds

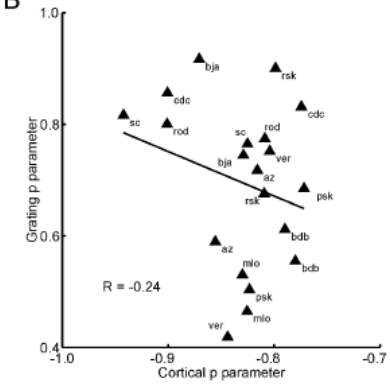
Robert O. Duncan* and Geoffrey M. Boynton
Systems Neurobiology Laboratory - B
The Salk Institute for Biological Studies
10010 North Torrey Pines Road
La Jolla, California 92037



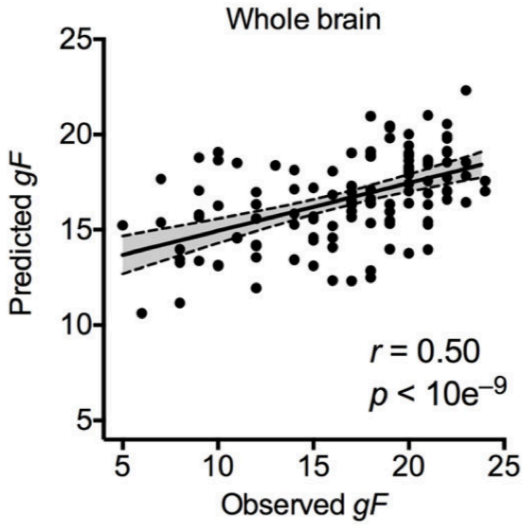


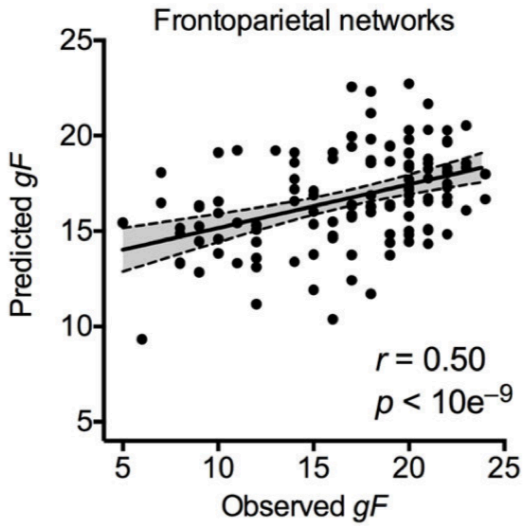


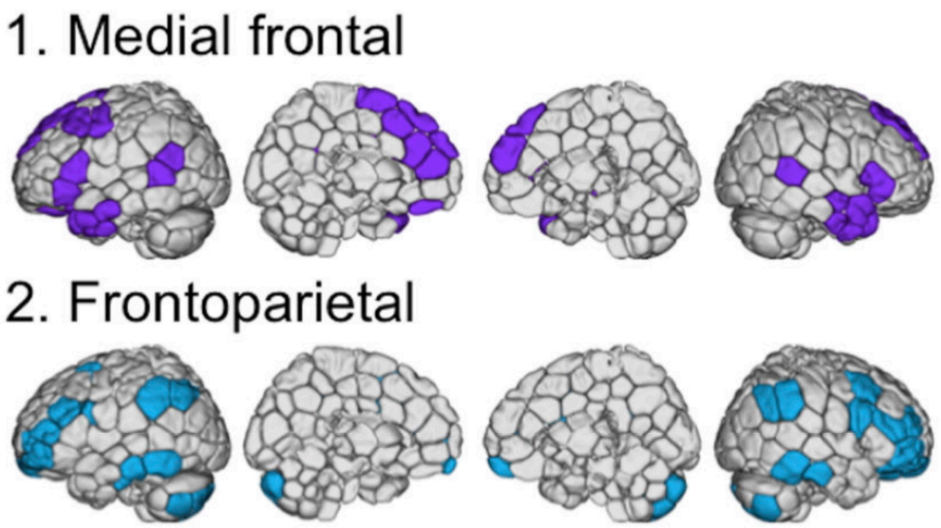




Intelligence







Finn et al. Nat Neurosci. 2015 November ; 18(11): 1664–1671. doi:10.1038/nn.4135.

BOLD magnitude in dorsal striatum predicts video game learning success

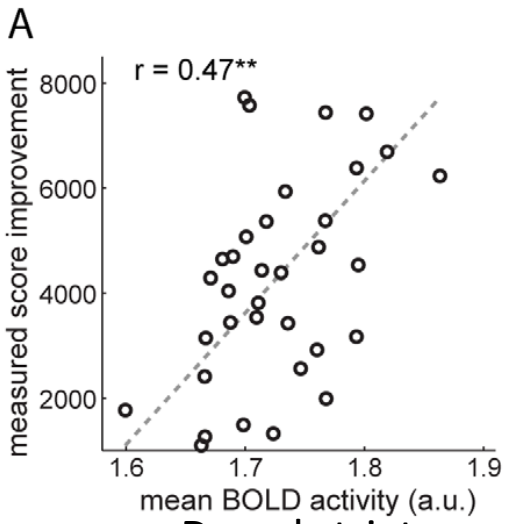
OPEN ACCESS Freely available online

PLoS one

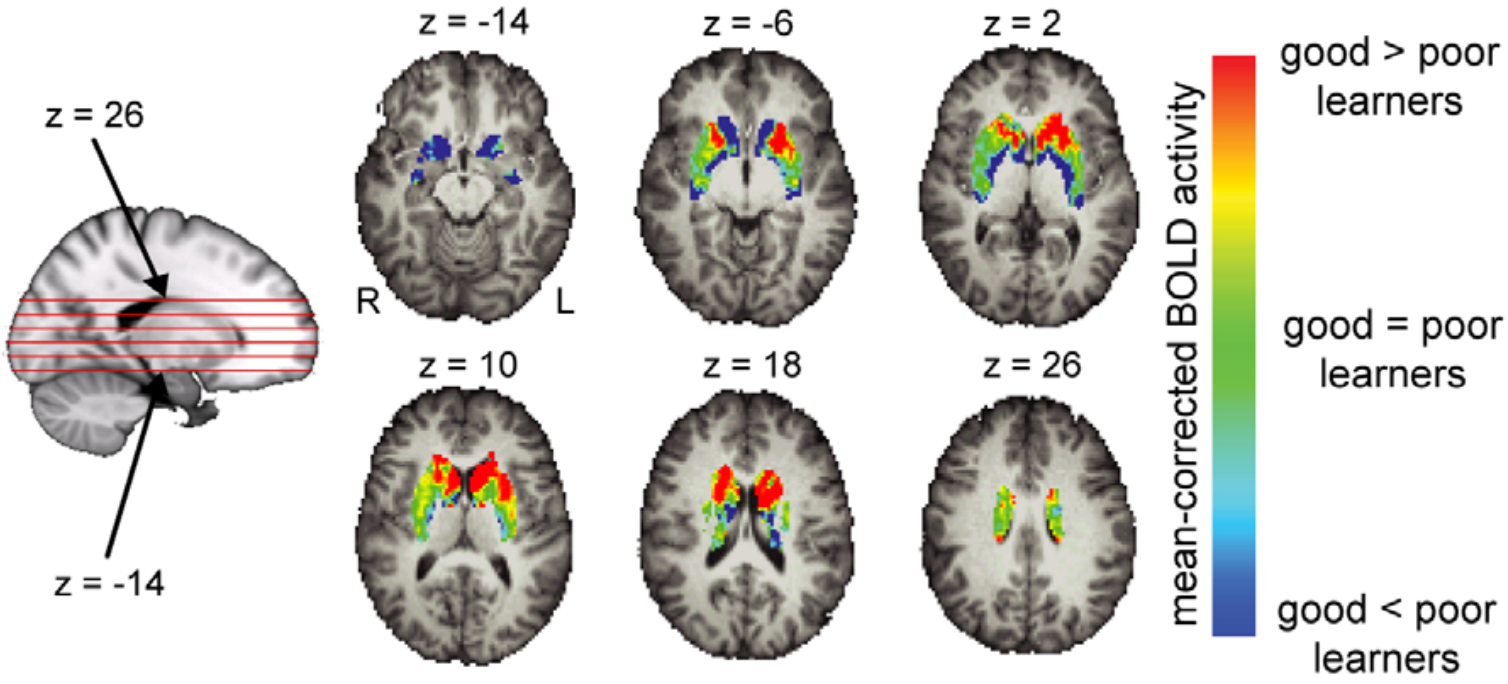
Predicting Individuals' Learning Success from Patterns of Pre-Learning MRI Activity

Loan T. K. Vo[1,2], Dirk B. Walther[3]*, Arthur F. Kramer[1,4], Kirk I. Erickson[5], Walter R. Boot[6], Michelle W. Voss[1,4], Ruchika S. Prakash[3], Hyunkyu Lee[1], Monica Fabiani[1,4], Gabriele Gratton[1,4], Daniel J. Simons[1,4], Bradley P. Sutton[1,7], Michelle Y. Wang[1,4,7,8]

2011



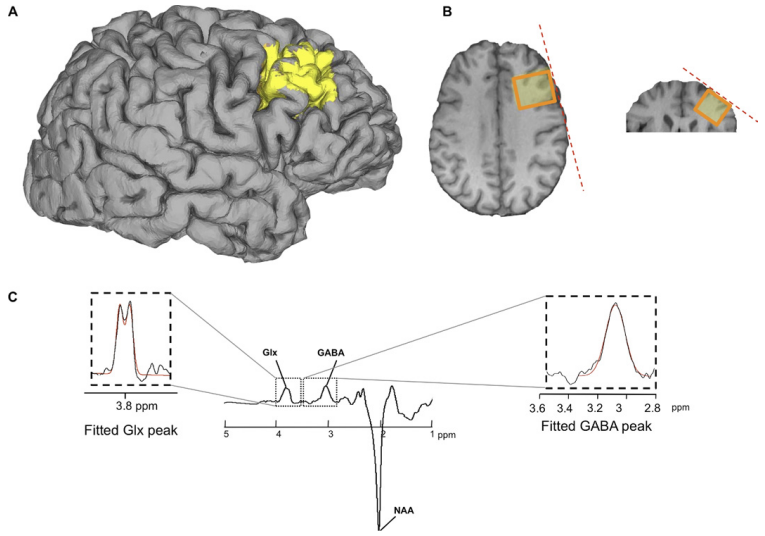
Dorsal striatum

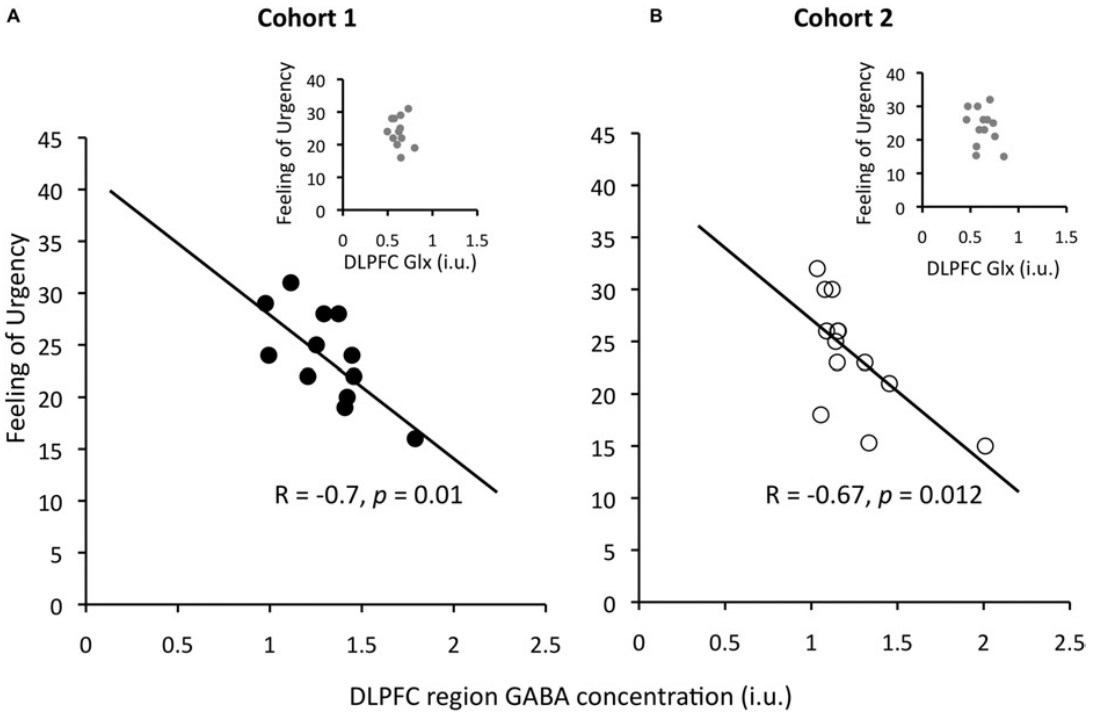


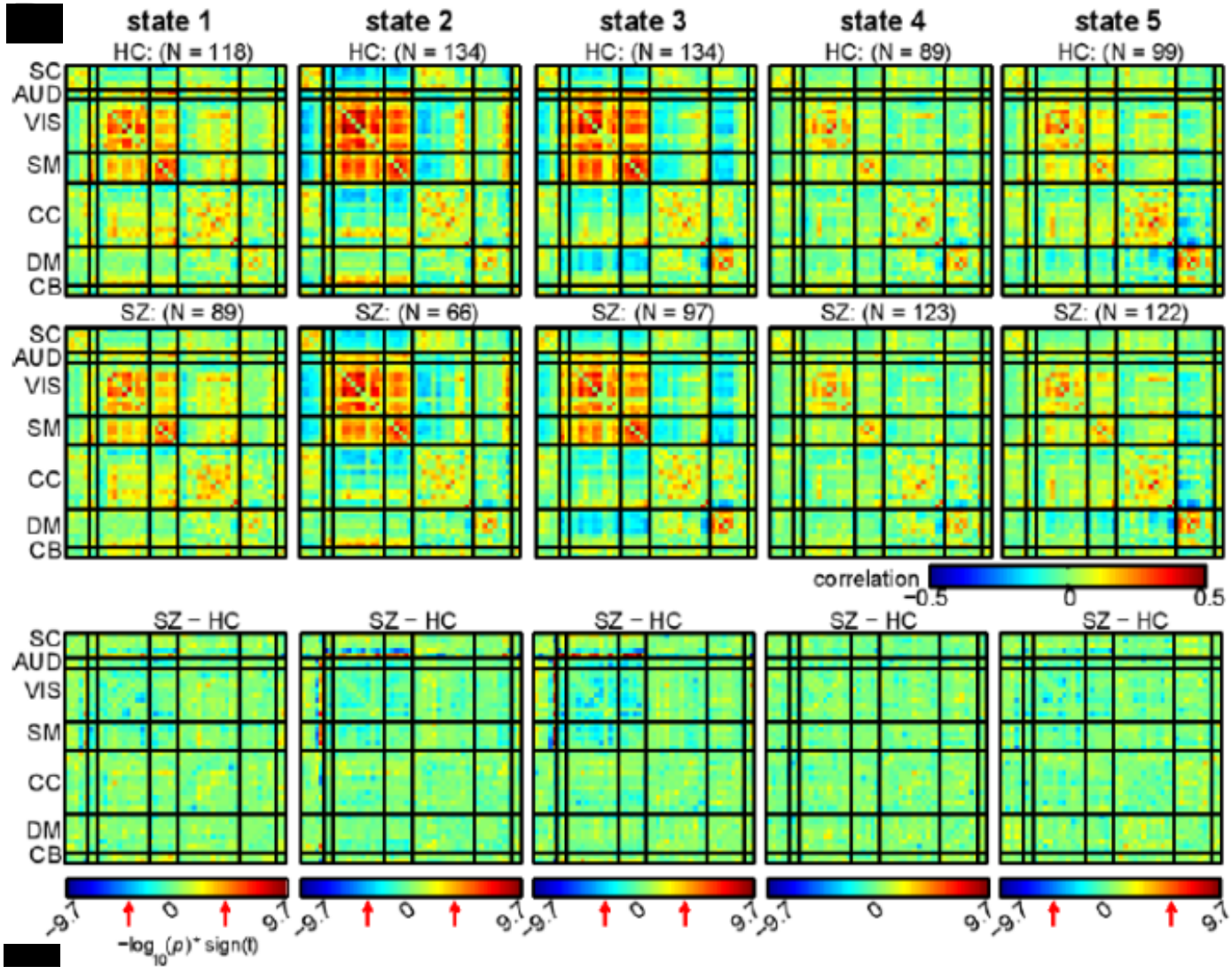
Dorsolateral Prefrontal γ-Aminobutyric Acid in Men Predicts Individual Differences in Rash Impulsivity

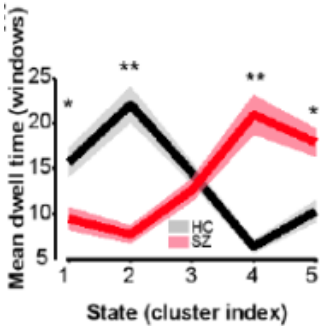
Frederic Boy, C. John Evans, Richard A.E. Edden, Andrew D. Lawrence, Krish D. Singh, Masud Husain, and Petroc Sumner

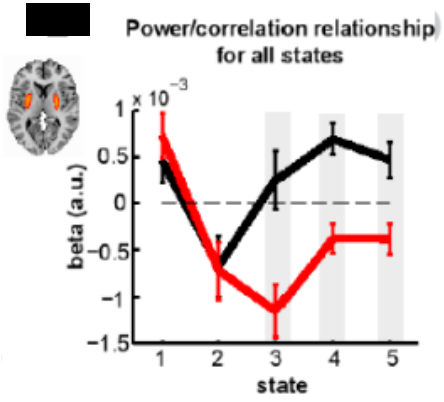
Biol Psychiatry 2011: 70: 866-872











Putamen - Sensorimotor hypo-connectivity

E. Damaraju, J. Turner, A. Preda, T. Van Erp, D. Mathalon, J. M. Ford, S. Potkin, and V. D. Calhoun, "Static and dynamic functional network connectivity during resting state in schizophrenia," in American College of Neuropsychopharmacology, Hollywood, CA, 2012.

Nature Reviews Neuroscience | AOP, published online 16 March 2011; doi:10.1038/nrn3000

PERSPECTIVES

OPINION

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

Ryota Kanai and Geraint Rees

Intelligence

Personality

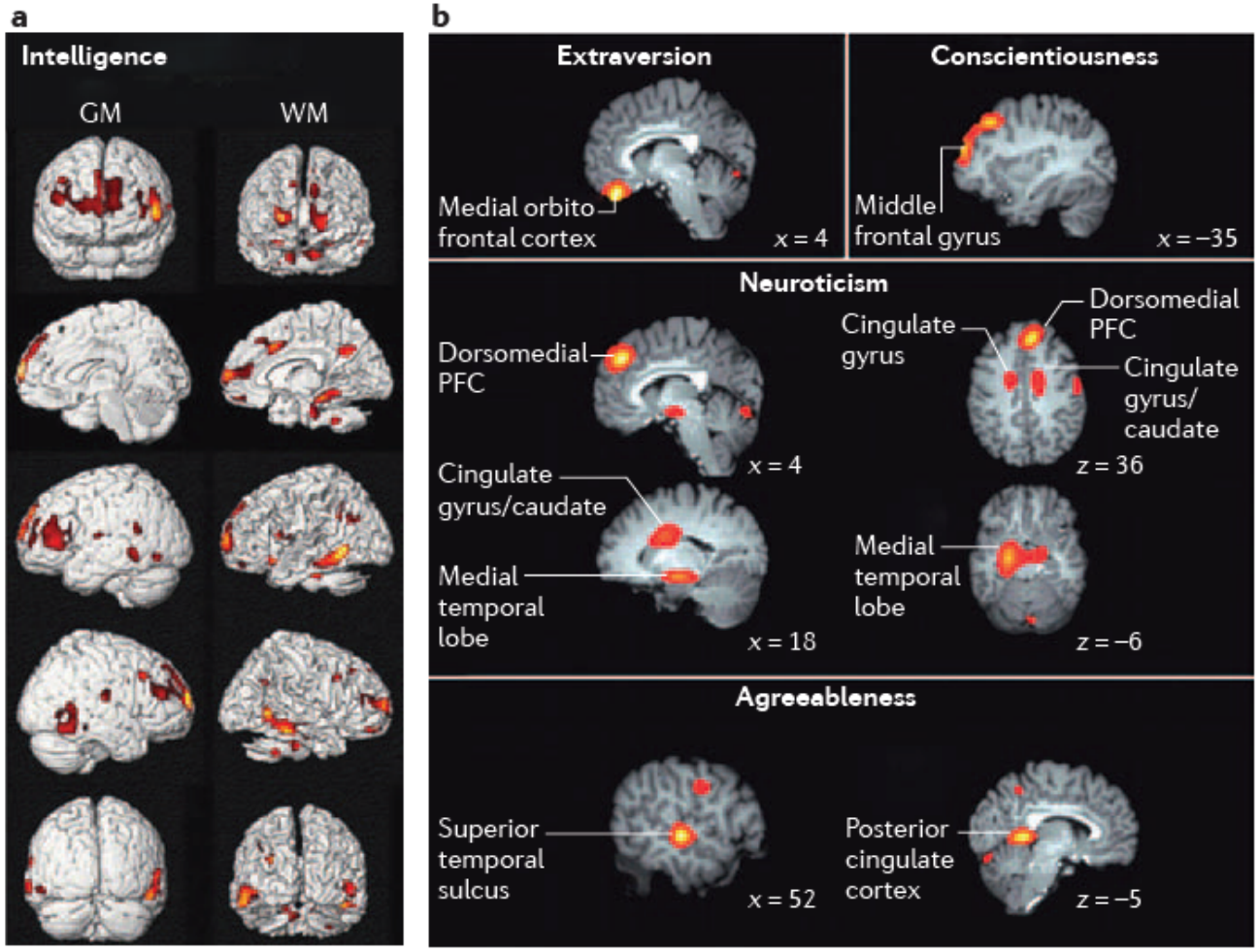


Figure 4 | **Brain structure correlates of higher cognitive functions. a** | Grey matter (GM; left panel) and white matter (WM; right panel) correlates of general intelligence. Greater grey matter and white matter volumes in specific brain areas are associated with higher intelligence. **b** | Grey matter 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

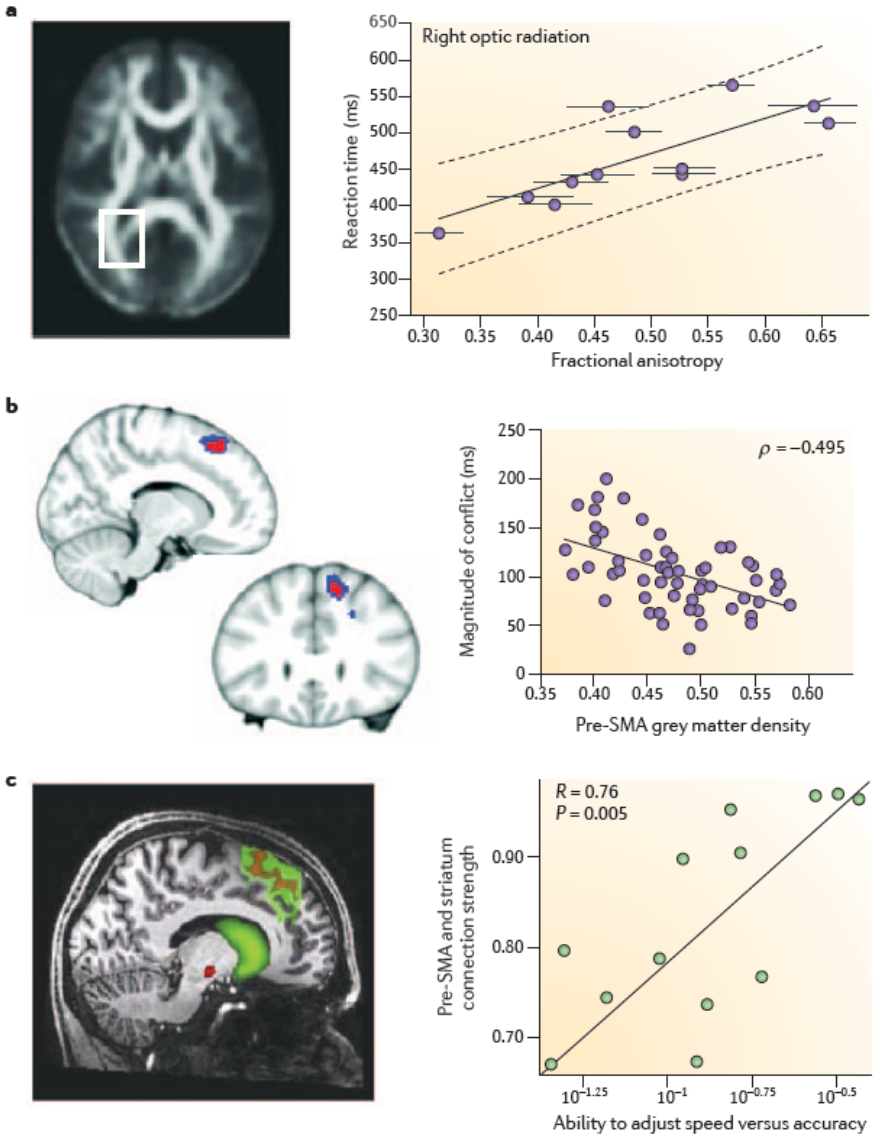


Figure 2 | **Structural bases of inter-individual differences in action and decision making. a** | The speed of reaction time in making a visual choice correlates with the fractional anisotropy (a measure of white matter integrity) of the right optic radiation (indicated by the white box). **b** | Grey 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

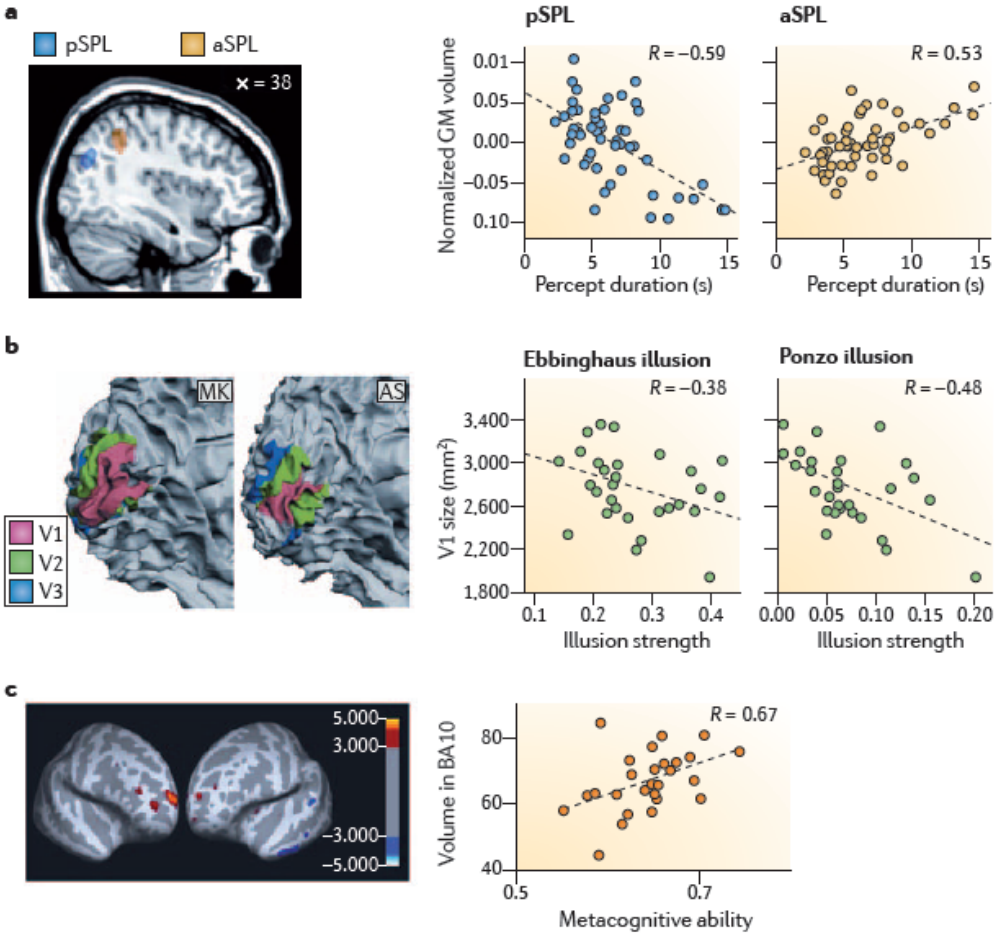


Figure 3 | **Structural bases of inter-individual differences in conscious perception. a** | Structural correlates of inter-individual differences in the duration of one percept in a perceptual rivalry task (in which a single visual input can have conflicting interpretations) (left panel). A larger posterior 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.

Current Procedural Terminology (CPT) Code for fMRI issued in 2007

Cogn Behav Neurol. 2007 Sep;20(3):141-4.

Clinical functional magnetic resonance imaging.

Hart J Jr[1], Rao SM, Nuwer M.

Author information

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.

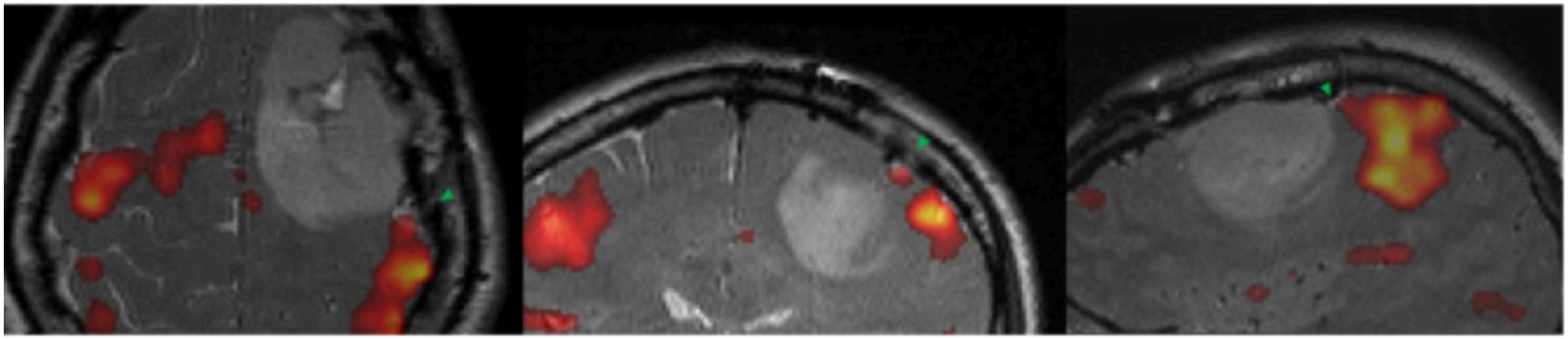
DESIGN: Description of CPT codes.

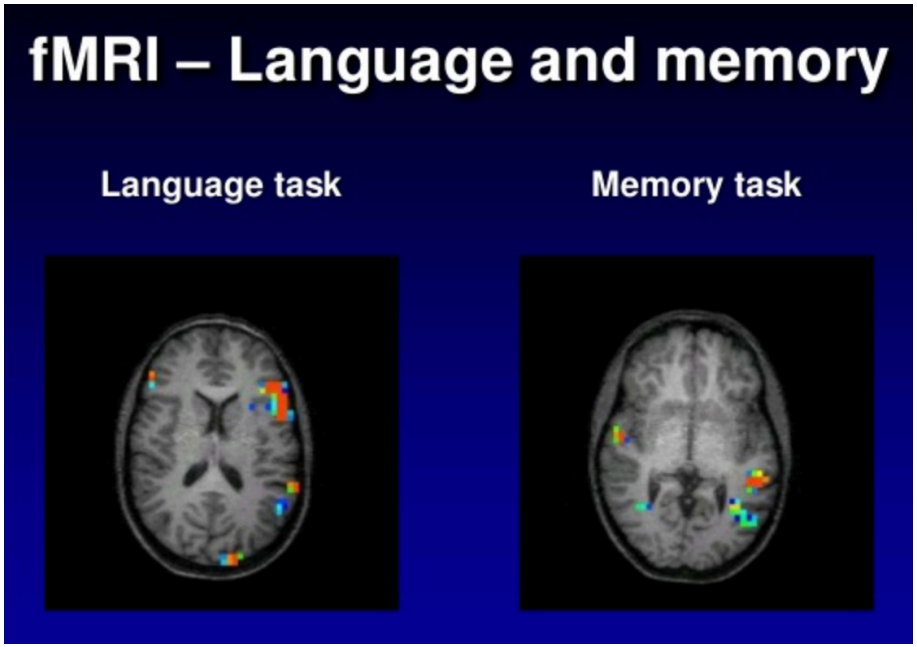
RESULTS: CPT code 70554: MRI, brain, fMRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration. CPT code 70555: MRI, brain, fMRI; requiring physician or psychologist administration. This is to be 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)





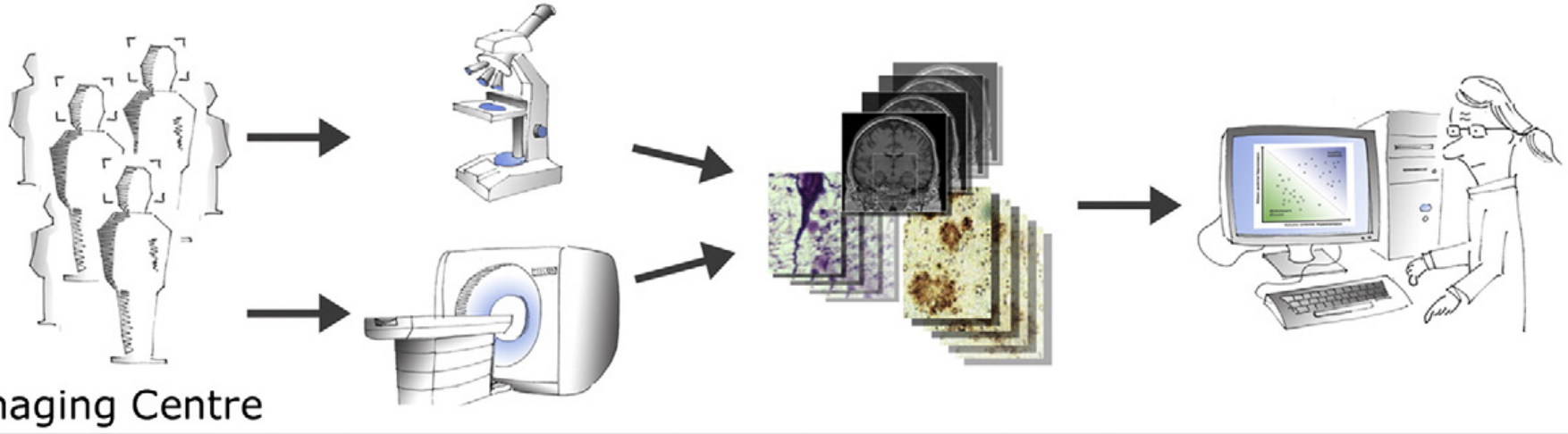
Issues:

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



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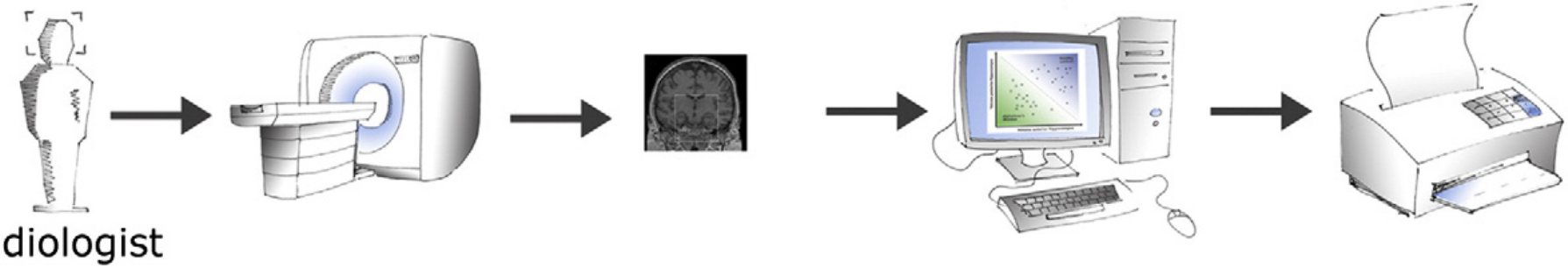
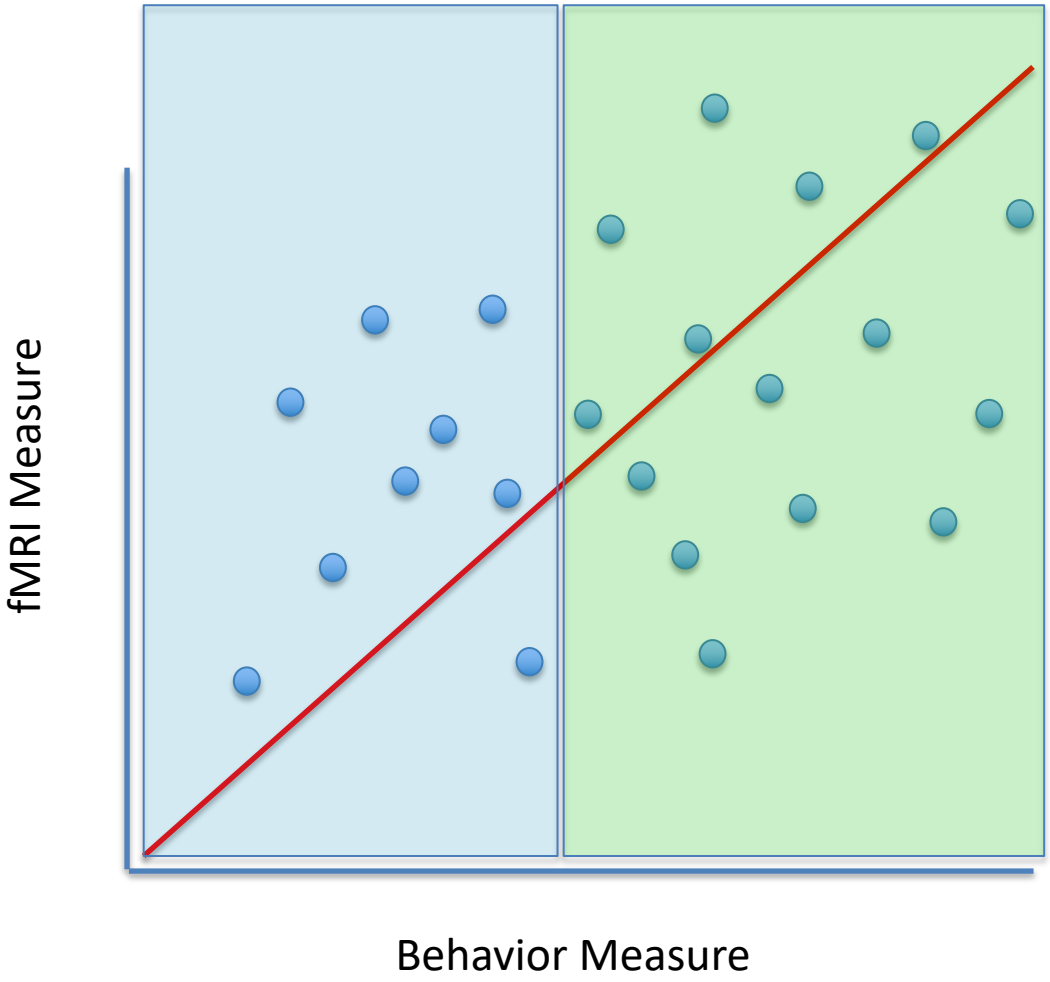
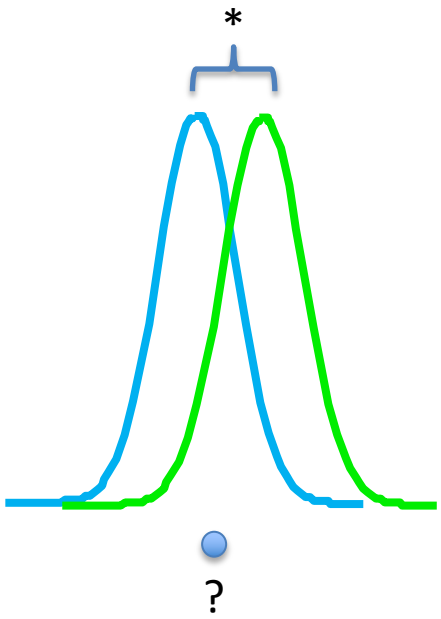


Radiologist

The challenge of going from group studies to individual assessment

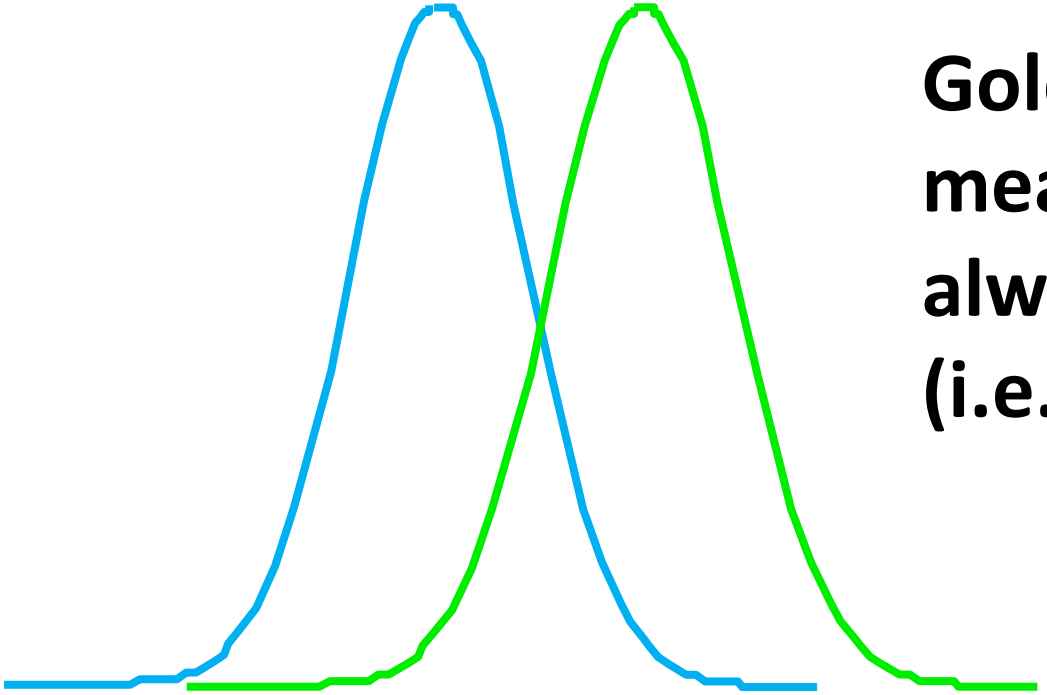




Typical fMRI Studies

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*

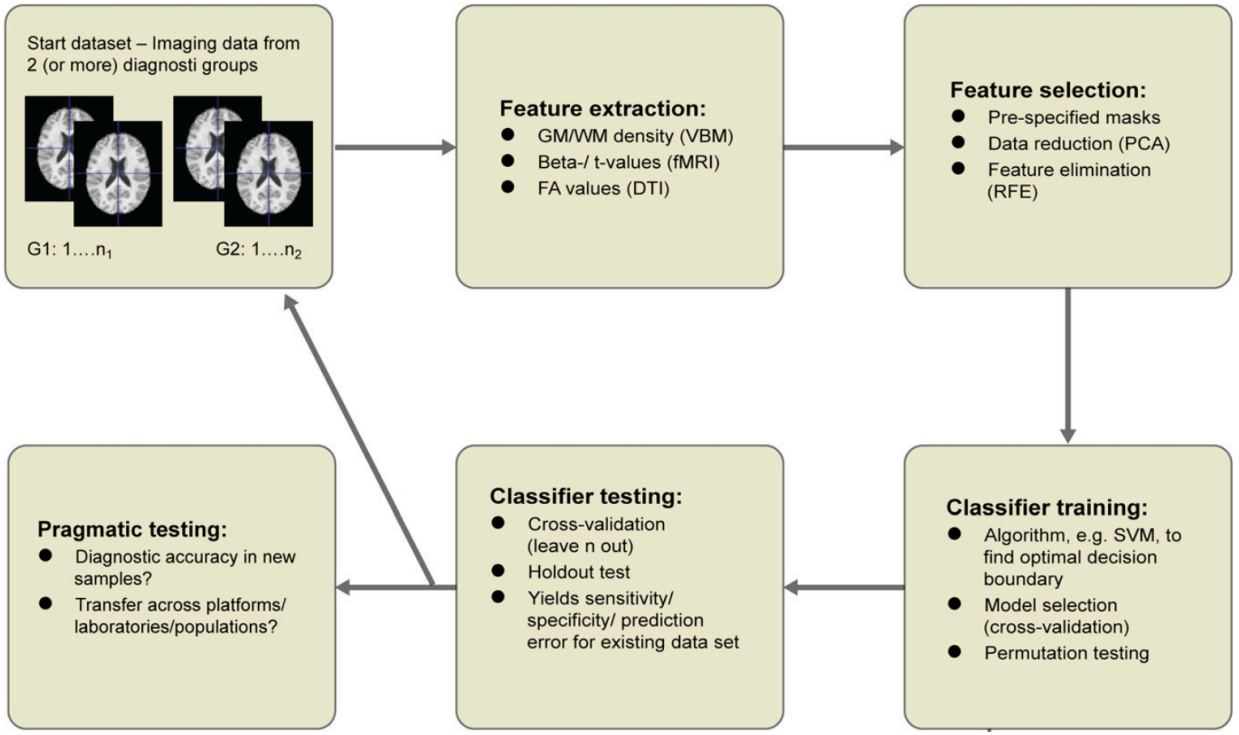
A biomarker has been defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

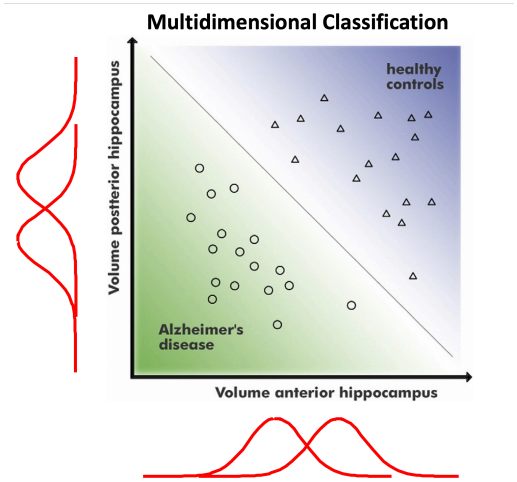
Cell PRESS

Neuron
Review

The Challenges and Promise of Neuroimaging in Psychiatry

David E.J. Linden[1,*]
[1]MRC 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) diagnosti groups
G1: 1....n_1
G2: 1....n_2
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 training:
Algorithm, e.g. SVM, to find optimal decision boundary
Model selection (cross-validation)
Permutation testing
Classifier testing:
Cross-validation (leave n out)
Holdout test
Yields sensitivity/ specificity/ prediction error for existing data set
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

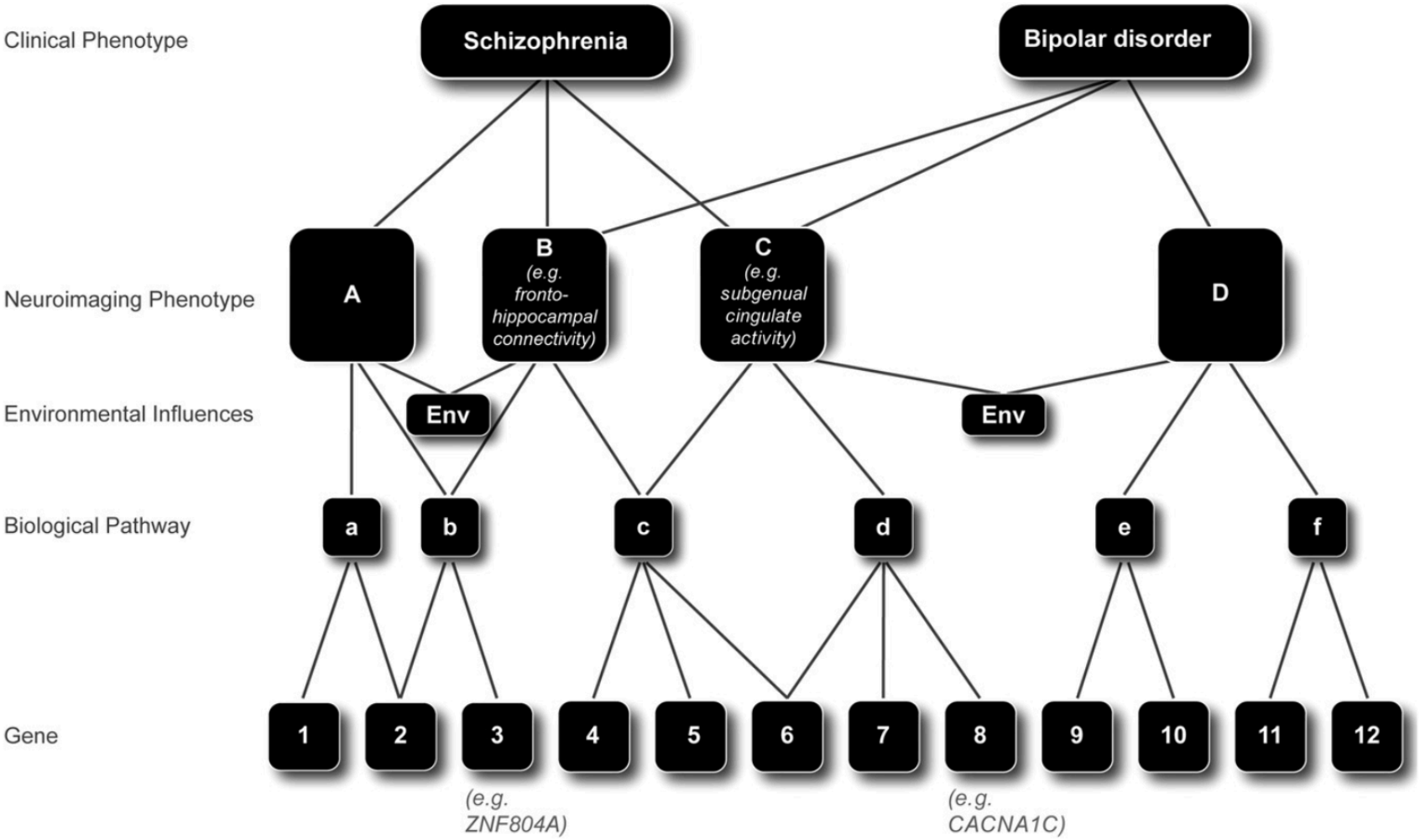
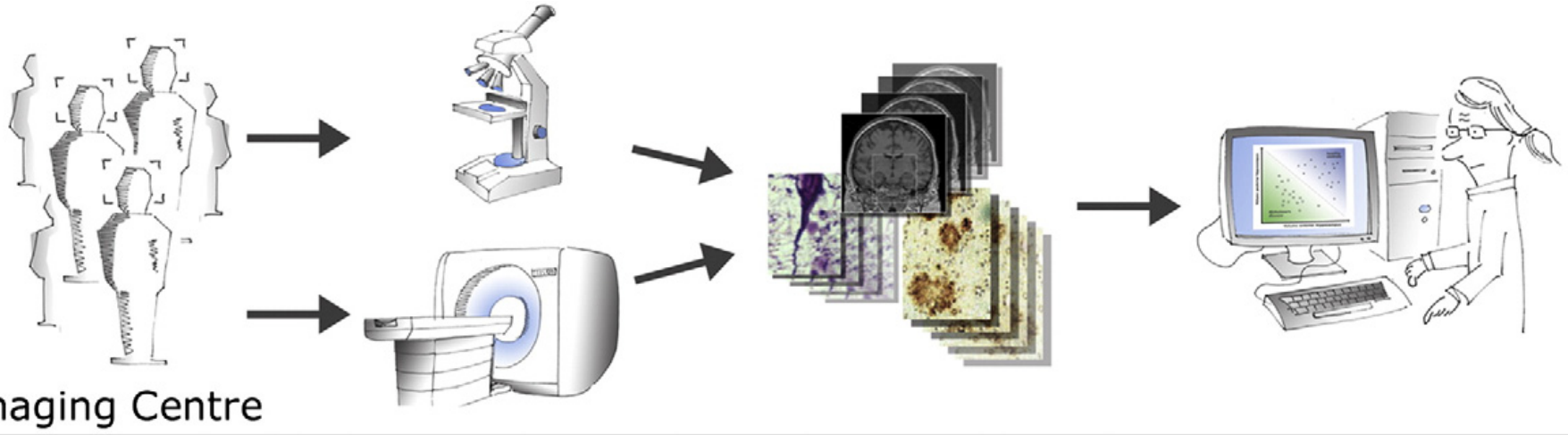


Figure 2. A Highly Simplified Model of the Genetic Pathways in Polygenic Psychiatric Diseases, Using the Examples of Schizophrenia and Bipolar Disorder

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.



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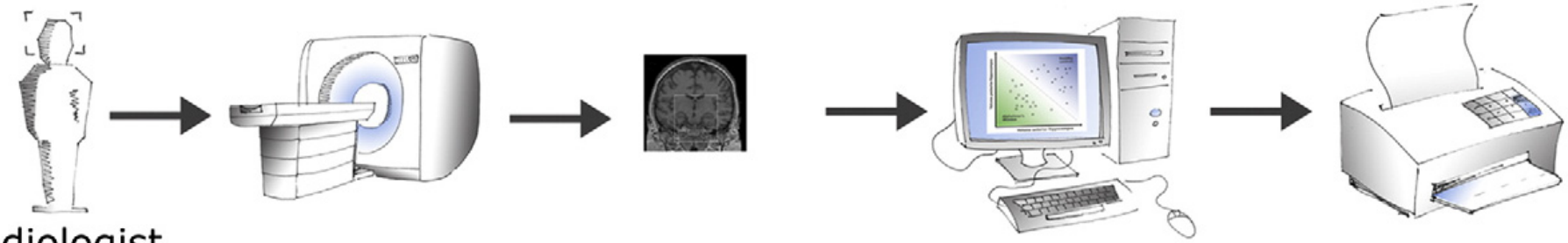


Radiologist

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

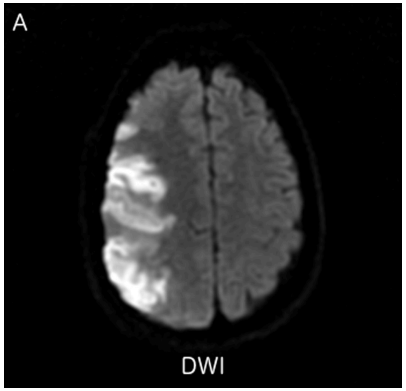
Published in final edited form as:
Top Magn Reson Imaging. 2017 April ; 26(2): 91–96. doi:10.1097/RMR.0000000000000119.

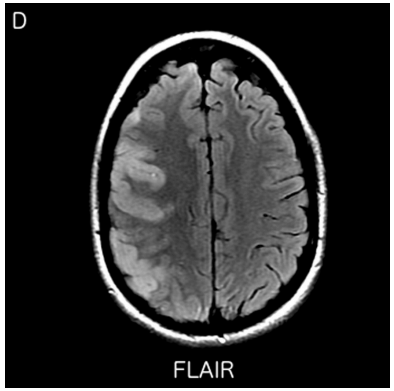
Resting State BOLD MRI for Perfusion and Ischemia

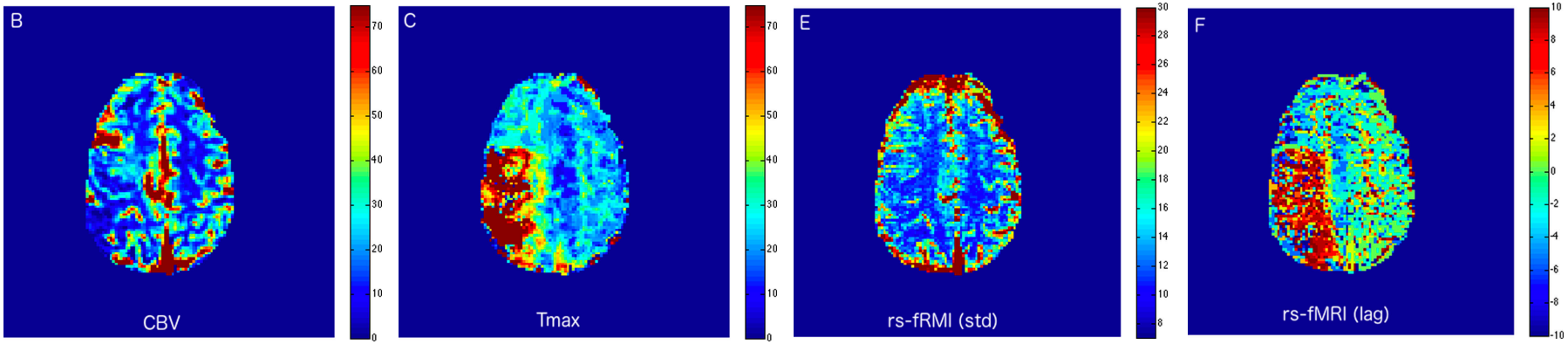
Hannes Kroll, MD[1], **Greg Zaharchuk, MD, PhD**[1], **Thomas Christen, PhD**[2], **Jeremy Heit, MD, PhD**[1], and **Michael Iv, MD**[1,#]

[1]Department of Radiology, Division of Neuroimaging & Neurointervention, Stanford University, Stanford, CA

[2]Richard M. Lucas Center for Imaging, Stanford University, Stanford, CA







Gd Gd-delay

Neurofeedback

Study	Disorder	Brain Region	Regulation Instructions	Control Condition	Outcome
Linden et al (2012) (9)	MDD	Brain areas active while viewing positive pictures	Increase activity	Mental rehearsal outside of the scanner	Decreased depressive symptoms
Young et al (2014) (10)	MDD	Amygdala	Increase activity	Alternate region of interest	Decreased state anxiety and increased state happiness
Young et al (2017) (11)	MDD	Amygdala	Increase activity	Alternate region of interest	Decreased depressive symptoms
Hamilton et al (2016) (12)	MDD	Salience network	Decrease activity	Yoked sham	Decreased emotional response to negative scenes and self-descriptive adjectives
Mehler et al (2018) (13)	MDD	Brain areas active while viewing positive pictures	Increase activity	Alternate region of interest	Decreased depressive symptoms in both groups
Gerin et al (2016) (24)	PTSD	Amygdala	Decrease activity	None	Decreased symptoms
Nicholson et al (2017) (25)	PTSD	Amygdala	Decrease activity	None	Decreased dissociative symptoms
Zotev et al (2018) (26)	PTSD	Amygdala	Increase activity	Alternate region of interest	Decreased symptoms in both groups
Zweerings et al (2018) (27)	PTSD	ACC	Decrease activity	None	Decreased intrusion and avoidance scores, increased positive affect
Ruiz et al (2013) (16)	Schizophrenia	Insula	Increase activity	None	Increased recognition of disgust facial expressions
Cordes et al (2015) (17)	Schizophrenia	ACC	Increase activity	None	No behavioral/clinical measure
Dyck et al (2016) (18)	Schizophrenia	ACC	Increase activity	None	Reduced auditory verbal hallucinations, increased positive mood
Orlov (2018) (19)	Schizophrenia	STG	Decrease activity	None	Reduced auditory verbal hallucinations
Li et al (2013) (20)	Addiction	ACC, mPFC	Decrease ACC, Increase mPFC	None	Reduced subjective craving to smoke
Hanlon et al (2013) (3)	Addiction	ACC, mPFC	Decrease ACC, Increase mPFC	None	No behavioral/clinical measure
Karch et al (2015) (21)	Addiction	Prefrontal areas active when viewing pictures of alcohol	Decrease activity	Yoked sham	Decreased ratings of craving
Buyukturkoglu et al (2015) (28)	OCD/Anxiety	Insula	Decrease activity	None	Decreased negative valence and disgust ratings for symptom-provoking images
Scheinost et al (2013) (14)	OCD/Anxiety	Orbitofrontal Cortex	Bidirectional	Yoked sham	Decreased contamination anxiety
Zilverstand (2015) (15)	Spider Phobia/Anxiety	Insula and DLPFC	Increase DLPFC Decrease insula	Mental rehearsal inside of the scanner	Decreased ratings of spider fear
Sitaram et al (2014) (29)	Personality Disorder - Psychopathy	Insula	Increase activity	None	No behavioral/clinical measure
Paret et al (2016) (30)	Personality Disorder - Borderline	Amygdala	Decrease activity	None	Decreased dissociative experiences
Alegria et al (2017) (23)	ADHD	Inferior prefrontal gyrus	Increase activity	Alternate region of interest	ADHD symptom reduction, improved sustained attention
Zilverstand (2017) (22)	ADHD	ACC	Increase activity	Mental rehearsal inside of the scanner	Improved cognitive functioning

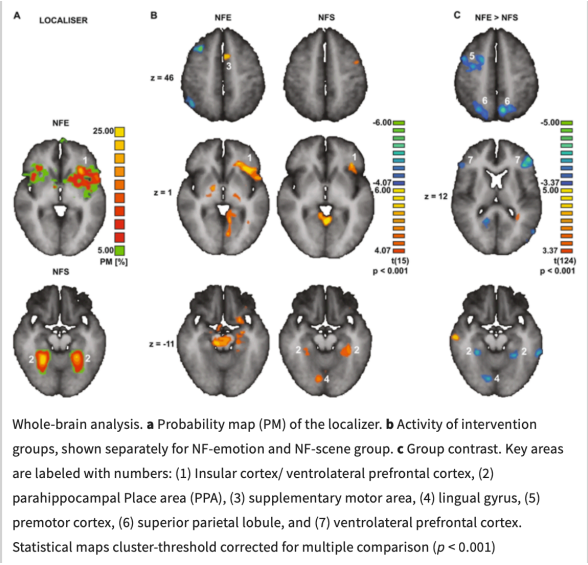
https://www.upmcphysicianresources.com/-/media/physicianresources/pdf-publications/psychiatry/psychiatry_synergies_winter-2019_final.pdf?la=en&hash=3DA0A42CFA9EF2327AFEAB1FDFCFBBCA1C689E62

Neurofeedback for Depression

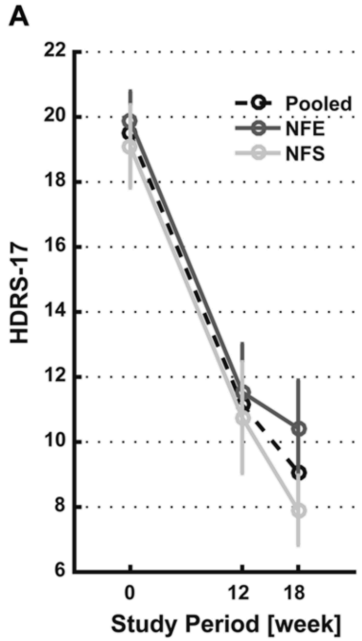
Targeting the affective brain—a randomized controlled trial of real-time fMRI neurofeedback in patients with depression

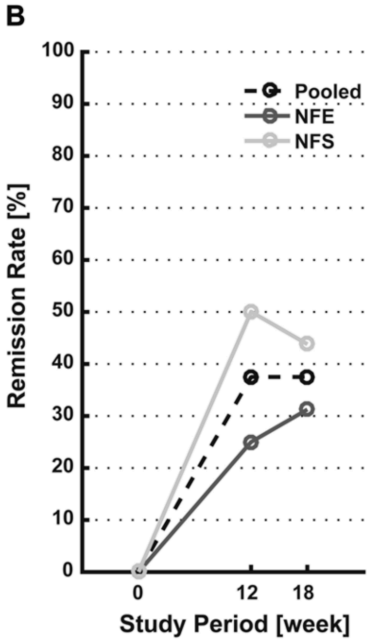
David M. A. Mehler, Moses O. Sokunbi, Isabelle Habes, Kali Barawi, Leena Subramanian, Maxence Range, John Evans, Kerenza Hood, Michael Lührs, Paul Keedwell, Rainer Goebel & David E. J. Linden

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

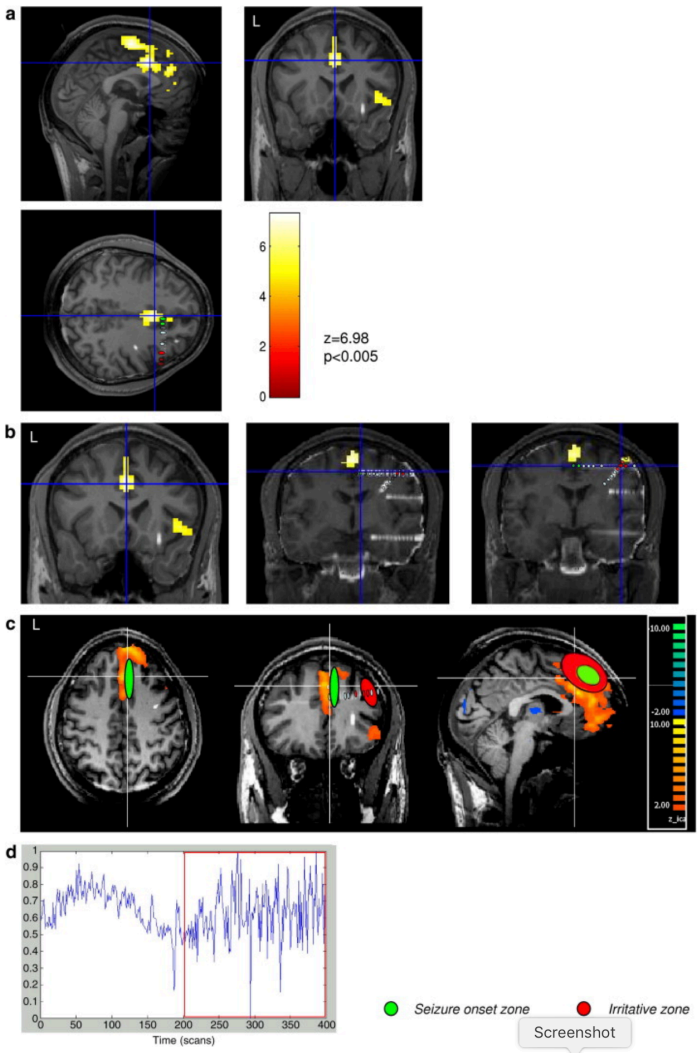


Whole-brain analysis. **a** Probability map (PM) of the localizer. **b** Activity of intervention groups, shown separately for NF-emotion and NF-scene group. **c** Group contrast. Key areas are labeled with numbers: (1) Insular cortex/ ventrolateral prefrontal cortex, (2) parahippocampal Place area (PPA), (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 ($p < 0.001$)



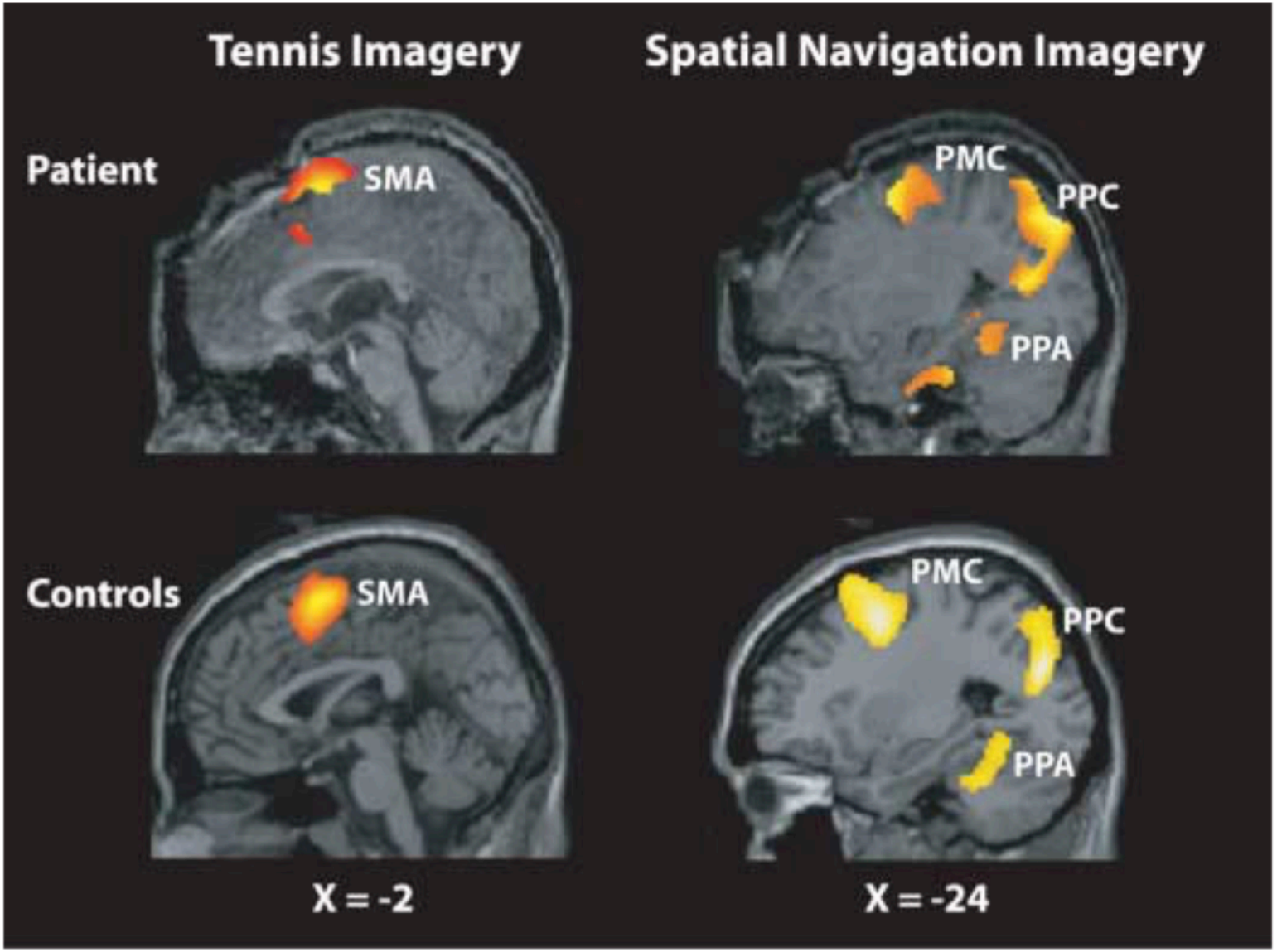


Epilepsy Localization



Thornton, R. C., et al. NeuroImage 53 (1), pp. 196-205 (2010).

Communicating with Locked In Patients



Owen, A. M. et al, Science 313, p. 1402 (2006)

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**