FOCUS ON HUMAN BRAIN MAPPING REVIEW

nature neuroscience

Building better biomarkers: brain models in translational neuroimaging

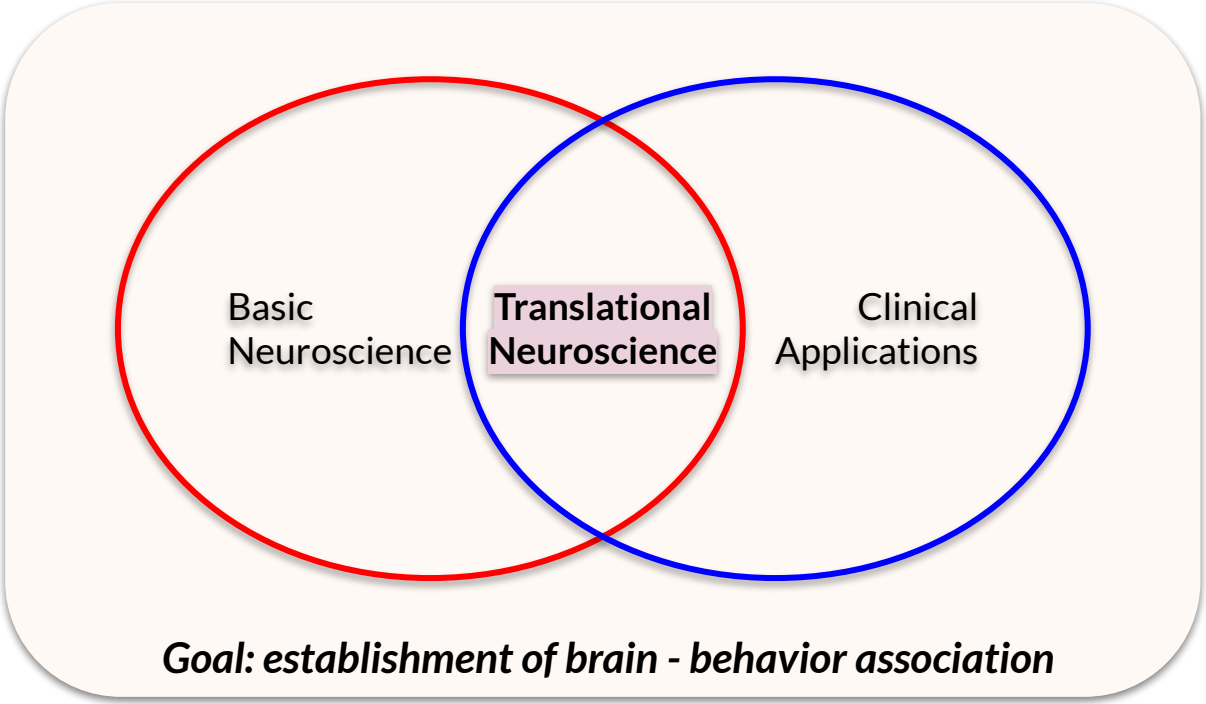
Choong-Wan Woo[1–4], Luke J Chang[5], Martin A Lindquist[6] & Tor D Wager[3,4]

2020.06.01

Computational Clinical Science Lab

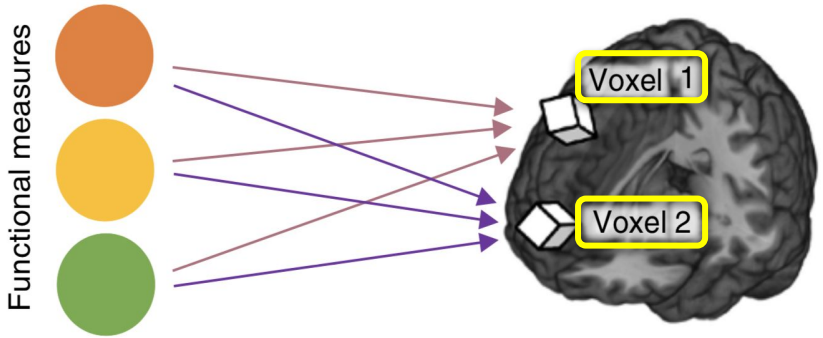
Jihyun Hur

Translational Neuroscience



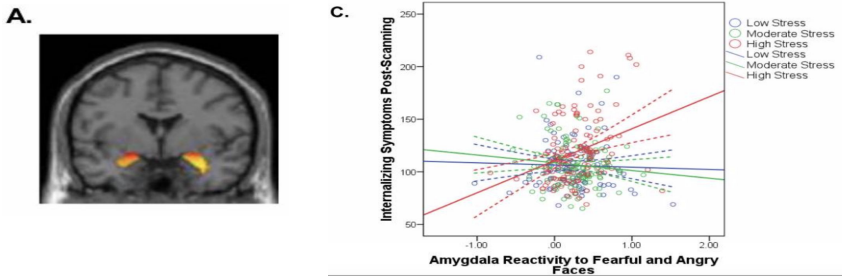
Early: Traditional Brain Mapping

Traditional Brain Mapping



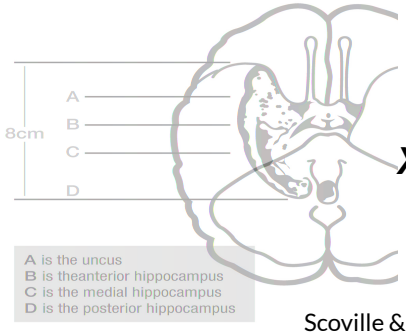
Woo et al. (2017)

Traditional Study Example :



Swartz et al. (2015)

Foundation I: Lesion Studies



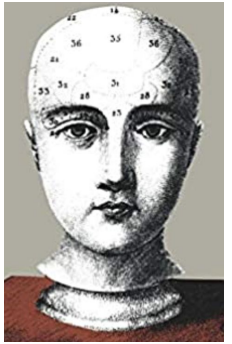
X 10 cases ***=> Amnesia***

Scoville & Milner (1957)

Foundation II: Theory of Modularity

"Faculty Psychology … the mental causation of behavior typically involves the simultaneous activity of a variety of distinct psychological mechanisms"

Fodor (1983)



Problems of Traditional Brain Mapping

1. *Central problem: the main goal of traditional brain mapping!*

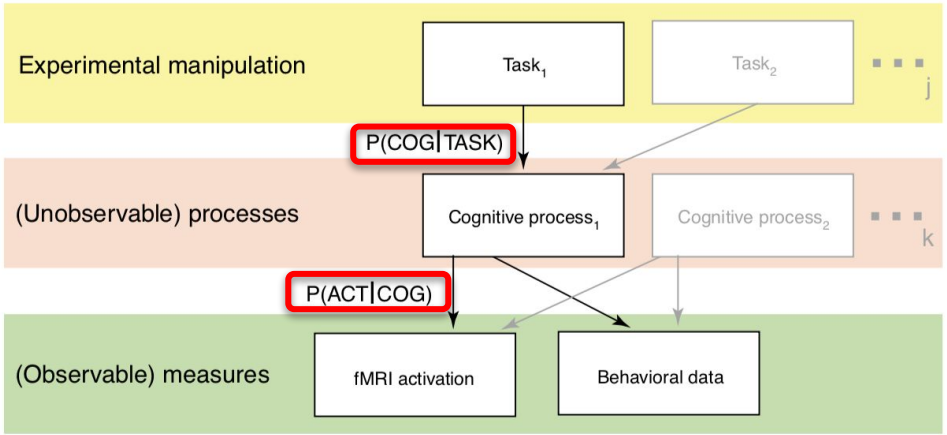
   (= to understand localized brain function)

2. *A voxel = ~5.5 million neurons*

3. *Reverse Inference*

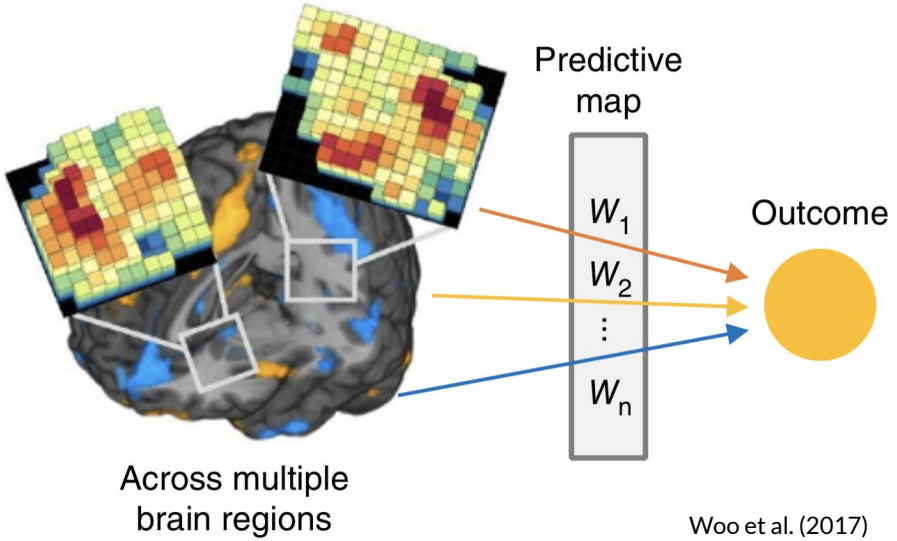
   P(COG|ACT) != P(ACT|COG)

$$P(COG_X|ACT_Z) = \frac{P(ACT_Z|COG_X)P(COG_X)}{P(ACT_Z|COG_X)P(COG_X) + P(ACT_Z|\sim COG_X)P(\sim COG_X)}$$

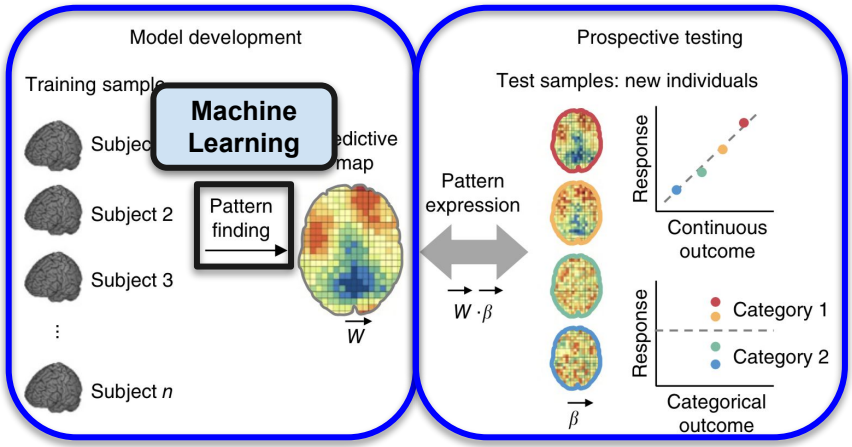


Poldrack (2006)

Now: Predictive Modeling



Woo et al. (2017)



Woo et al. (2017)

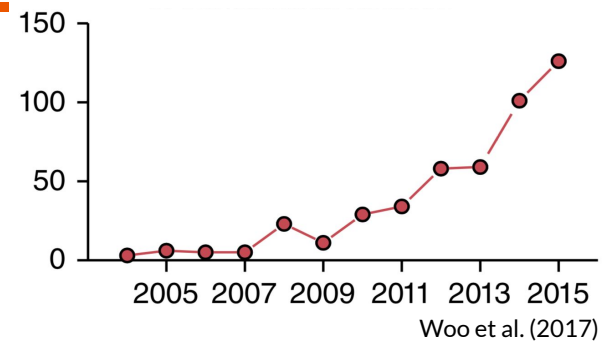
*Assumption: "many features of neurologic and psychiatric disorders are **encoded in distributed neural systems**"*

Benefits:

- *Direction of Inference*
- *Integrate brain regions and make a single best guess*
- *Cross-validation*
- *Information from multiple spatial scales*

Current State of Clinical Predictive Modeling

Number of Publications



Woo et al. (2017)

Research Topics

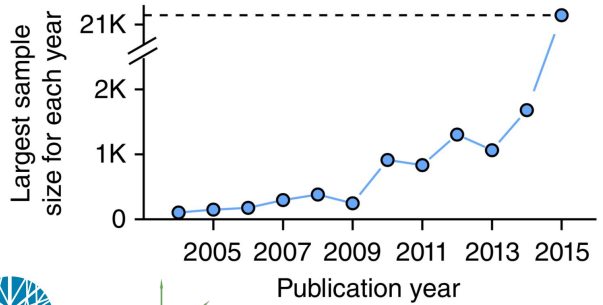
Past:

- *Alzheimer's disease (AD)*

Now:

- *Parkinson's disease*
- *Pain disorders*
- *Psychosis*
- *Depression ...*

Sample Size



Research Goals

1. ***Patients vs. Health***
2. ***Difficult classification***

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

ABIDE
Autism Brain Imaging Data Exchange

ADNI
Alzheimer's Disease Neuroimaging Initiative

OpenfMRI

NITRC

OpenNEURO

1) Risk Assessment, Conversion Prediction and Early Detection

Goals

: who is **at risk**?
: who will **convert into a disease state**?
: who is **at the early stage of a disease**?

SPARE-AD ↑, More AD-like

Model I: Spatial Pattern of Abnormality for Recognition of Early AD (SPARE-AD)

Structural MRI ⇨ Regional Volumetric Maps ⇨ High-Dimensional Classification ⇨ SPARE-AD

Training: ADNI — Alzheimer's Disease Neuroimaging Initiative

Testing: BLSA — Baltimore Longitudinal Study of Aging

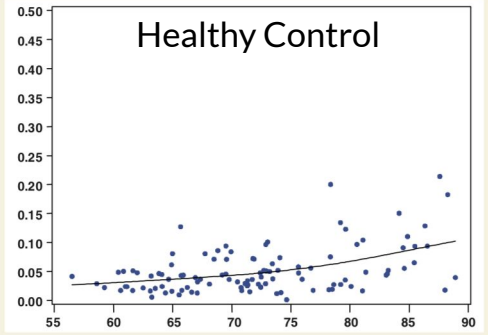


Figure 4 Rate of SPARE-AD change as a function of average age during follow-up period, for the 109 CN individuals.

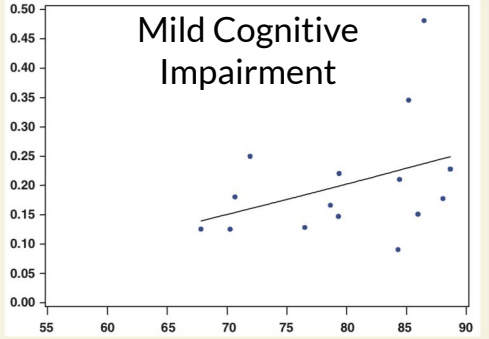
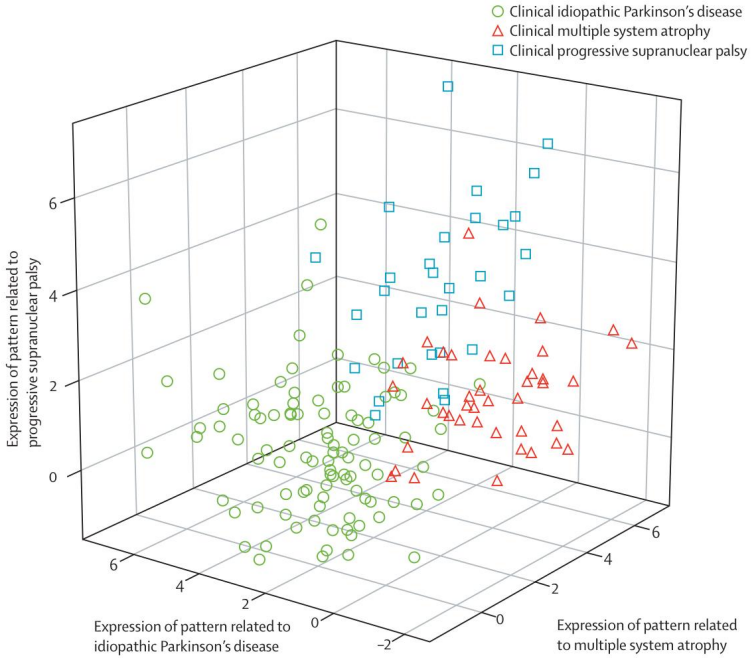


Figure 5 SPARE-AD annual change rates plotted against age for all MCI individuals.

Davatzikos et al. (2009)

2) Differential Diagnosis[1] & Subtyping[2]

Study I: Parkinson's disease[1]



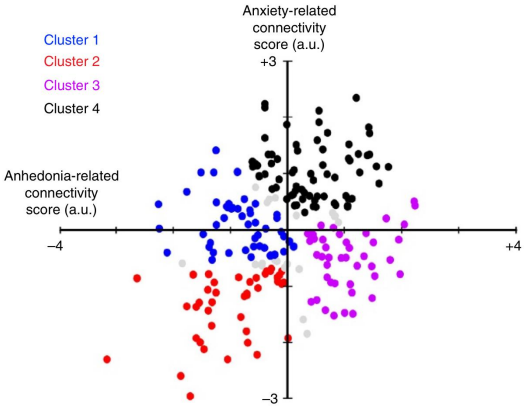
3D plot of FDG-PET pattern expression

	All patients
Idiopathic Parkinson's disease	
Sensitivity	84% (81/96)
Specificity	97% (69/71)
Positive predictive value	98% (81/83)
Negative predictive value	82% (69/84)
Atypical parkinsonian syndrome	
Sensitivity	82% (58/71)
Specificity	98% (94/96)
Positive predictive value	97% (58/60)
Negative predictive value	88% (94/107)
Multiple system atrophy	
Sensitivity	85% (29/34)
Specificity	96% (25/26)
Positive predictive value	97% (29/30)
Negative predictive value	83% (25/30)
Progressive supranuclear palsy	
Sensitivity	88% (21/24)
Specificity	94% (34/36)
Positive predictive value	91% (21/23)
Negative predictive value	92% (34/37)

Data are % (calculation).

Tang et al. (2010)

Study II: Depression[2]



Drysdale et al. (2017)

3) Predicting Treatment Outcome

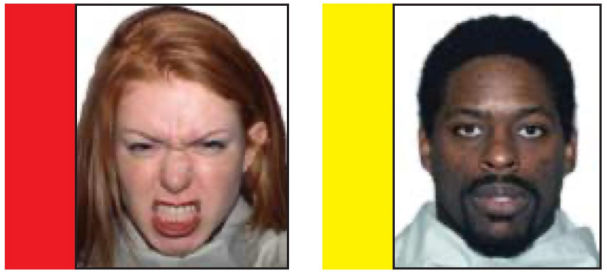
Goal *To **customize treatment** based on brain measures **(= precision medicine)***

Research

- *Mostly focused on **depression and anxiety disorders***
- *Mostly predicted **cognitive behavioral therapy (CBT)** response*

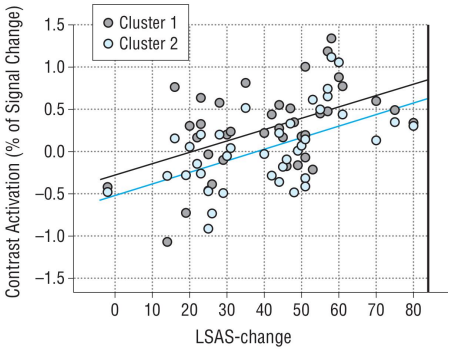
Study I: Social Anxiety Disorders with CBT

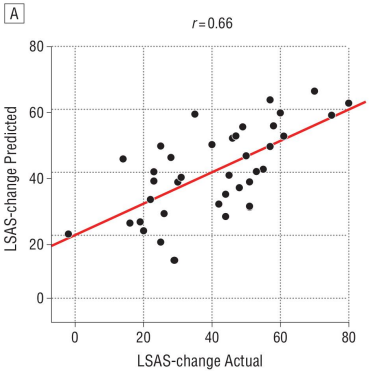
Functional MRI



Angry face Neutral face

LSAS: Liebowitz Social Anxiety Scale





Doehrmann et al. (2013)

Four Characteristics of Desirable Model

1. Diagnostic Value
2. Neuroscientific Validity
3. Deployability and Scalability
4. Generalizability

Diagnostic Value

Predicted class \ True class	Positive	Negative	Measures
Positive	True positive *TP*	False positive *FP*	Positive predictive value (PPV) $\frac{TP}{TP+FP}$
Negative	False negative *FN*	True negative *TN*	Negative predictive value (NPV) $\frac{TN}{FN+TN}$
Measures	Sensitivity $\frac{TP}{TP+FN}$	Specificity $\frac{TN}{FP+TN}$	Accuracy $\frac{TP+TN}{TP+FP+FN+TN}$

Vihinen (2012)

Sensitivity — How robustly the measure responds when the outcome is present

Specificity — Whether the measure responds only in the presence of the target outcome

C.f. Predictive Value and Base Rate (Prevalence)

A

$$\text{PPV}_{\text{P (Chronic pain | Positive Biomarker)}} = \frac{\text{SENSITIVITY}_{\text{P (Positive Biomarker | Chronic pain)}} \times \text{PREVALENCE}_{\text{P (Chronic Pain)}}}{\text{PROBABILITY OF POSITIVE BIOMARKER}_{\text{P (Positive Biomarker)}}}$$

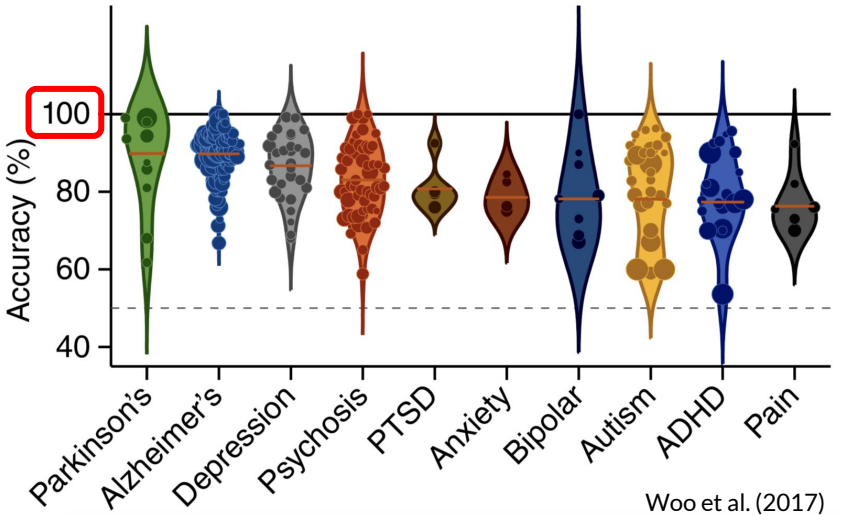
B

$$\text{NPV}_{\text{P (No pain | Negative Biomarker)}} = \frac{\text{SPECIFICITY}_{\text{P (Negative Biomarker | No pain)}} \times \text{1 - PREVALENCE}_{\text{P (No pain)}}}{\text{PROBABILITY OF NEGATIVE BIOMARKER}_{\text{P (Negative Biomarker)}}}$$

Robinson et al. (2016)

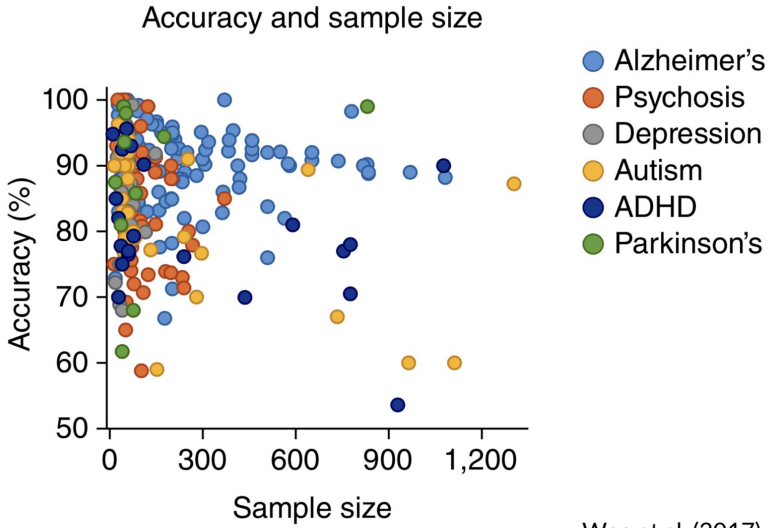
Diagnostic Value - Accuracy Issues

1. Biases in Accuracy



Woo et al. (2017)

2. Variability in Accuracy based on Sample Size



Woo et al. (2017)

Why Accuracy Bias, and How to Reduce it

Accuracy is inflated because of:

1. **Dependence of test datasets**
2. **Overfitting**

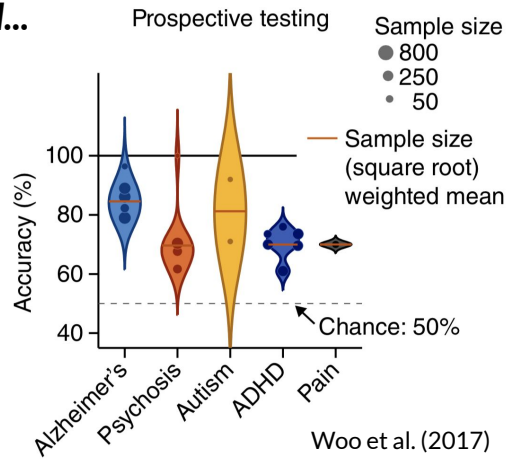
Solutions:

➡️ **Testing on an independent sample**

➡️ **Testing only one model**

Currently in the field...

Only ~9%!



Woo et al. (2017)

➡️ ***Reserve hold-out test data!***

Neuroscientific Validity

Plausibility

- fMRI signal in the ventricles?
  → implausible

Interpretability

- Machine Learning algorithms
  → too many features
  → LASSO / ridge-regularization

Systematic Approach

1. Summarize and visualize the model in **human-readable way**
2. **Evaluate the neuroscientific plausibility** of the predictive weights
3. Examine **confounding factors**

Deployability and Scalability, Generalizability

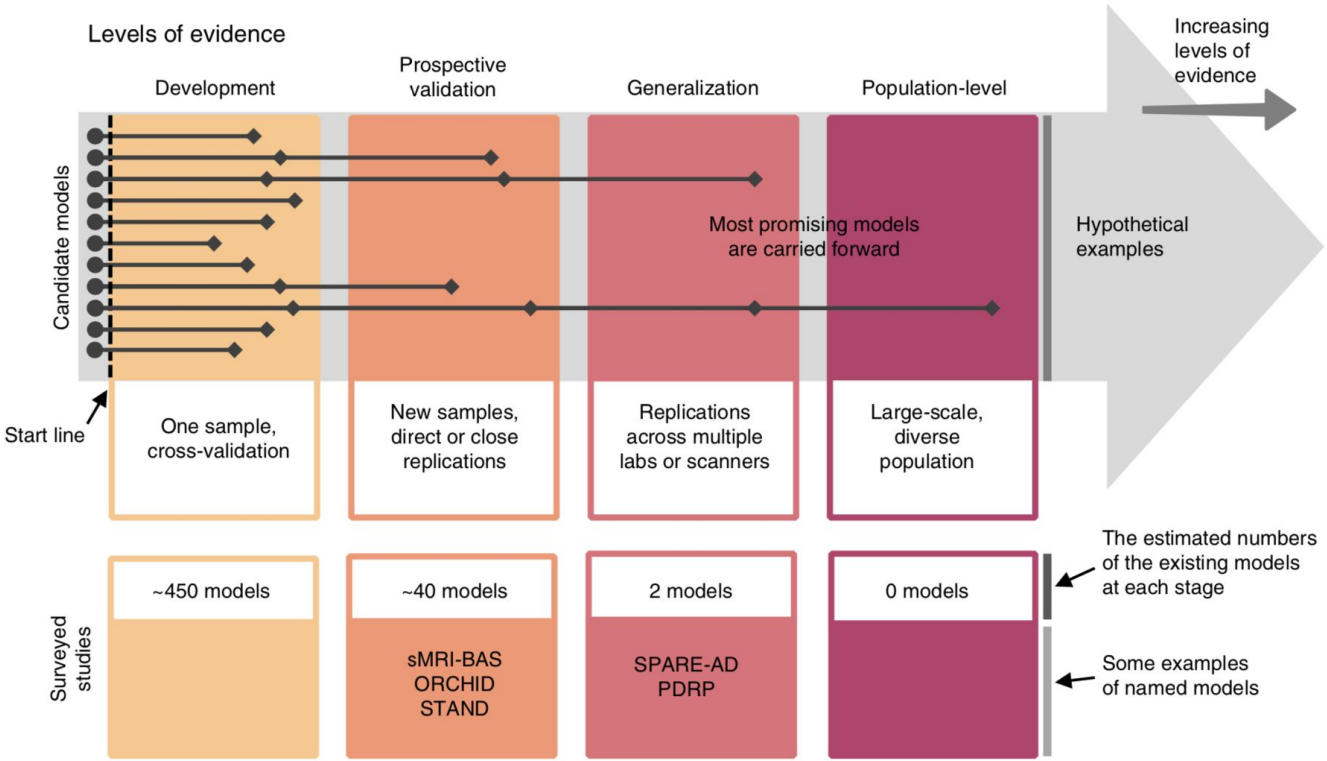
- ***Deployability and Scalability:***
  - *Easily applicable to new individuals and shareable across labs*
  - *Standardized data formats and software (= named models like SPARE-AD)*

- ***Generalizability:***
  - *To new individuals*
  - *Across labs, scanners, and minor variants in testing conditions*
  - *Similar results to other outcomes with the same construct (e.g. mathability)*

Ecologically valid datasets : *have samples that are representative of the broader population*

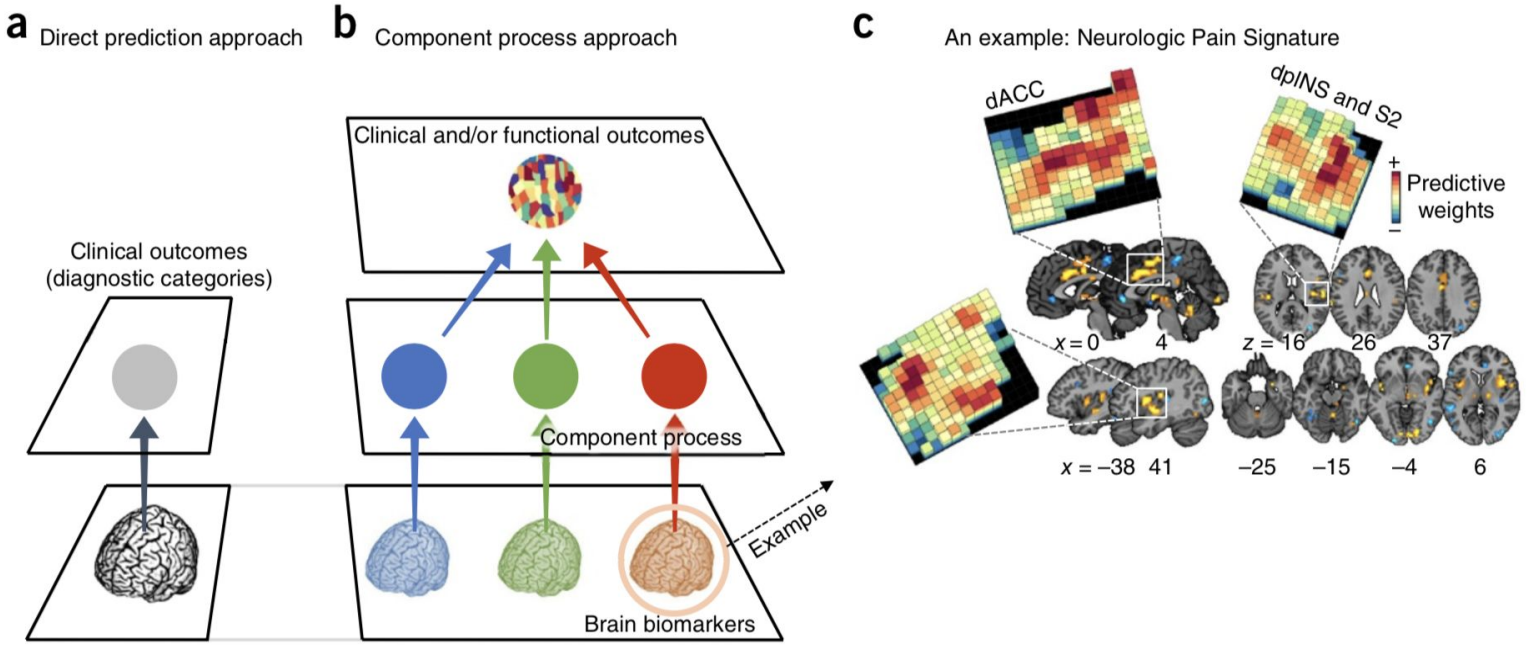
Big data approaches : *test specificity over multiple alternatives (open-process)*

Shareable Research Products



Woo et al. (2017)

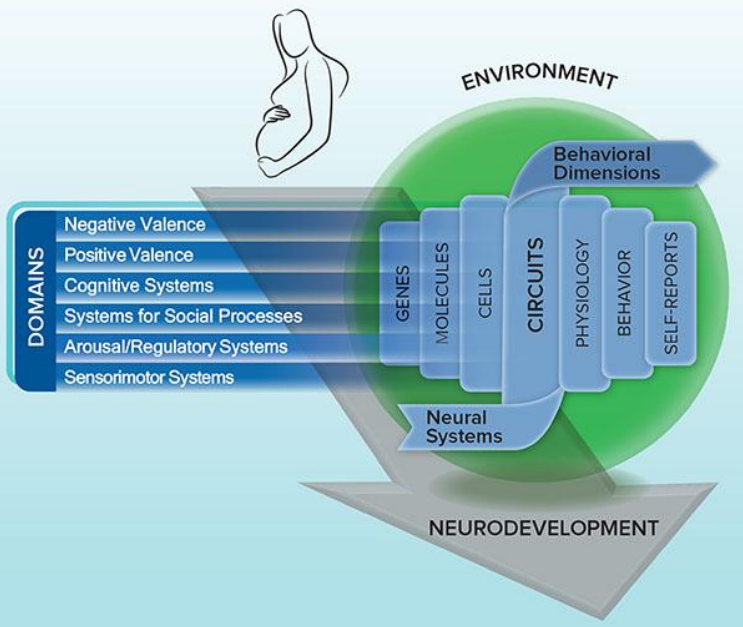
Process-based predictive models



Woo et al. (2017)

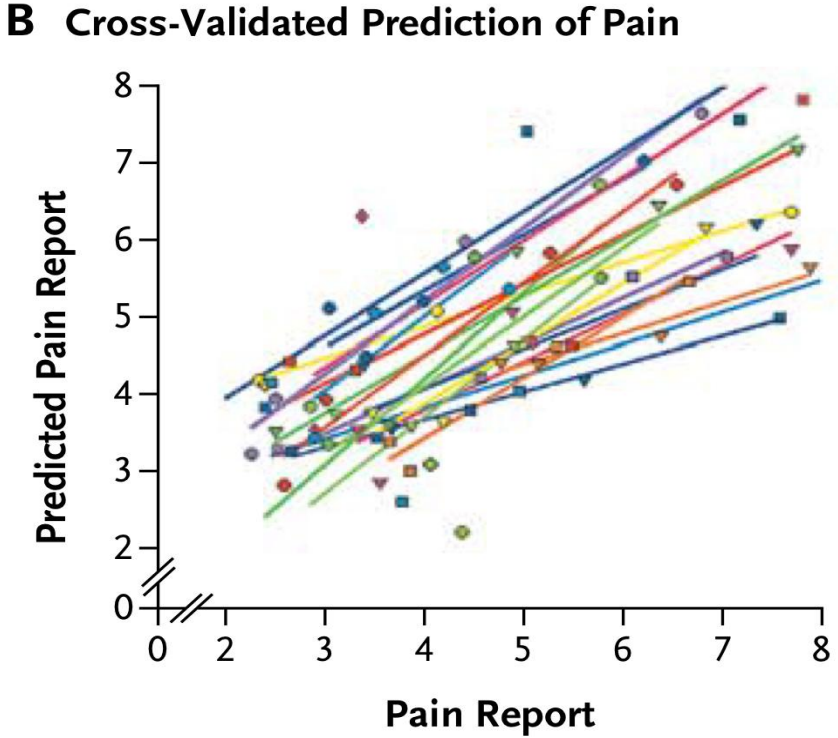
Process-based predictive models

Research Domain Criteria (RDoC)



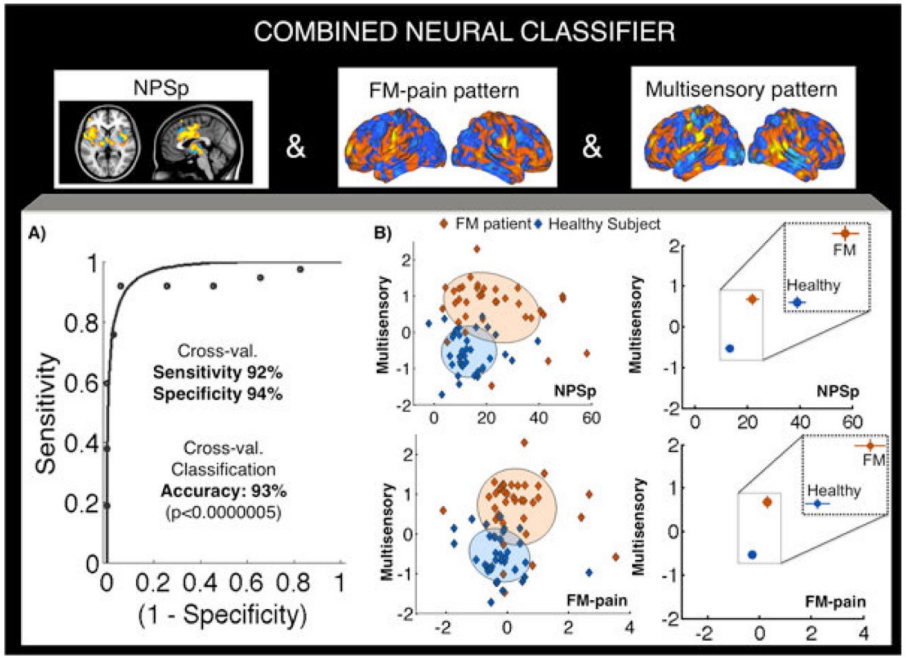
https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml

Study I: Neurologic Pain Signature



Process-based predictive models

Study II: Clinical Pain Components



Lopez-Sola et al. (2017)

Conclusion: Summary

Box 2 Recommendations for future efforts

Model development:

- Increase focus on classification and prediction problems that cannot be easily achieved with existing clinical measures. Problems include early detection, prognosis, differential diagnosis, patient stratification and predicting treatment response (**Fig. 2c**).
- Increase focus on process-based predictive models and intermediate basic processes that may map more closely onto patterns of brain activity than clinical categories themselves and may reveal patterns of dysfunction and neuropathology across disorders (**Fig. 4b**).
- Homogeneous samples can be used for discovery, but the models should eventually be tested on more ecologically valid (i.e., more heterogeneous) samples.

Model validation:

- Plan proper prospective tests with independent test data from the early stages of study design and analysis planning (**Fig. 2e**).
- Test model specificity over multiple alternative conditions (for example, differential diagnoses, multiple cognitive and affective processes).
- Demonstrate models' neuroscientific validity (see "A systematic approach to improving neuroscientific validity").

Cumulative science:

- Treat brain models as sharable research products that can be tested and annotated across different laboratories.
- Name newly developed predictive models to facilitate subsequent model-sharing and prospective testing (**Table 2**).
- Identify promising models and test them in increasingly broad and rigorous ways.

Big data approaches:

- Include multiple disease groups and task conditions in large-scale data initiatives. Important problems such as patient stratification and specificity testing can only be achieved with data that cut across multiple conditions and diagnoses.
- Establish quality-control standards and abide by established ones.
- When developing models on multisite data, carefully consider issues of variables that may be unbalanced across study sites (for example, patient/control ratios and measurement variances), and thus create confounds. Where such confounds are unavoidable, consider a strategy of developing models on one sample and then testing generalizability to other samples, rather than pooling data across sites.

“This new way of thinking about neuroimaging results integrates ideas from machine learning, big data, reproducible research and open science to bring translational goals within reach.”

Woo et al. (2017)

Thank you!

References

Swartz, J.R., Knodt, A.R., Radtke, S.R. & Hariri, A.R. A neural biomarker of psychological vulnerability to future life stress. *Neuron* **85**, 505–511 (2015).

Poldrack, R.A. Can cognitive processes be inferred from neuroimaging data? *Tren ds Cogn. Sci.* **10**, 59–63 (2006).

Wager, T.D. *et al.* An fMRI-based neurologic signature of physical pain. *N. En gl. J. Med.* **368**, 1388–1397 (2013).

Fodor, J.A. *The Modularity of Mind* (MIT Press, 1983).

Scoville, W.B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20**, 11–21 (1957).

Davatzikos, C., Xu, F., An, Y., Fan, Y. & Resnick, S.M. Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. *Brain* **132**, 2026–2035 (2009).

Tang, C.C. *et al.* Differential diagnosis of Parkinsonism: a metabolic imaging study using pattern analysis. *Lan cet Neurol.* **9**, 149–158 (2010).

Drysdale, A.T. *et al.* Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat. Med.* (2016).

Doehrmann, O. *et al.* Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. *JAMA Psychiatry* **70**, 87–97 (2013).

Robinson, M. et al., The effect of base rate on the predictive value of brain biomarkers. *J Pain.* **17**, 637-641. (2016).

López-Solà, M. *et al.* Towards a neurophysiological signature for fibromyalgia. *Pain* (2016).

Woo, C. W., Chang, L. J., Lindquist, M. A., Wager, T. D. Building better biomarkers: brain models in translational neuroimaging. *Nat. Neurosci.* **20**, 365-377.

Vihinen, M. How to evaluate performance of prediction methods? Measures and their interpretation in variation effect analysis. *BMC Genomics* **13**, S2. (2012).