4.  E. Thompson, F. J. Varela, *Trends Cogn. Sci.* **5**, 418 (2001).
5.  K. Murphy, R. M. Birn, P. A. Bandettini, *Neuroimage* **80**, 349 (2013).
6.  J. Cacioppo, L. G. Tassinary, G. G. Berntson, *The Handbook of Psychophysiology* (Cambridge University Press, New York, 2007).
7.  R. L. Buckner, F. M. Krienen, B. T. T. Yeo, *Nat. Neurosci.* **16**, 832 (2013).
8.  M. E. Raichle, *Annu. Rev. Neurosci.*, **38**, 433 (2015).
9.  M. E. Raichle, *Science* **314**, 1249 (2006).
10. S. M. Smith *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 13040 (2009).
11. M. E. Raichle *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 676 (2001).
12. M. D. Fox *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 9673 (2005).
13. R. L. Buckner, J. R. Andrews-Hanna, D. L. Schacter, *Ann. N.Y. Acad. Sci.* **1124**, 1 (2008).
14. J. R. Andrews-Hanna, J. S. Reidler, J. Sepulcre, R. Poulin, R. L. Buckner, *Neuron* **65**, 550 (2010).
15. R. L. Buckner, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 10769 (2010).
16. M. G. Bright, K. Murphy, *Neuroimage* **114**, 158 (2015).
17. C. P. Pawela *et al.*, *Neuroimage* **49**, 2467 (2010).
18. A. D. Craig, *Nat. Rev. Neurosci.* **3**, 655 (2002).
19. H. D. Critchley, Y. Nagai, M. A. Gray, C. J. Mathias, *Auton. Neurosci.* **161**, 34 (2011).
20. J. Fan *et al.*, *J. Neurosci.* **32**, 11176 (2012).
21. T. Eilam-Stock *et al.*, *Brain* **137**, 153 (2014).

# The predictive mapping approach in neuroimaging

**Choong-Wan Woo and Tor D. Wager***

For the past 20 years, neuroimaging techniques have transformed how we study psychology and medicine. Data from neuroimaging can constrain psychological theories, resolve some theoretical debates, and be used to develop new hypotheses about human cognition and emotions by providing a grounding in neurophysiology (*1*). In medicine, neuroimaging provides promising measures that can serve as biomarkers for brain-related disorders, such as psychiatric and neurologic disorders (*2, 3*). Neuroimaging can also connect psychology to biology and medicine, which can help researchers understand how the mind and the body interact and thereby treat medical conditions more effectively (for example, understanding the placebo effect) (*4*).

Despite these promises, neuroimaging has not followed the quick and easy path to success that was initially envisioned. One important reason is that too little effort has gone into developing neuroimaging markers that are sensitive and specific to particular mental processes or health-related outcomes and can be prospectively applied to new data. The dominant paradigm in neuroimaging has focused on brain "maps," not markers. Brain maps identify anatomical regions associated with particular mental processes. This paradigm does not adequately address the many-to-many relationships between brain regions and mental processes: One brain region can be involved in multiple processes, and one process can be distributed across many regions. Thus, we cannot make inferences about which mental process is engaged based on brain maps. Markers, by contrast, are multivariate patterns of brain activity optimized to be sensitive and specific to a particular type of mental process. Without markers, the inferences we can make about brain representations are fundamentally limited (*5*).

## Do we really have neuroimaging markers?

It might seem that neuroimaging markers for mental processes already exist, but in fact, we have been using neuroimaging findings as brain markers without properly assessing their sensitivity and specificity. For example, amygdala activity has often been used as a brain marker for negative emotion. However, the amygdala is a large anatomical structure comprising heterogeneous neuronal populations that encode various physical and mental

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**FIGURE 1. Traditional versus predictive mapping. (A)** Traditional mapping approaches (including univariate analysis) aim to obtain the functional architecture of the brain by localizing effects in the brain. This approach often entails low sensitivity and specificity. **(B)** The predictive mapping approach aims to develop a multivariate, brain-wide predictive (decoding) model that is sensitive and specific to the outcome of interest.
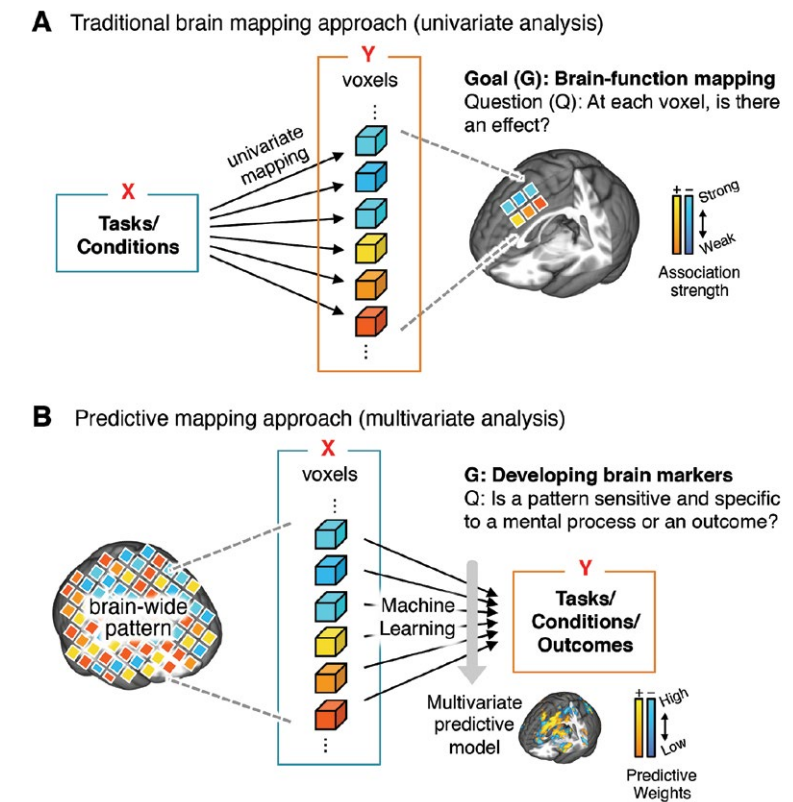
events (*6*). Therefore, averaged functional brain activity within this region is not very useful as a brain marker because of its low specificity (*7*).

In order to be considered as a marker, the brain measure used should show high sensitivity and specificity to the mental event or process of interest. Sensitivity accounts for whether a test—in this case, a brain marker—shows positive results when a target psychological or behavioral process is engaged, while specificity describes whether the test shows positive results that are exclusive to the target process being engaged. Sensitivity and specificity can tell us the diagnostic performance of the brain measure in question and enable us to make inferences or predictions about mental processes or outcomes of interest.

## Traditional brain mapping approaches

Traditional brain mapping approaches—often called "mass-univariate analysis" or "statistical parametric mapping"—have been extremely useful in the development of neuroimaging. However, these approaches are of little help in identifying and utilizing brain markers with established sensitivity and specificity. The main goal of the traditional approach is to map different mental functions onto specific brain regions to localize brain functions. As Figure 1A demonstrates, in this framework, tasks or conditions are independent variables, and each voxel's fMRI signal becomes a dependent variable. The most
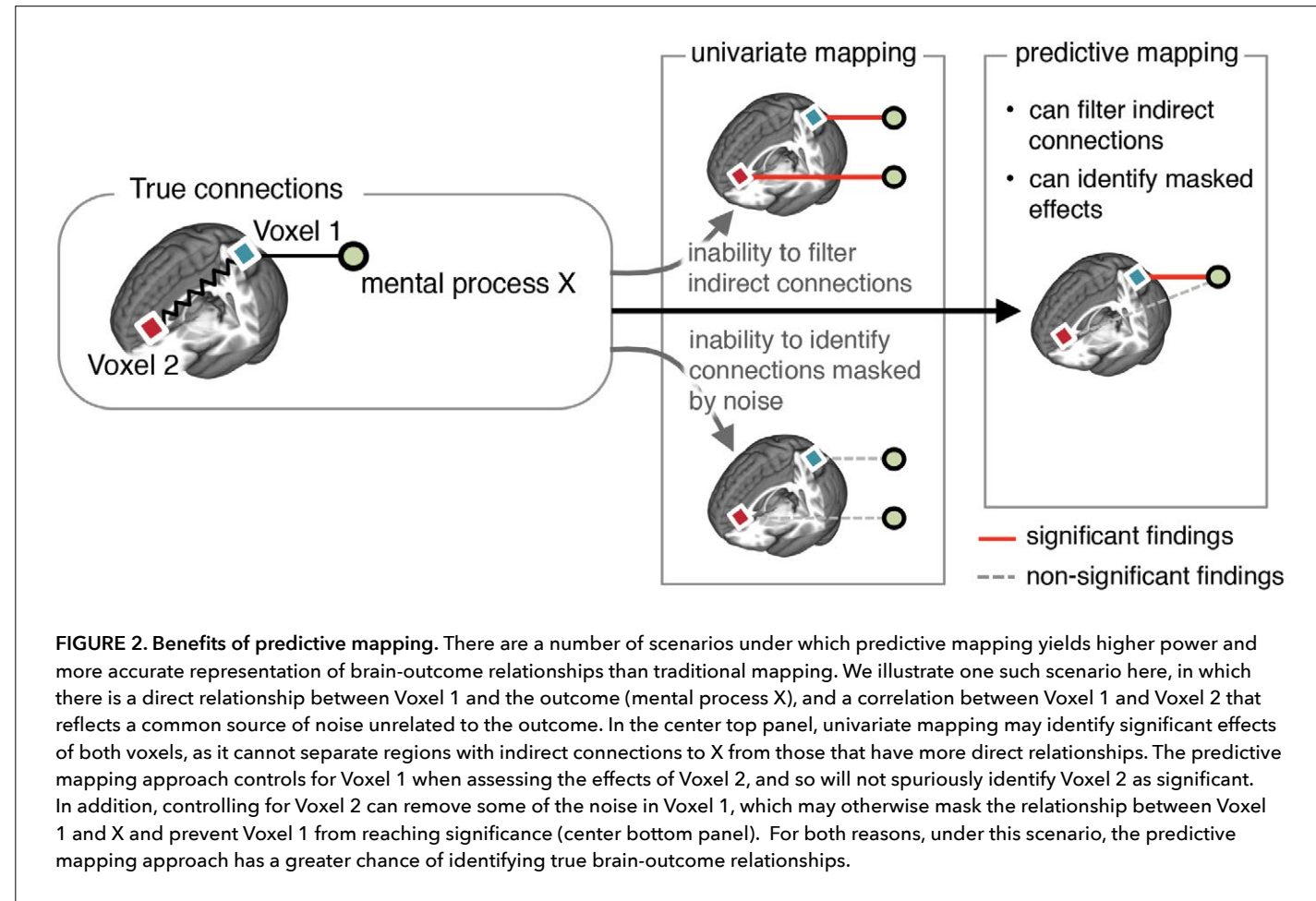
important question answered by the traditional approach is whether there is an effect in each voxel or region.

This traditional approach has, at best, low sensitivity to the effects of task conditions because it assumes independence among voxels or regions. However, psychological and behavioral processes and related outcomes result from integrated circuit dynamics. Thus, the effects of task conditions—and the relationships between brain activity and behavioral/psychological outcomes—are likely to be distributed across brain regions and voxels. Analyses that consider only information in a single voxel or region, as the mass-univariate approach does, are unlikely to capture the full effects of tasks. In addition, the univariate approach involves a large number of statistical tests and requires a correction for multiple comparisons (*8*). The correction for multiple tests focuses on controlling false positives and in turn increases false negatives, which results in low sensitivity (*8*). With low sensitivity, many of the voxels activated in relation to a task or outcome will be missed, providing a poor assessment of the pattern across the brain. This, in turn, undermines efforts to establish replicability across studies (*9, 10*). Furthermore, as illustrated in Figure 2, traditional brain mapping has a limited ability to detect the unique relationships between mental functions and brain regions, which could undermine the specificity of the resulting brain maps.

## Developing neuroimaging markers: The predictive mapping approach

The predictive mapping approach can resolve the issues described above and provide neuroimaging markers with quantitatively characterized measures of diagnostic performance. Predictive mapping aims to develop multivariate, systems-level predictive models (or decoding models) that are sensitive and specific to particular outcomes of interest (see, for example, *11*). As Figure 1B shows, one of the main features that distinguishes predictive mapping from traditional

FIGURE 2. Benefits of predictive mapping. There are a number of scenarios under which predictive mapping yields higher power and more accurate representation of brain-outcome relationships than traditional mapping. We illustrate one such scenario here, in which there is a direct relationship between Voxel 1 and the outcome (mental process X), and a correlation between Voxel 1 and Voxel 2 that reflects a common source of noise unrelated to the outcome. In the center top panel, univariate mapping may identify significant effects of both voxels, as it cannot separate regions with indirect connections to X from those that have more direct relationships. The predictive mapping approach controls for Voxel 1 when assessing the effects of Voxel 2, and so will not spuriously identify Voxel 2 as significant. In addition, controlling for Voxel 2 can remove some of the noise in Voxel 1, which may otherwise mask the relationship between Voxel 1 and X and prevent Voxel 1 from reaching significance (center bottom panel). For both reasons, under this scenario, the predictive mapping approach has a greater chance of identifying true brain-outcome relationships.

approaches is that the assignment of independent and dependent variables is reversed.

The predictive mapping approach helps to solve the low sensitivity and specificity problem of traditional mapping in several ways. First, it can identify voxels that have selective relationships with the outcome (see Figure 2). Second, it uses distributed signals across many voxels without requiring thresholding and correction for multiple comparisons. Third, it is sensitive to information at multiple spatial scales, including large-scale information distributed across multiple systems and mesoscale information below the resolution of the imaging itself (so-called fMRI hyperacuity) (12). Assessing multivariate patterns rather than individual voxels is critical if information about outcomes is encoded in neuronal population codes (13). Furthermore, assessing large-scale patterns across systems is critical if mental states are encoded across systems (14). A related approach, called information-based mapping (15), also uses multivariate patterns to predict outcomes. However, it still focuses on local effects (using searchlights, or spatial moving windows), and thus is subject to limited sensitivity and massive multiple comparisons. In contrast, the predictive mapping

approach focuses on developing one unified predictive model based on brain-wide patterns of brain activity.

In the predictive mapping approach, machine learning techniques become crucial because analyses based on large-scale population codes are subject to the high-dimensionality problem. High-dimensional data, in which there are many more predictors than observations ($p \gg n$; often called the "curse of dimensionality"), causes problems with model optimization because the parameter space is underconstrained by the data (16). Some machine learning algorithms, such as support vector machines and regularized regression, can provide stable prediction models even for the high-dimensional data with a guarantee of good generalization capacity (17, 18).

**Precisely defined model and prospective testing: benefits for translational research**

In addition to benefits in sensitivity and specificity, the predictive mapping approach can provide precisely defined models that can be prospectively tested on new datasets.

In traditional mapping approaches, replication and hypothesis testing depends heavily on anatomical definitions that are often heuristic and ambiguous, leading

to flexibility in how researchers identify what counts as an a priori hypothesis and, in turn, increases in false positive results and reduced specificity (19). For example, "amygdala activity" does not provide a reproducible definition of precisely (a) which voxels in the amygdala should be activated (there are typically hundreds); and (b) the relative expected intensity of activity across each voxel. *Any* significant result anywhere in the amygdala can count as amygdala activation, and this flexibility leads to spurious findings. In contrast, the predictive mapping approach can minimize biases in measuring, testing, and replicating effects in new individuals and studies through predictive models defined by precise patterns of brain activity, which can provide a priori predictions and testing procedures.

Precisely defined predictive models (based on multivariate patterns of neuroimaging data) provide several advantages for basic and translational research. First, hypotheses are precisely specified in terms of spatial patterns, and responses in these patterns are falsifiable and readily testable, providing a foundation for strong inference (20, 21). Second, precisely specified models are research products that can be shared and tested across laboratories, enabling a cumulative understanding of their properties across test conditions and study populations. Third, some predictive models can be prospectively applied to new individual participants, which is critical for clinical and legal applications. Fourth, well-defined predictive models can serve as a means of bringing together basic and clinical research, as diverse research groups can communicate with each other through tests of predictive models, facilitating translation of findings from one setting (e.g., basic research) into new contexts (e.g., clinical assessment).

**Conclusions**

Recent advances have provided promise and hope that we can use neuroimaging to better understand the human mind, including the neurophysiology that underlies behavior and brain-related illnesses. However, a wide gap still exists between neuroimaging data and the mental processes we want to measure. Part of the problem is that we do not have neuroimaging markers that are sensitive and specific enough to accurately indicate when a particular class of mental process is engaged. The predictive mapping approach we outline here can be used to develop neuroimaging markers that have better sensitivity and specificity compared to the traditional univariate mapping approach. The predictive mapping approach can also provide precisely defined predictive models that can be prospectively tested in new individuals and studies, and thereby turn the predictive models into research products and/or clinical tools. This characteristic can allow neuroimaging markers to be easily accessed and tested by other researchers and laboratories, promoting replicability and facilitating translation from laboratory to clinic. All together, the predictive mapping approach has the potential to facilitate neuroimaging marker discovery and validation for both basic and clinical science.

**References**
1. M. Mather, J. T. Cacioppo, N. Kanwisher, *Perspect. Psychol. Sci.* **8**, 108 (2013).
2. D. Borsook, L. Becerra, R. Hargreaves, *Discov. Med.* **11**, 209 (2011).
3. D. Borsook, L. Becerra, R. Hargreaves, *Discov. Med.* **11**, 197 (2011).
4. T. D. Wager, L. Y. Atlas, *Nat. Rev. Neurosci.* **16**, 403 (2015).
5. R. A. Poldrack, *Neuron* **72**, 692 (2011).
6. J. J. Paton, M. A. Belova, S. E. Morrison, C. D. Salzman, *Nature* **439**, 865 (2006).
7. W. A. Cunningham, T. Brosch, *Curr. Dir. Psychol. Sci.* **21**, 54 (2012).
8. T. Nichols, S. Hayasaka, *Stat. Methods Med. Res.* **12**, 419 (2003).
9. T. Yarkoni, *Perspect. Psychol. Sci.* **4**, 294 (2009).
10. K. S. Button *et al.*, *Nat. Rev. Neurosci.* **14**, 365 (2013).
11. T. D. Wager *et al.*, *New Engl. J. Med.* **368**, 1388 (2013).
12. Y. Kamitani, F. Tong, *Nat. Neurosci.* **8**, 679 (2005).
13. A. P. Georgopoulos, A. B. Schwartz, R. E. Kettner, *Science* **233**, 1416 (1986).
14. L. J. Chang, P. J. Gianaros, S. B. Manuck, A. Krishnan, T. D. Wager, *PLOS Biol.* **13**, e1002180 (2015).
15. N. Kriegeskorte, R. Goebel, P. Bandettini, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 3863 (2006).
16. R. Clarke *et al.*, *Nat. Rev. Cancer* **8**, 37 (2008).
17. V. Vapnik, *The Nature of Statistical Learning Theory* (Springer, New York, 1995).
18. T. Hastie, R. Tibshirani, J. H. Friedman, *The Elements of Statistical Learning : Data Mining, Inference, and Prediction*. (Springer, New York, 2nd ed., 2009).
19. J. P. Simmons, L. D. Nelson, U. Simonsohn, *Psychol. Sci.* **22**, 1359 (2011).
20. K. R. Popper, *The Logic of Scientific Discovery* (Basic Books, New York, 1959).
21. J. R. Platt, *Science* **146**, 347 (1964).