北京師範大學心理学部

Developmental Population Neuroscience

发展人口神经科学（人脑谱图方法学）

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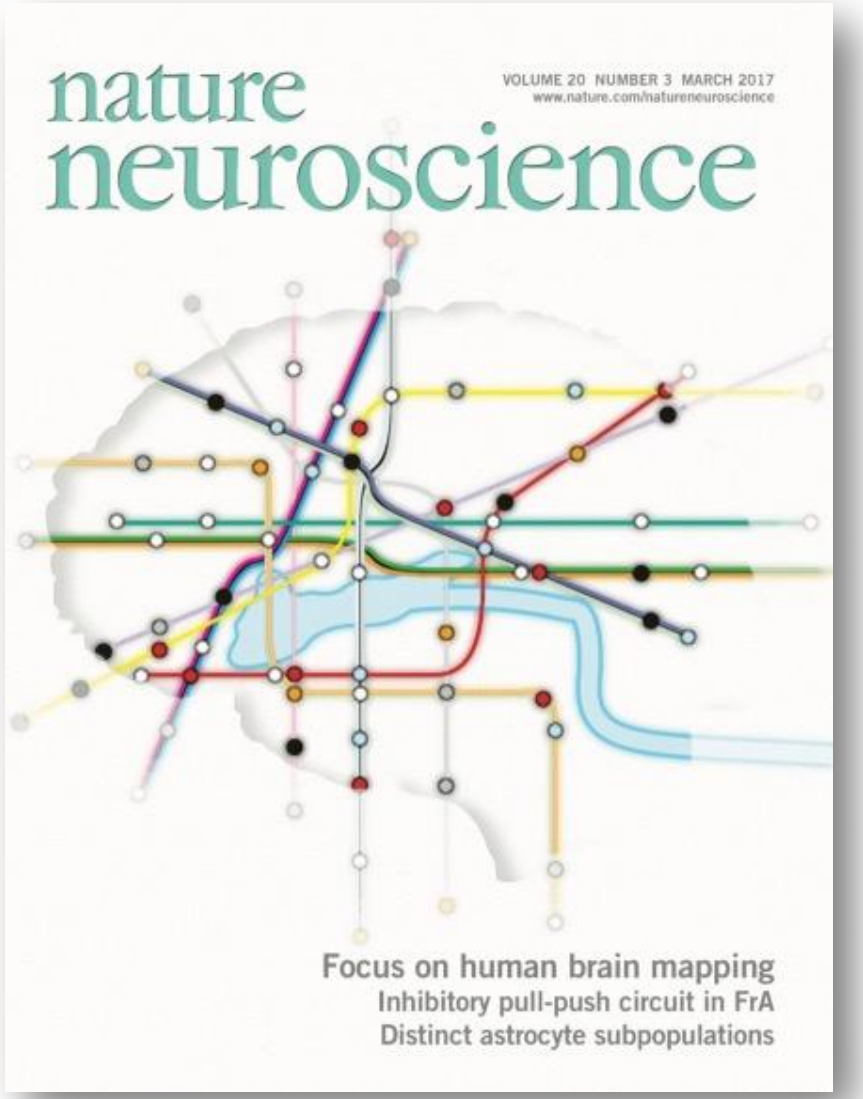
Chinese Data-sharing Warehouse for In-vivo Imaging Brain

Methodology for Human Brain Mapping



Focus on Human Brain Mapping (2017)

EDITORIAL

nature neuroscience

Focus on human brain mapping

We present a special issue highlighting considerations and recent developments in noninvasive techniques that improve our understanding of neural measurements in humans, bridging the gap between human and animal research in neuroscience.

Neuroscientists endeavor to understand how the brain develops and controls our perception of the world and our interactions with it. Animal models enable investigations of the genetic, molecular, cellular, circuit-level and neurophysiological mechanisms underlying these processes. Noninvasive technologies such as magnetic resonance imaging (MRI), magnetoencephalography (MEG) and electroencephalography (EEG) complement these approaches by assessing human brain structure and neural responses to complex behaviors. In this issue, *Nature Neuroscience* presents a series of commissioned pieces that discuss recent progress in several noninvasive techniques and put forth conceptual frameworks under which we can examine neuroimaging data to deepen our understanding of these rich data sets. These advances may help connect findings from various species and achieve a more complete picture of the brain's structure and function.

In light of growing concerns about the robustness and reproducibility of functional MRI (fMRI) research findings, the Organization for Human Brain Mapping has created the Committee on Best Practices in Data Analysis and Sharing (COBIDAS) to delineate standards for reporting MRI methods, analyses and data sharing. On page 299, the COBIDAS comments on reproducibility pertaining to MRI-based research and on the sociological impediments to adopting their suggested practices. (For our editorial stance on recent concerns about fMRI research, please see our accompanying editorial http://dx.doi.org/10.1038/nn.4521.)

fMRI data are acquired in high resolution across three spatial dimensions and time, yet standard analysis methods do not always take advantage of the richness of these data. On page 304, Nicholas Turk-Browne and colleagues discuss advanced fMRI analysis techniques that uncover unique insight into neural computations in humans, enable shared inferences about neural processes across multiple humans and describe a computing infrastructure for performing these cutting-edge analyses.

MRI also provides an unparalleled opportunity to noninvasively measure brain structure. On page 314, Jason Lerch and colleagues present the next installment of *Nature Neuroscience*'s series promoting data quality. This piece provides an overview of the structural and diffusion MRI methods used to examine neuroanatomy at macroscopic, mesoscopic and microscopic scales, accompanied by important considerations for acquiring, analyzing and interpreting MRI data. The authors also briefly cover studies of human structural neurodevelopment and MRI applications in population neuroscience, a field that examines epidemiological and genetic influences on human brain structure.

Moving from neuroimaging data acquired with magnetic fields of typically 3 Tesla or more to measurements at the femtotesla scale (10^{-15} Tesla), MEG enables the detection of magnetic inductions that are generated by neuronal activity. On page 327, Sylvain Baillet reviews several aspects of MEG that are advantageous for examining neural processing in humans relative to EEG, fMRI or positron emission tomography (PET). The review also discusses the application of machine-learning techniques to MEG data, developments in making MEG data available on a larger scale ('big data') and some major conceptual advances provided by MEG research so far.

The complexity of neuroimaging data sets allows researchers to examine properties of collective neural activity at the level of networks. On page 340, Michael Breakspear provides an essential introduction to models of large-scale brain dynamics for neuroscientists. In his paper, he outlines core theoretical concepts for examining neural activity using this framework, as well as considerations and insights that might arise when this framework is applied to different modalities of neuroimaging data (fMRI, EEG, etc.). On page 353, Danielle Bassett and Olaf Sporns discuss parallel efforts in examining networks at the genetic, molecular, neuronal, regional and behavioral scale, and they encourage the neuroscience community to consider network-level research questions that bridge across scales and species.

Neuroimaging data are often used as 'biomarkers' for particular behavioral traits or disordered processes in the brain. On page 365, Tor Wager and colleagues provide a critical review of translational research in which neuroimaging data are used to predict clinical outcomes. Based on their survey of the published literature, they propose general recommendations for building better neuroimaging biomarkers for health and disease.

Given the breadth of human brain mapping techniques available in neuroscience research, it is difficult to cover each of these approaches in one journal issue. The methodologies highlighted in this focus issue are by no means intended to define the scope of neuroimaging work considered for publication at *Nature Neuroscience*. Rather, these pieces were commissioned to inform our readers about exciting advances in the field and to highlight some of the areas in which the field is rapidly developing. It is our hope that the neuroscience community at large will consider these noninvasive approaches as essential tools that provide substantial insights into brain structure and function, when combined with strong research questions, experimental rigor in study design and informed choices in data acquisition and analyses. With this issue, we celebrate the valuable neuroscientific contributions from human brain mapping, and we look forward to working closely with the neuroimaging community to develop and publish new, exciting neuroscience research using these techniques. ■

nature neuroscience

Fostering reproducible fMRI research

The validity of conclusions drawn from functional MRI research has been questioned for some time now. *Nature Neuroscience* and *Nature Communications* are committed to working with neuroimaging researchers to improve the robustness and reproducibility of their work.

Functional magnetic resonance imaging (fMRI) measures neural activity indirectly via the changes in the blood-oxygenation-level-dependent (BOLD) signal. It has been widely used by cognitive neuroscientists and psychologists to examine the neural correlates of higher cognitive functions in humans, such as decision-making, emotion regulation, social interactions and consciousness. Over the years, fMRI methods have become more refined, both in terms of the spatial and temporal resolution of imaging data and in terms of the statistical approaches used to analyze them. Researchers are no longer limited to making differential measurements of neural responses to various stimuli or task demands. Rather, current practices include decoding the information content from neural activations and using patterns of neural connectivity to predict an individual's cognitive abilities and traits.

Despite this remarkable progress, there are inherent challenges in fMRI studies. For example, we currently do not know the exact relationship between neuronal activity and the BOLD signal, making it hard to draw causal conclusions. Additionally, humans are highly variable in their task performance and their neural activity, as these can be influenced by mood, level of alertness, motivation, health and other factors. Finally, fMRI's dependence on image-processing pipelines and statistical analysis routines opens the door to any number of errors that can be introduced during the extraction of results. As a consequence, criticisms have been raised, suggesting that some fMRI findings are only modestly reproducible (Bennet, C.M. & Miller, M.B. Ann. *NY Acad. Sci.* **1191**, 133–155, 2010), and that some results could be interpreted as being overinflated or spurious (Eklund, A., Nichols, T.E. & Knutsson, H. *Proc. Natl. Acad. Sci. USA* **113**, 7900–7905, 2016), incorrectly suggesting that a positive result is present (a 'false positive'). Unfortunately, such reports have unintentionally harmed this technique's reputation and called into question the merit of published fMRI research. Are these criticisms warranted and, even if the answer is 'no', how can the scientific community address the negative connotations associated with this research?

Even with the innumerable parameters that may differ between individual fMRI studies—study and task designs, scanner protocols, subject sampling, image preprocessing and analysis approaches, choice of statistical tests and thresholds, and correction for multiple comparisons, to name a few—many findings are reliably reproduced across labs. For example, the brain regions associated with valuation, affect regulation, motor control, sensory processing, cognitive control and decision-making show concordance across different fMRI studies in humans; these findings have also been supported by animal research drawing on more invasive and direct measures. These converging results should be highlighted in commentaries regarding research reproducibility, and critiques should be constructively balanced with potential solutions. In doing so, these critiques can provide an opportunity to revisit methods and highlight caveats, allowing the neuroimaging community to refine their methodological and analytical approaches and adopt practices that ultimately lead to more robust and reproducible results (http://www.ohbmbrainmappingblog.com/blog/keep-calm-and-scan-on).

One means of promoting reproducibility is to ensure transparent reporting of methodological details of study designs, data collection and analytical approaches, as well as any limitations to data interpretation. Papers sent out for peer review by journals within Nature Research include a completed methods reporting checklist and, upon acceptance, must comply with our reporting guidelines (http://www.nature.com/neuro/journal/v16/n11/full/nn0713-1.html), which ensure that authors are clear about several aspects of experimental design and analyses. To promote transparent methods reporting for MRI studies, we have developed an MRI-specific module to complement the methods reporting checklist. The aim is to capture essential MRI details that should be reported in every MRI-based research paper, and this module has been refined using suggestions recently provided by the neuroimaging community (https://doi.org/10.1101/054262). We hope these details will provide a clearer context within which our readers and reviewers can interpret MRI findings.

Beyond clearer methods reporting, reproducible science (Munafò, M.R. *et al. Nat. Hum. Behav.* **1**, 0021, 2017) can also be fostered by increasing data accessibility. As part of Nature Research's growing efforts to support open science, primary research papers published in Nature journals require mandatory statements about data accessibility upon formal acceptance and publication (http://www.nature.com/authors/policies/availability.html#data). We also encourage researchers to deposit their data sets in recommended data repositories (http://www.nature.com/sdata/policies/repositories) so that they can be aggregated for large-scale analyses across studies, potentially improving the statistical power and robustness of any conclusions that may arise from these analyses.

Nature Neuroscience and *Nature Communications* recognize and applaud the unique advances obtained through fMRI research in cognitive neuroscience, psychology and human behavior. As increasingly complex behavioral paradigms, analytical approaches and other noninvasive techniques are being implemented in fMRI-based research, we anticipate that this field will continue to evolve and grow. (*Nature Neuroscience* has assembled a Focus on Human Brain Mapping, highlighting exciting developments in fMRI and other noninvasive techniques: http://dx.doi.org/10.1038/nn.4521). As with all fields of scientific research, technological developments and critical analyses of published literature are important means with which to improve methods, provide more robust and reproducible contributions and expand scientific knowledge. We look forward to working closely with our authors and peer reviewers to encourage, develop and publish the very best (and reproducible) fMRI studies. ■

Study Neuroanatomy using MRI

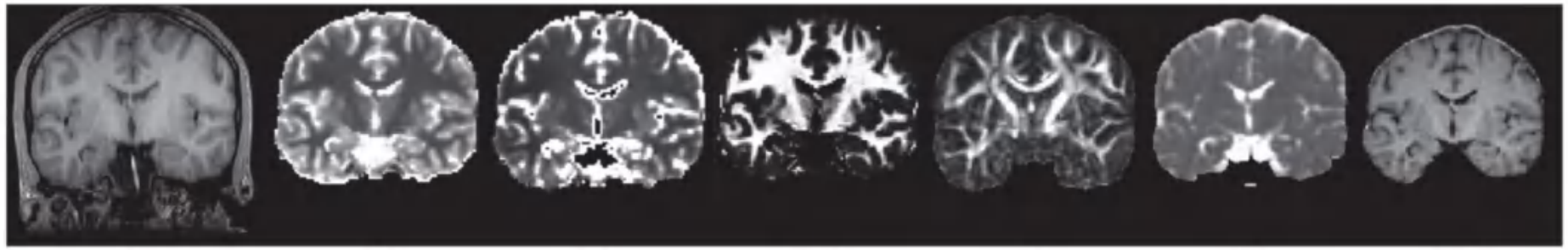


Figure 1 Coronal slices of multimodal images of brain structure acquired in members of a birth cohort when they reached 20 years of age. Leftmost: the T_1-weighted (T_1w) image most commonly used for analyzing brain volumes, voxel based morphometry, cortical thickness, etc. Next, from left to right, are quantitative T_1 and T_2 (qT_1 and qT_2, respectively) and myelin water fraction (MWF) maps, estimated using the multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) sequence[45]. Right three images: FA and mean diffusivity (MD), both from diffusion imaging, and (rightmost) a magnetization transfer ratio (MTR) map. These data indicate the types of rich information about brain structure that can be obtained from MRI in a single session. Sample images acquired from the ALSPAC MRI study, which was approved by the North Somerset and South Bristol Research Ethics Committee and the Baycrest Research Ethics Board and conducted in accordance with its guidelines. Informed written consent was obtained from all participants.

Lerch et al. (2017) *Nature Neuroscience*, 20:314-326

Study Neuroanatomy using MRI

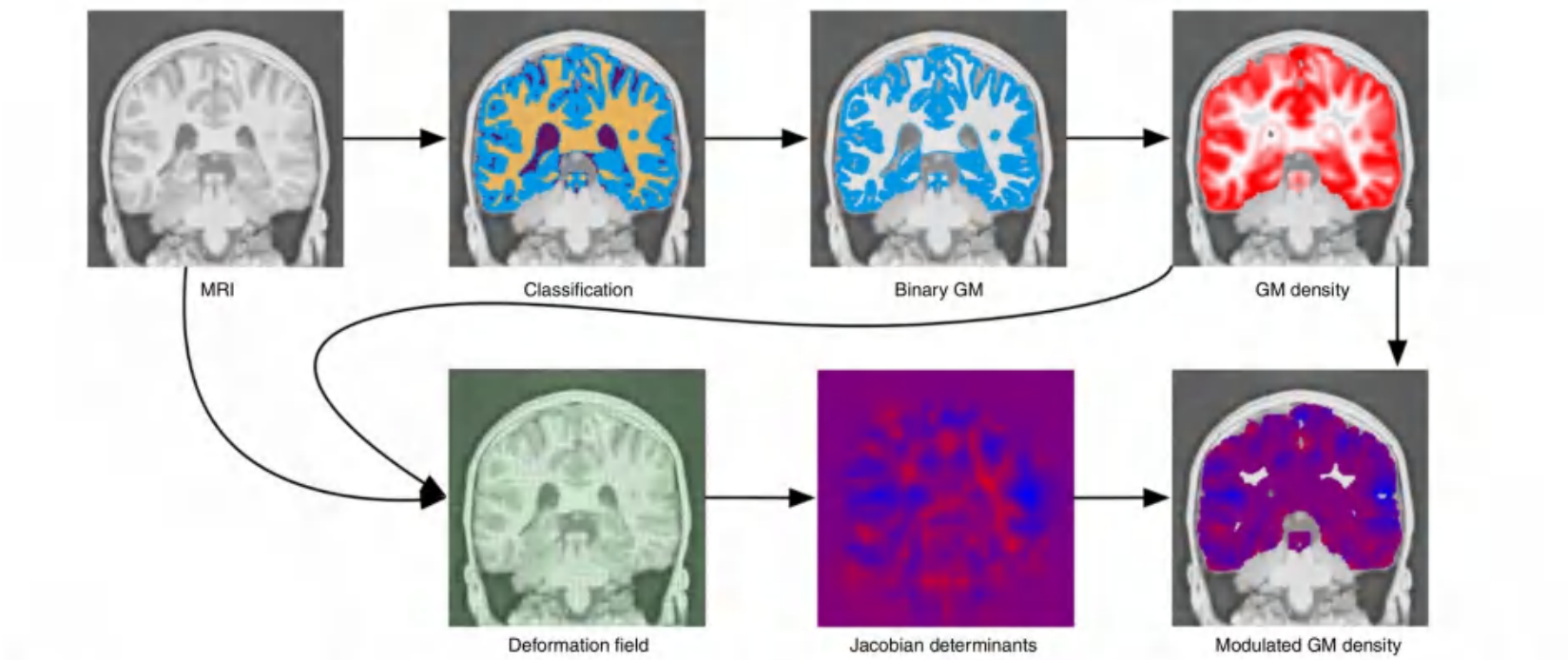


Figure 2 Voxel-based morphometry (VBM). VBM was the first widely adopted technique for determining alterations in neuroanatomy across sets of subjects. VBM entails classifying the brain (MRI) into white matter, gray matter (GM), cerebrospinal fluid and background (classification), extracting one of the classified tissues types (binary GM), then smoothing the extracted tissue type with a Gaussian kernel. The final product is thus an image (GM density), in linearly registered stereotaxic space, with values ranging from 0 to 1 representing the amount of gray matter within a local neighborhood as determined by the blurring kernel[8]. A modification to the basic VBM protocol was proposed in 2001 (ref. 11), wherein nonlinear registration, based on either aligning the T_1-weighted MRIs or the GM density maps, is incorporated to provide better spatial alignment. This optimized VBM procedure also combines the nonlinear registration (deformation field) with the tissue density map obtained from classic VBM by multiplying (or modulating) the tissue density map by the Jacobian determinant of the nonlinear deformation field to produce the modulated GM density map. Sample images were obtained from the POND study, which was approved by The Hospital for Sick Children Research Ethics Board and conducted in accordance with its guidelines. Informed written consent was obtained from all participants and/or their parents.

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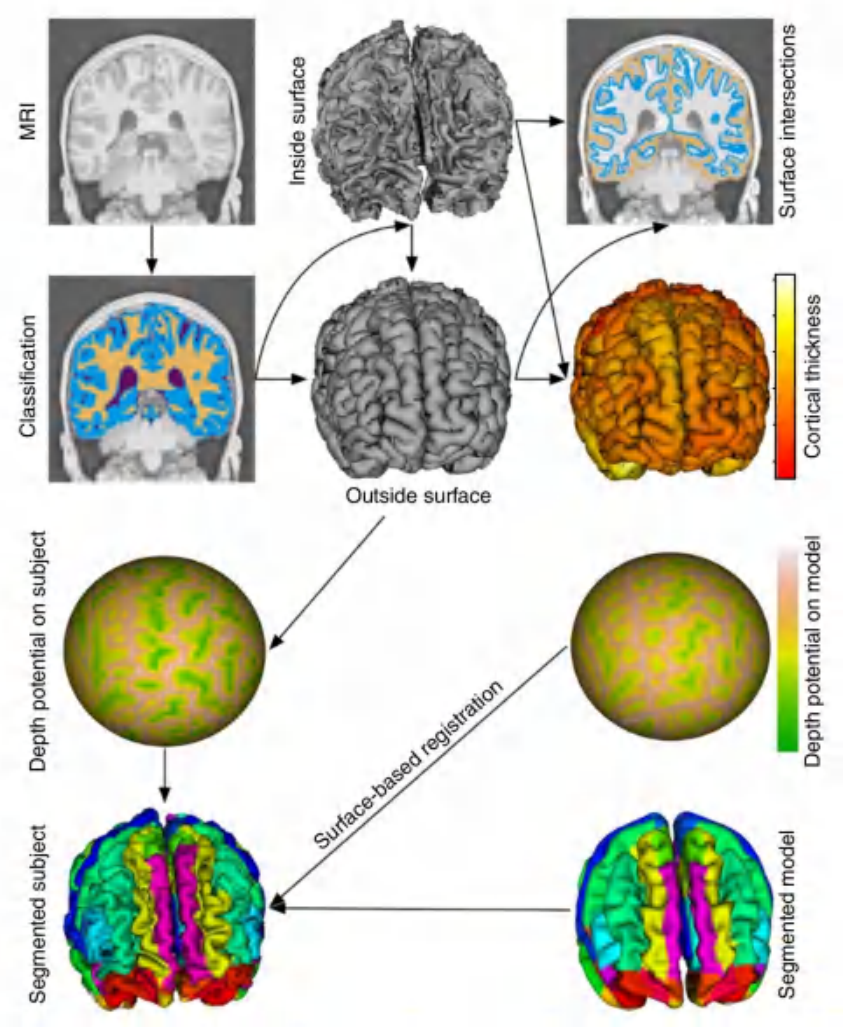

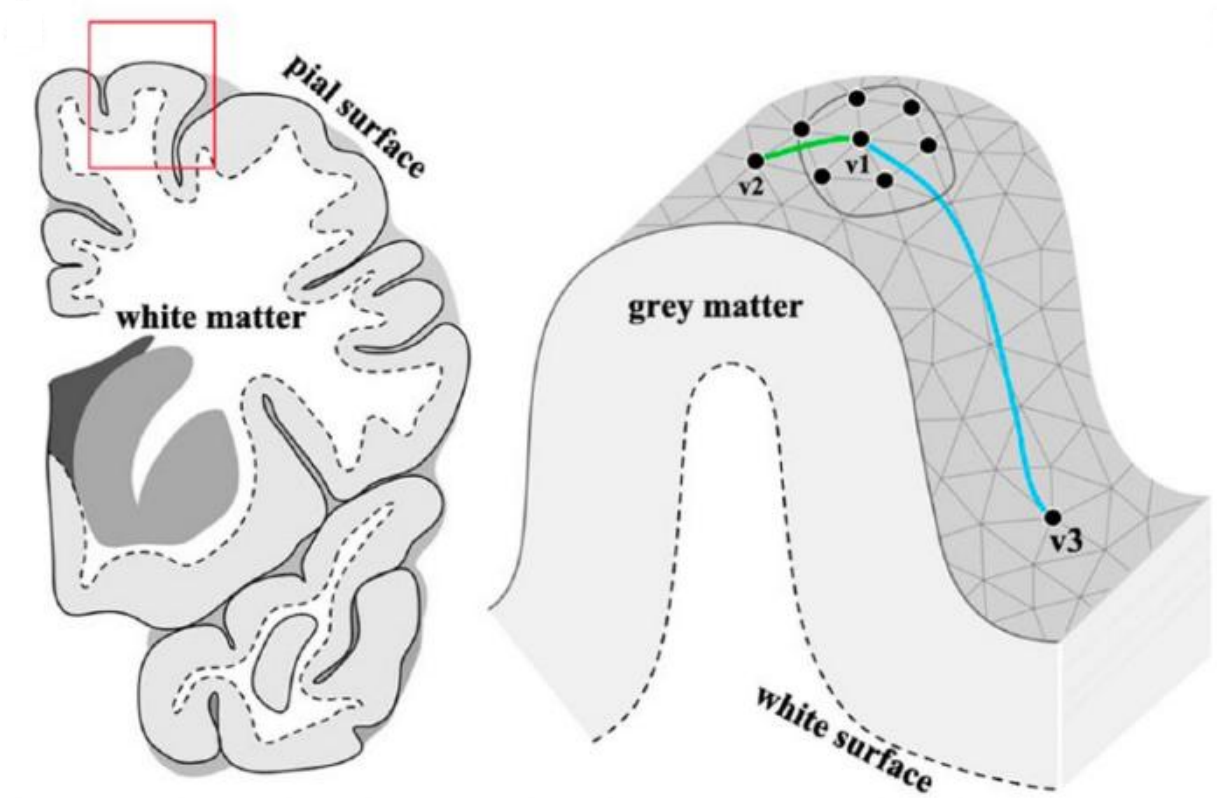

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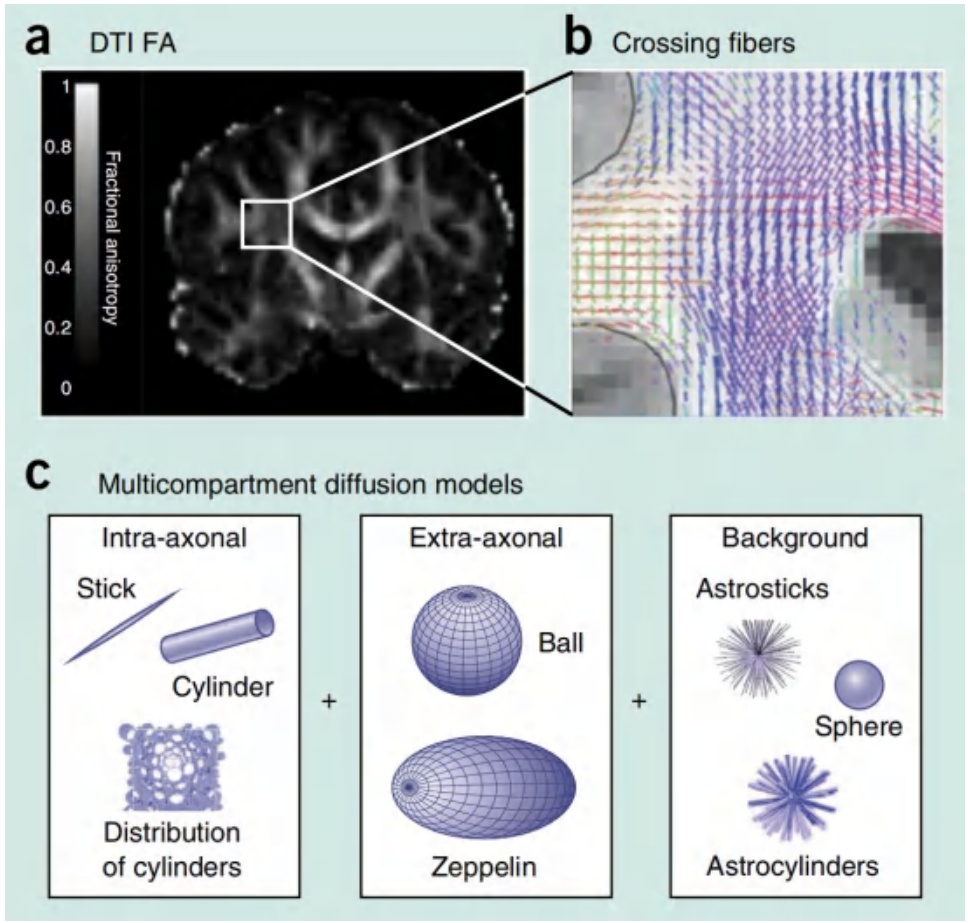

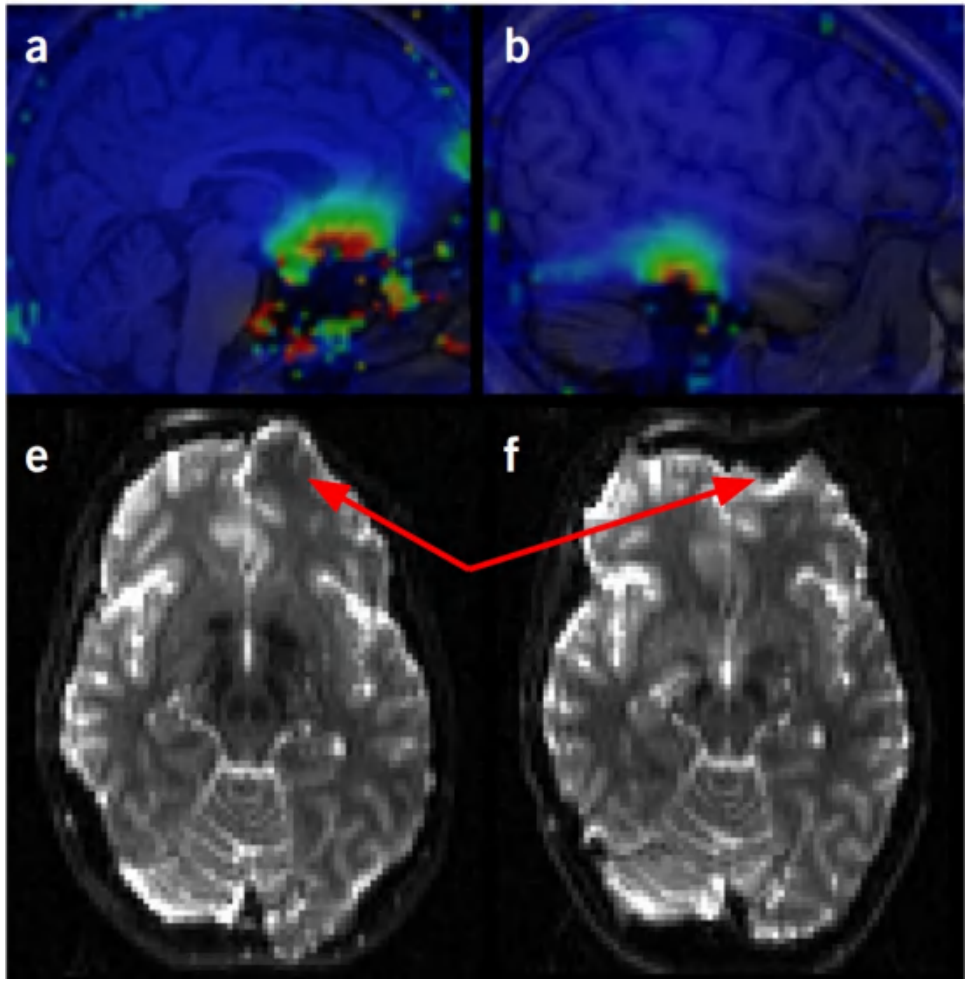

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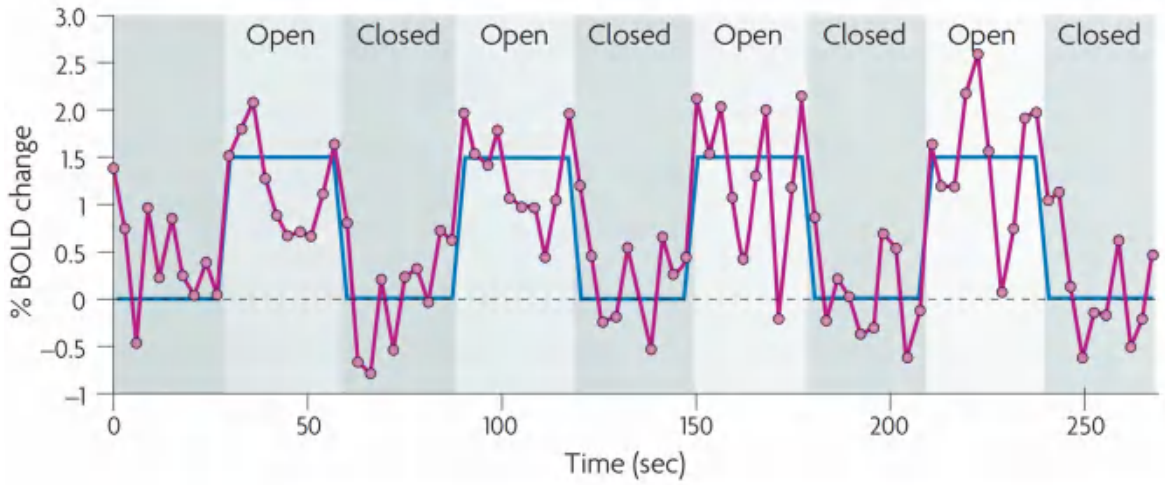
Computational Approaches to FMRI Analysis



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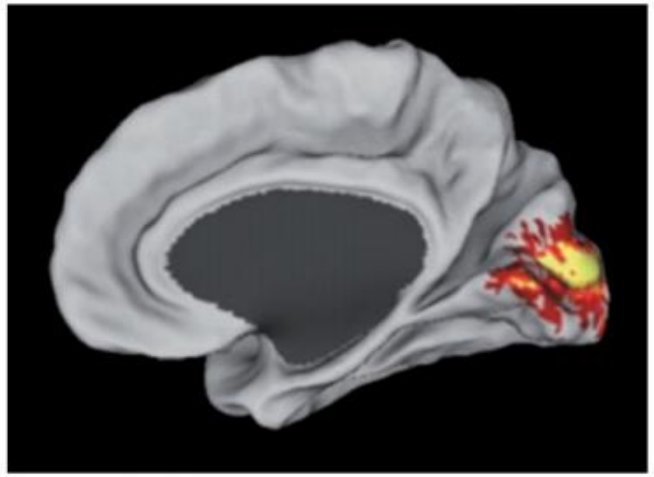

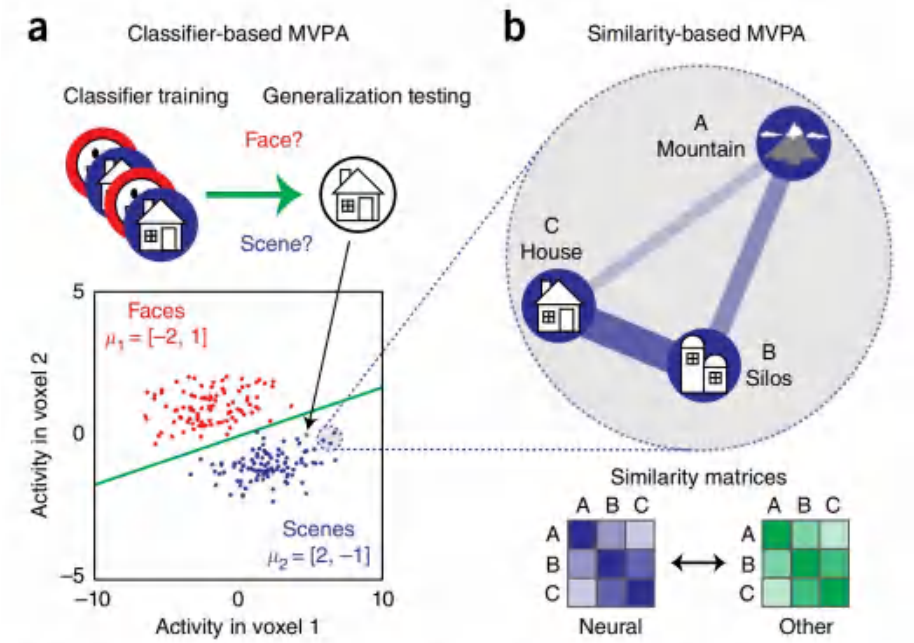

Figure 1 Types of MVPA. (**a**) Classifier-based MVPA involves learning a boundary that discriminates between fMRI patterns associated with different cognitive states (for example, attending to faces vs. scenes). (**b**) Similarity-based MVPA involves computing the matrix of pairwise distances between fMRI patterns and (optionally) comparing this matrix to other similarity matrices (for example, predictions from a cognitive theory about conceptual similarity). Adapted with permission from ref. 14, J.A. Lewis-Peacock and K.A. Norman, in *The Cognitive Neurosciences, fifth edition*, edited by Michael S. Gazzaniga and George R. Mangun, published by The MIT Press.

Cohen et al. (2017) *Nature Neuroscience*, 20:304-313; Fox & Raichle (2007) *Nature Reviews Neuroscience*, 8:700-711

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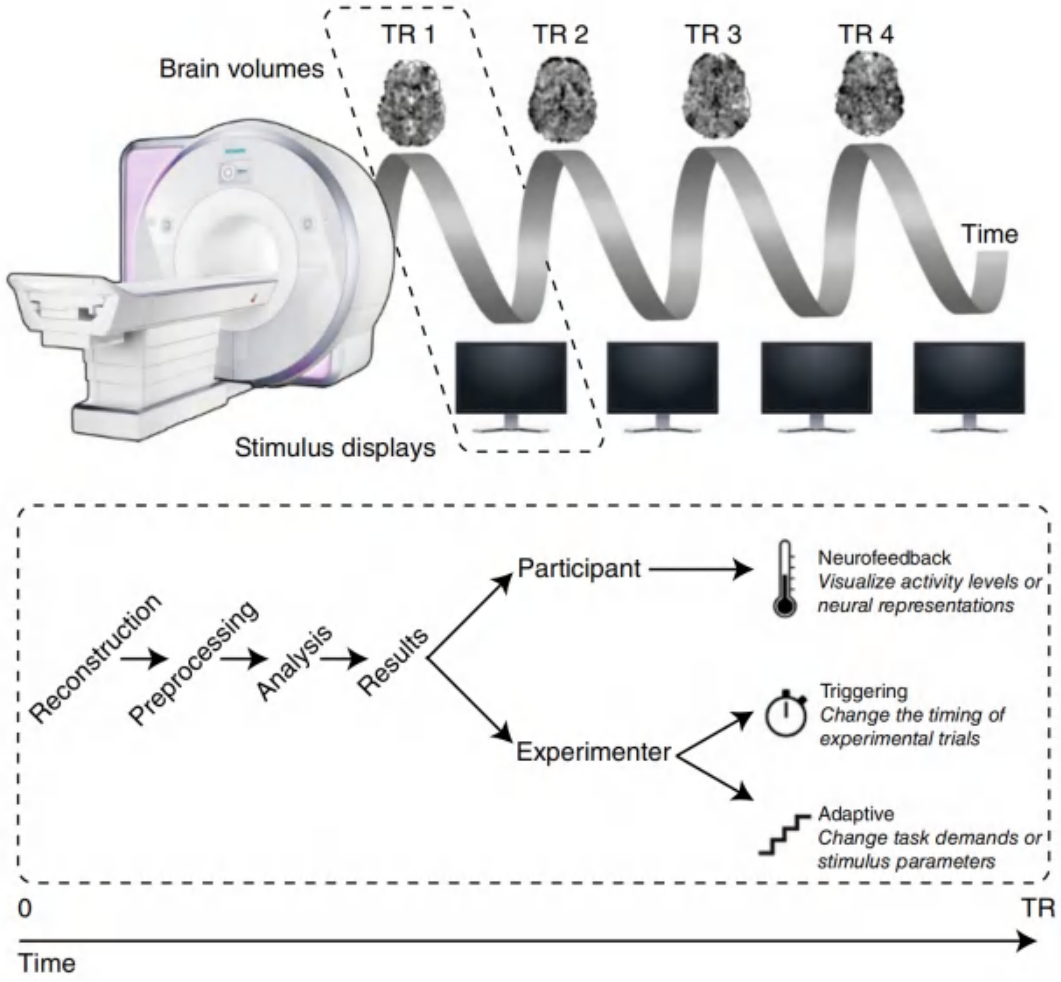

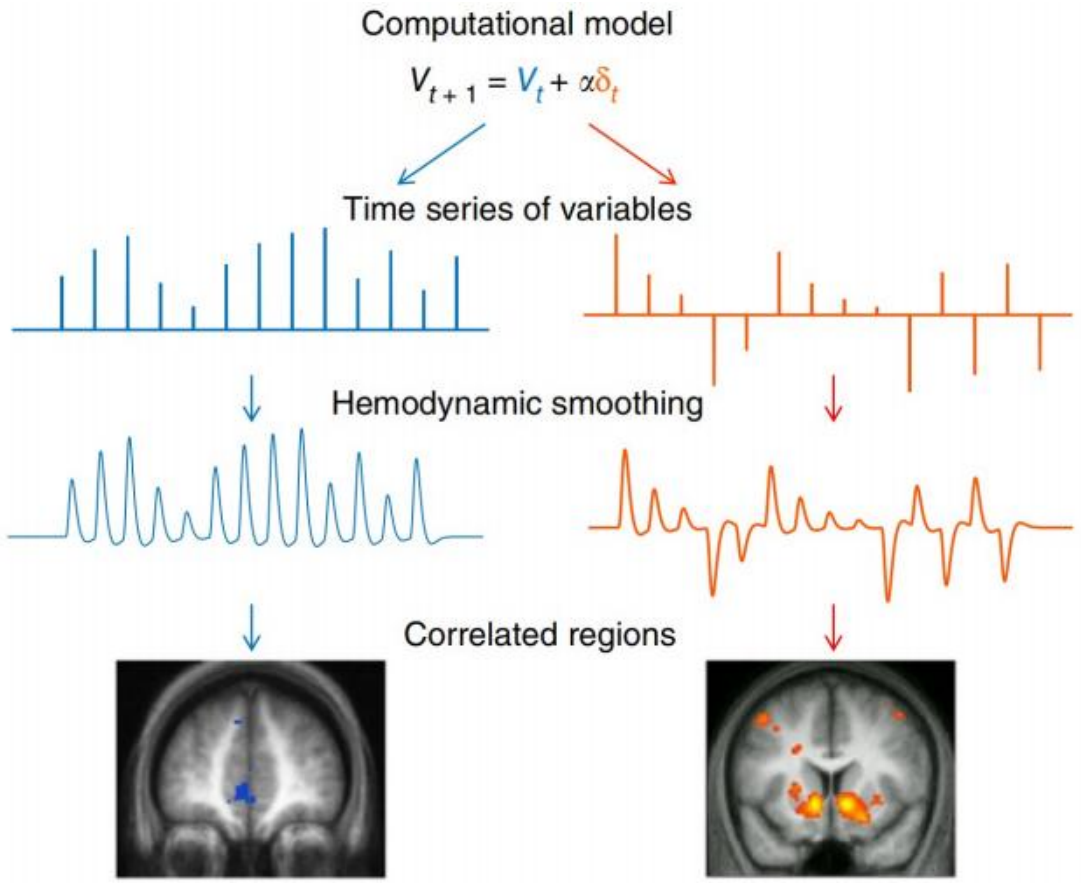

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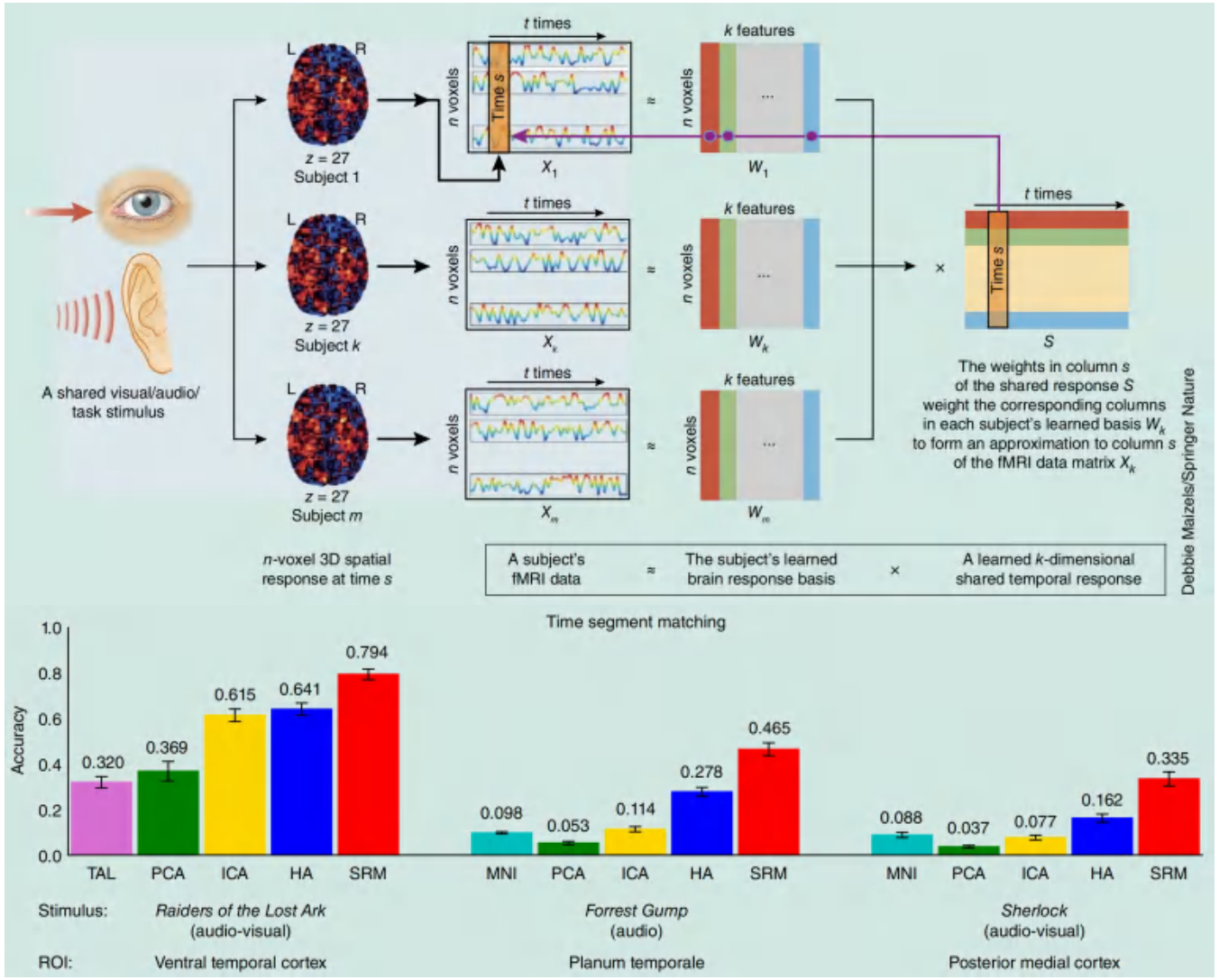

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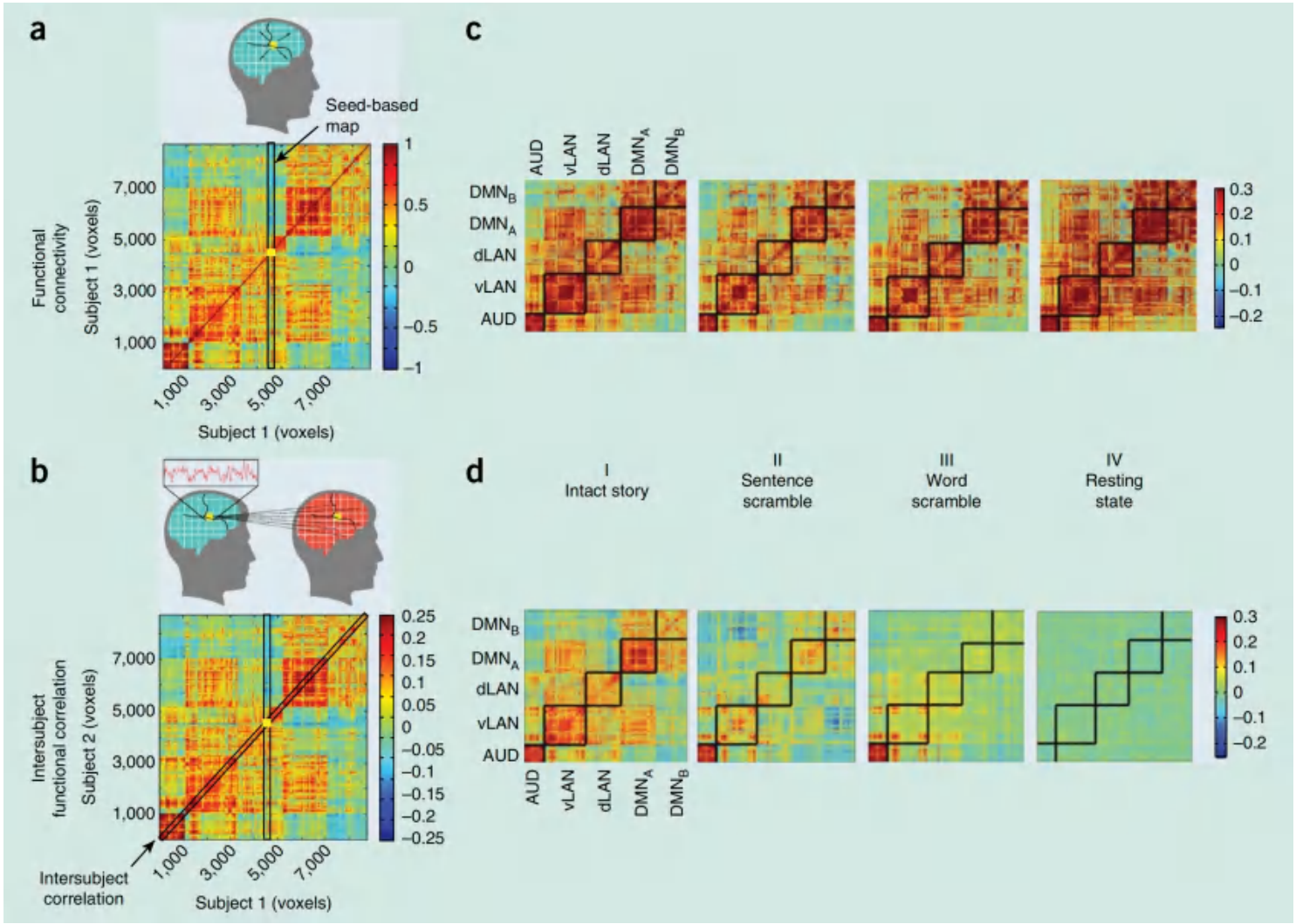

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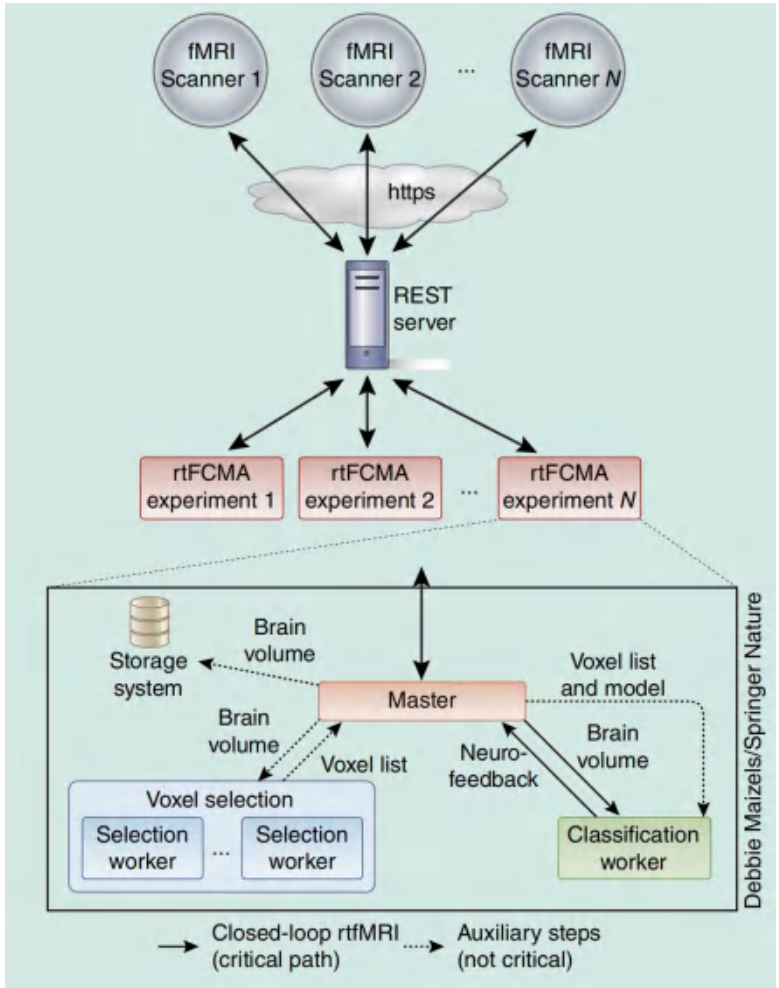

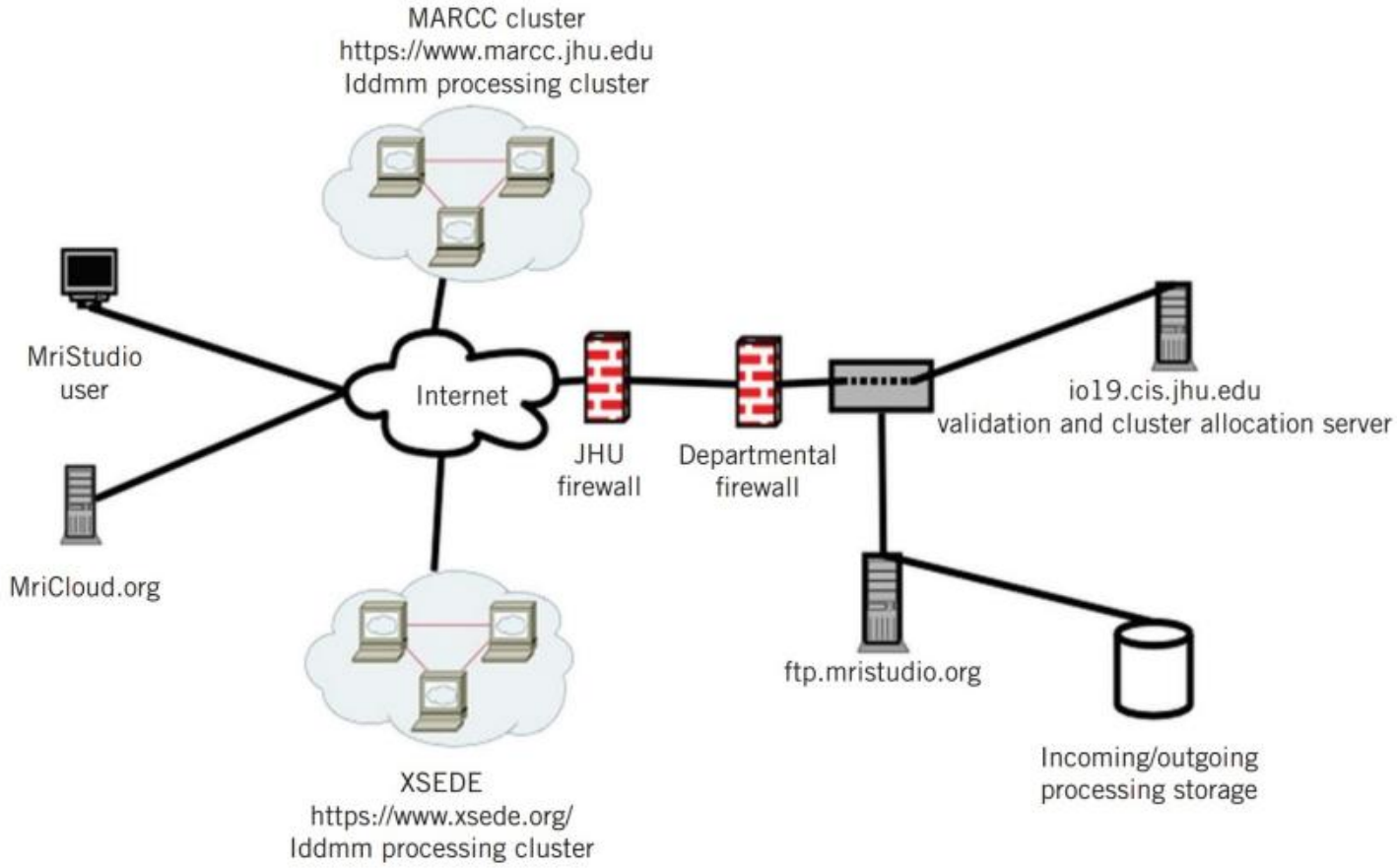

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MEG for Electrophysiology and Imaging

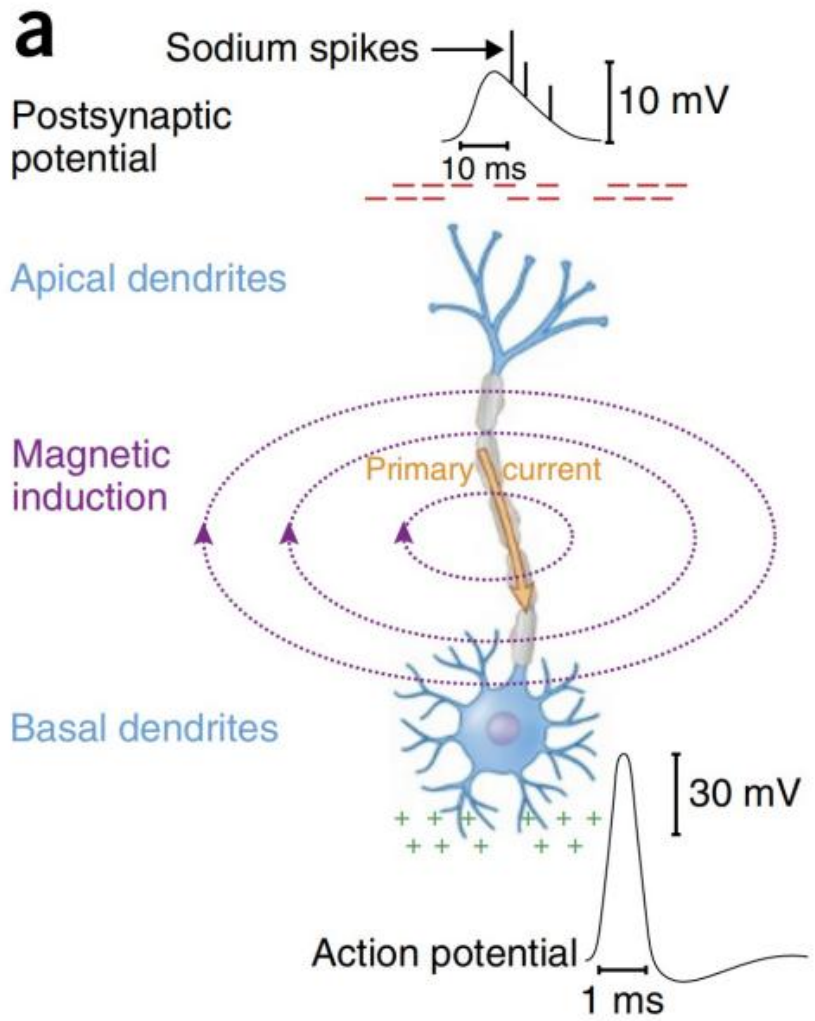

Figure 1 Cellular origins of MEG signals. (**a**) For simplicity, we take the cortical pyramidal neuron to epitomize the elementary cellular generator of MEG signals. All physiological currents from all cell types generate a magnetic induction; the elongated morphology of the pyramidal neuron constrains the net primary current circulation along the cell, which is a factor in creating greater signal strength in comparison to those from more stellate cellular morphologies. The primary current results from an imbalance in electrical potentials between the apical dendritic arborescence of the cell and its soma and more basal dendrites. The magnetic induction isolines in purple are perpendicular to the primary current flow and can be picked up outside the head. The sources are twofold: the postsynaptic potentials (PSPs), including fast, large-amplitude sodium spikes, and axonal discharges (action potentials, AP). The slower components of the PSPs are substantially smaller in amplitude than the APs. (**b**) At the scale of cell assemblies, the mass effect of slower PSPs is stronger than that of APs owing to their greater overlap in time without requiring rigorous synchronization. Computational models and empirical evidence show that a minimum of 10,000 to 50,000 cells are required to produce a signal detectable with MEG[8]. It is possible, in principle, that fast PSP spiking activity, and possibly shadows of APs, are detectable in MEG.

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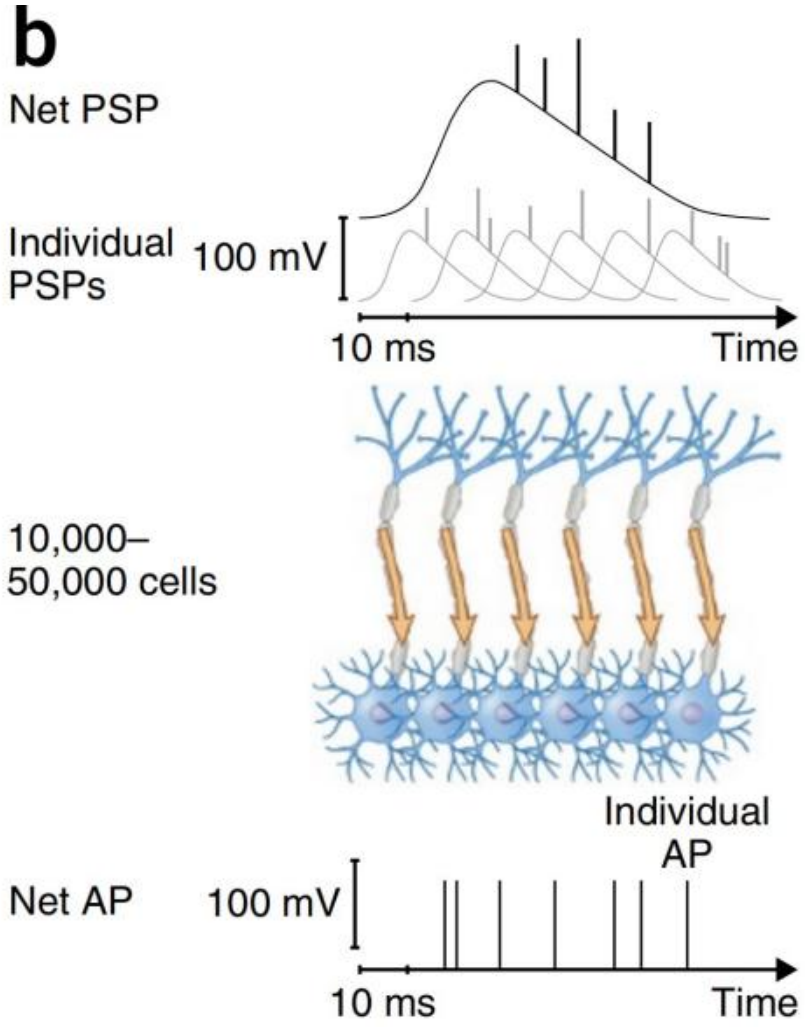
MEG for Electrophysiology and Imaging



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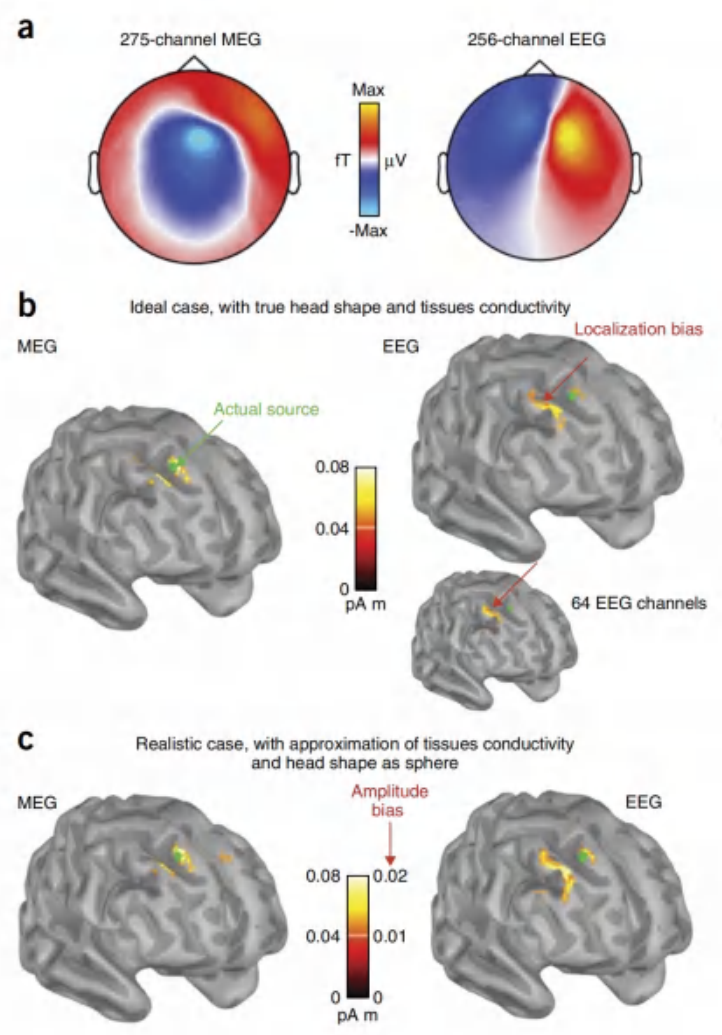

Figure 2 An example comparing MEG and EEG. Synthetic data were generated by impressing a simulated uniform current density on a 1-cm^2 patch of cortical surface (green in **b**,**c**). The cortical surface and the other tissue compartments (scalp, skull bone, cerebrospinal fluid) were that of the ICBM152 template, available in the Brainstorm open-source application[138]. The corresponding, ground-truth MEG data were simulated on the sensor configuration of a 275-channel CTF (axial gradiometers) system. The 256-channel EEG sensor configuration was that of Electrical Geodesics. The reference head model was derived using the OpenMEEG boundary element method[139] with default parameters, also available in Brainstorm. (**a**) Resulting MEG and EEG sensor topographies for the simulated cortical source. (**b**) Estimated cortically distributed currents using the weighted-minimum norm estimator available in Brainstorm, with default parameters (amplitude thresholded above 50% of maximum): the EEG source map has a localization bias pointing at the gyral crown lateral to the actual source location. This bias is emphasized when using a more typical electrode density of 64 channels (inset). (**c**) Source estimates obtained using approximations of the head model: three-shell concentric spheres adjusted to the scalp surface, and altered conductivity values (+25% for scalp, –25% for skull bone). As predicted from physics of magnetic induction, the MEG source map is immune to geometric and conductivity approximations, whereas the EEG is not. This latter has considerably lower amplitude than the actual current strength (note distinct color scales for MEG and EEG).

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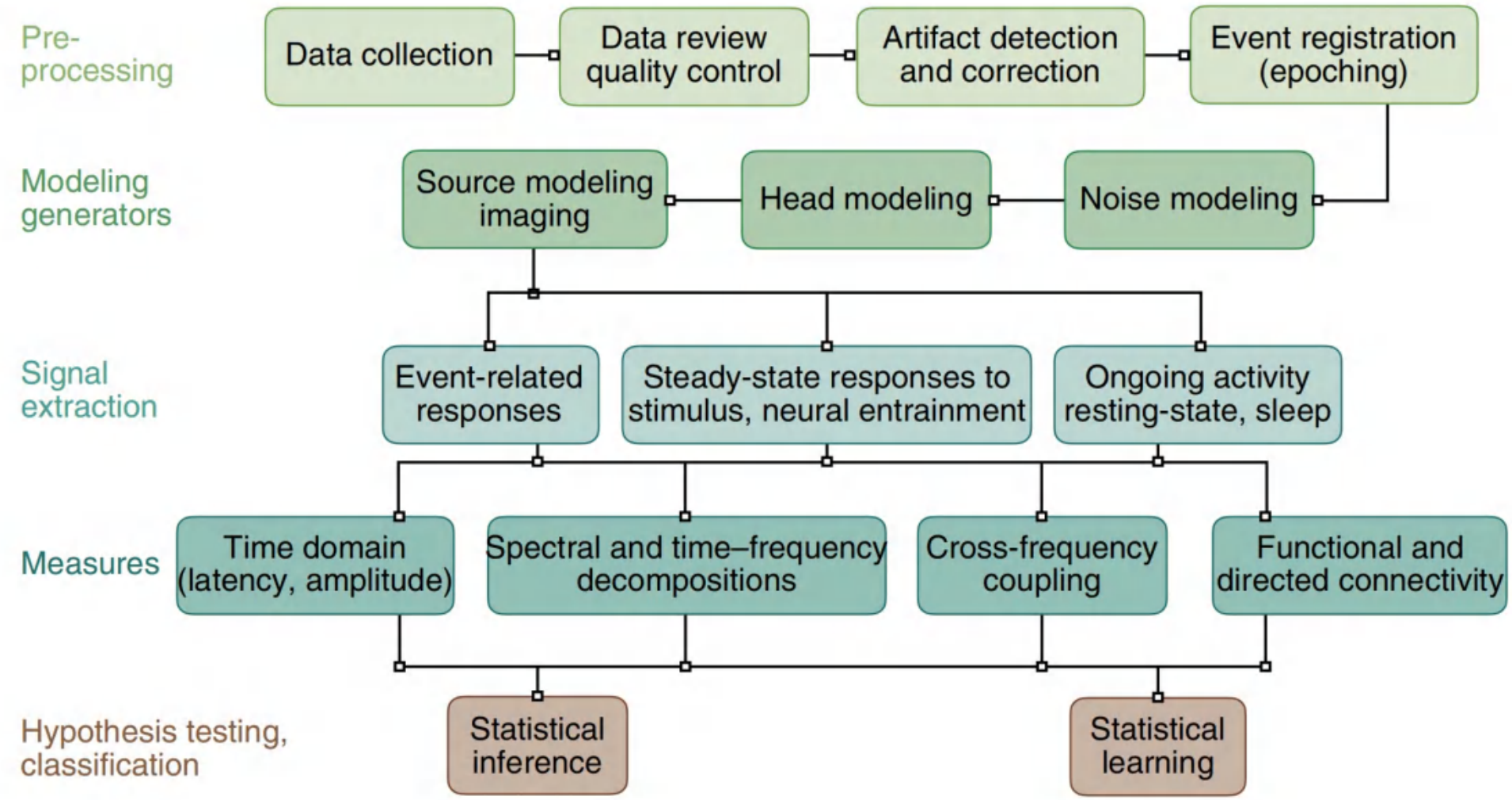

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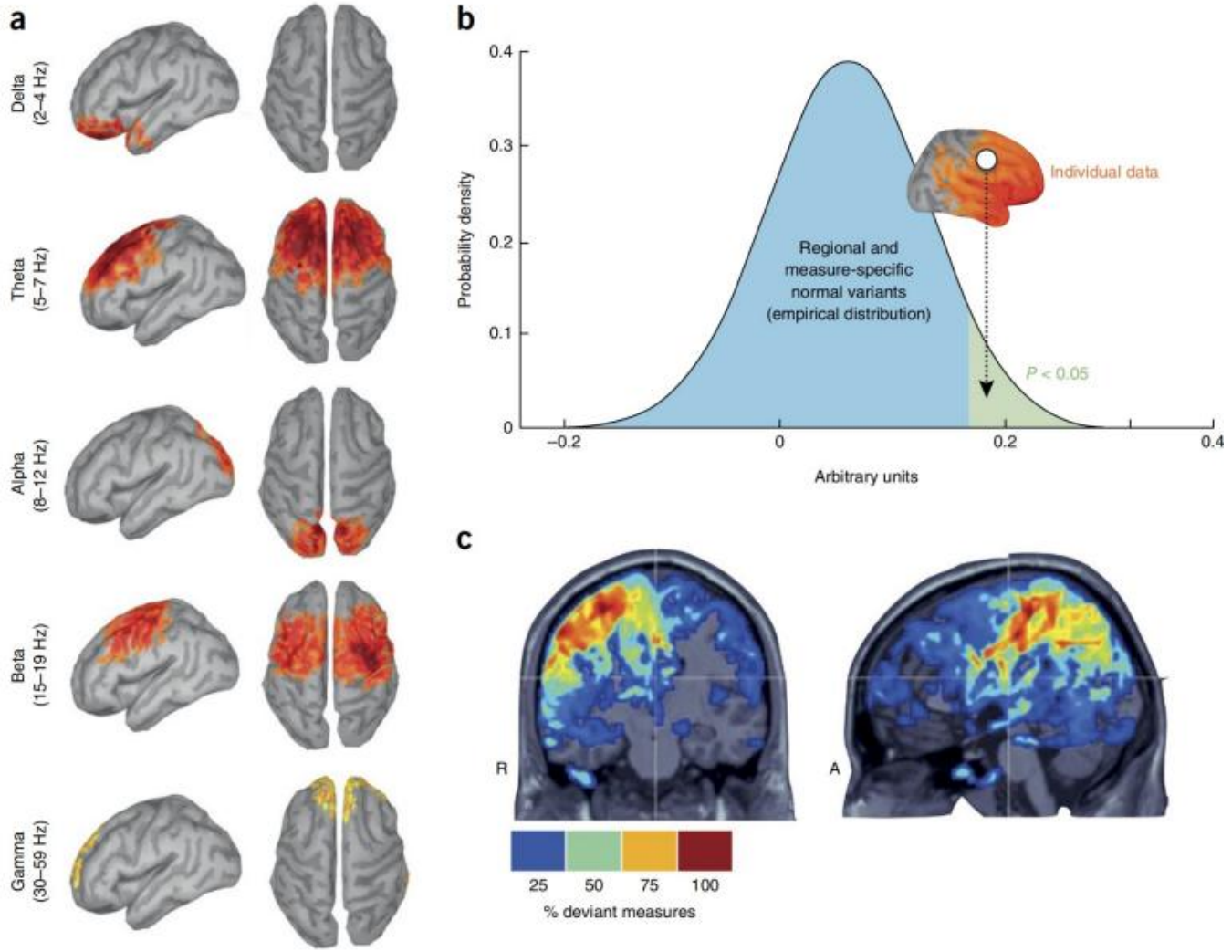

Figure 4 Toward big-data MEG. (a) Example of the outcome of an MEG imaging database (data from OMEGA84). Ninety-six healthy participants were scanned in the resting state for 15 min with their eyes open. MEG imaging of their cortical activity was performed using the same method as for Figure 2. The average distribution of the magnitude of ongoing brain rhythms (from delta to gamma) found in the cohort are registered to and represented on the Colin27 brain template cortical surface. (b) Large data repositories such as OMEGA can be used to establish normative and patient variants of any analytic measure taken from MEG source signals. This is illustrated here, where for each measure and each brain location, the values obtained in a tested individual or group dataset can be assessed with respect to their empirical distribution in the databank. (c) Practical summarizing and visualization solutions can reveal the anatomical locations where, for example, a single or cumulated measures from the individual data from one patient deviate from those observed in the reference normative repository. Here, for instance, the colored brain locations indicate where abnormal strengths of oscillatory brain activity have been detected in the resting state and in multiple frequency bands in a patient with epilepsy.

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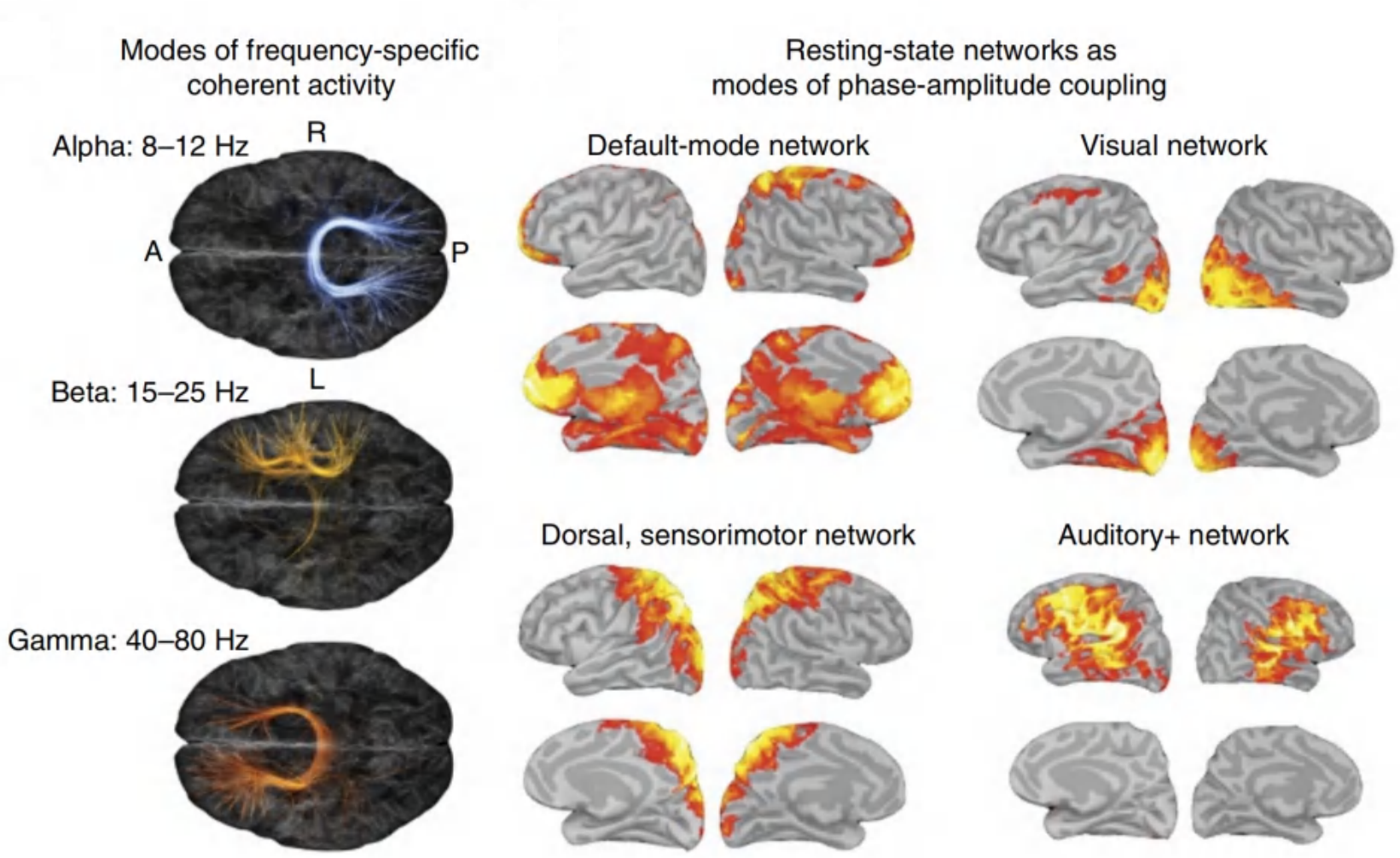

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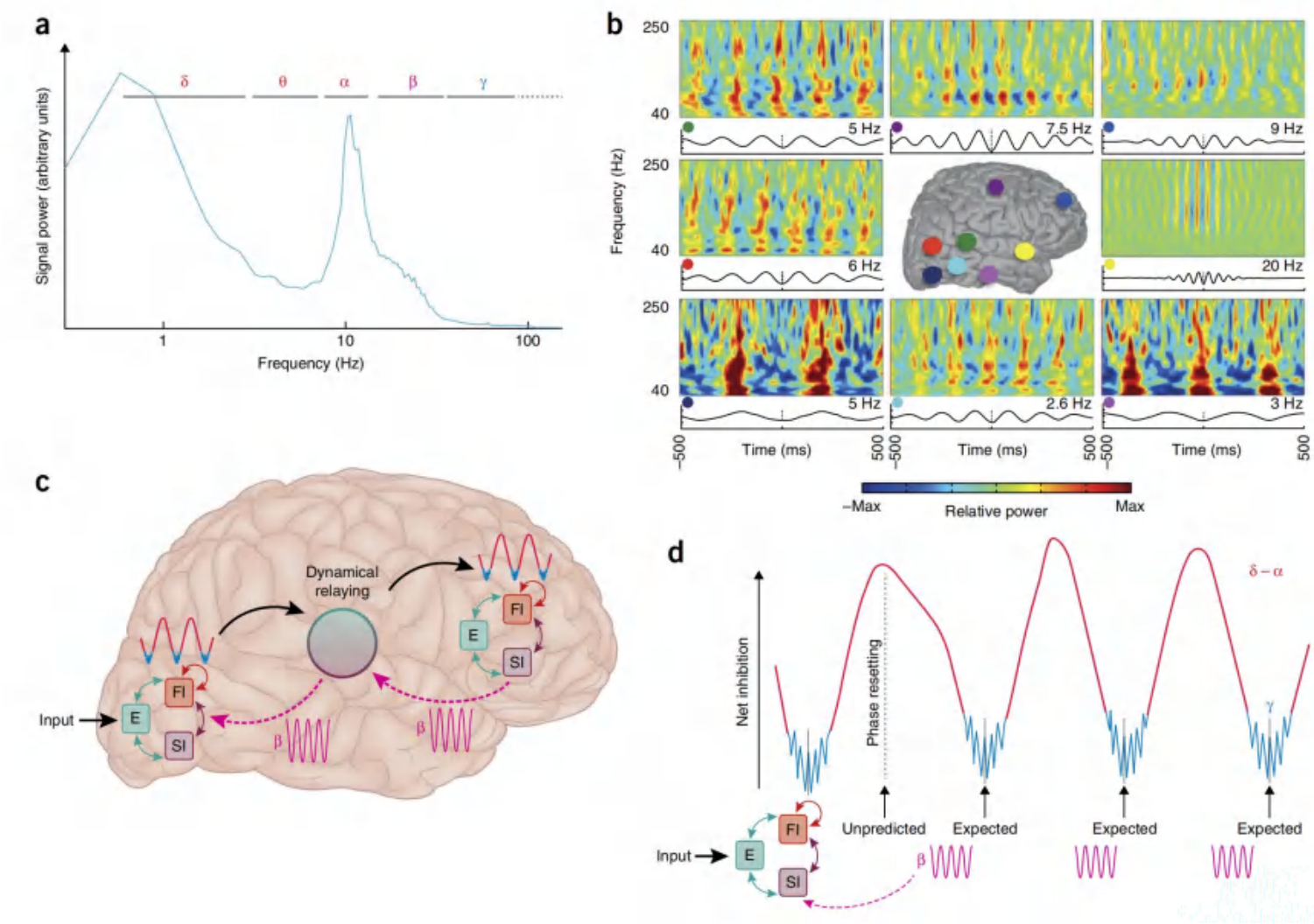

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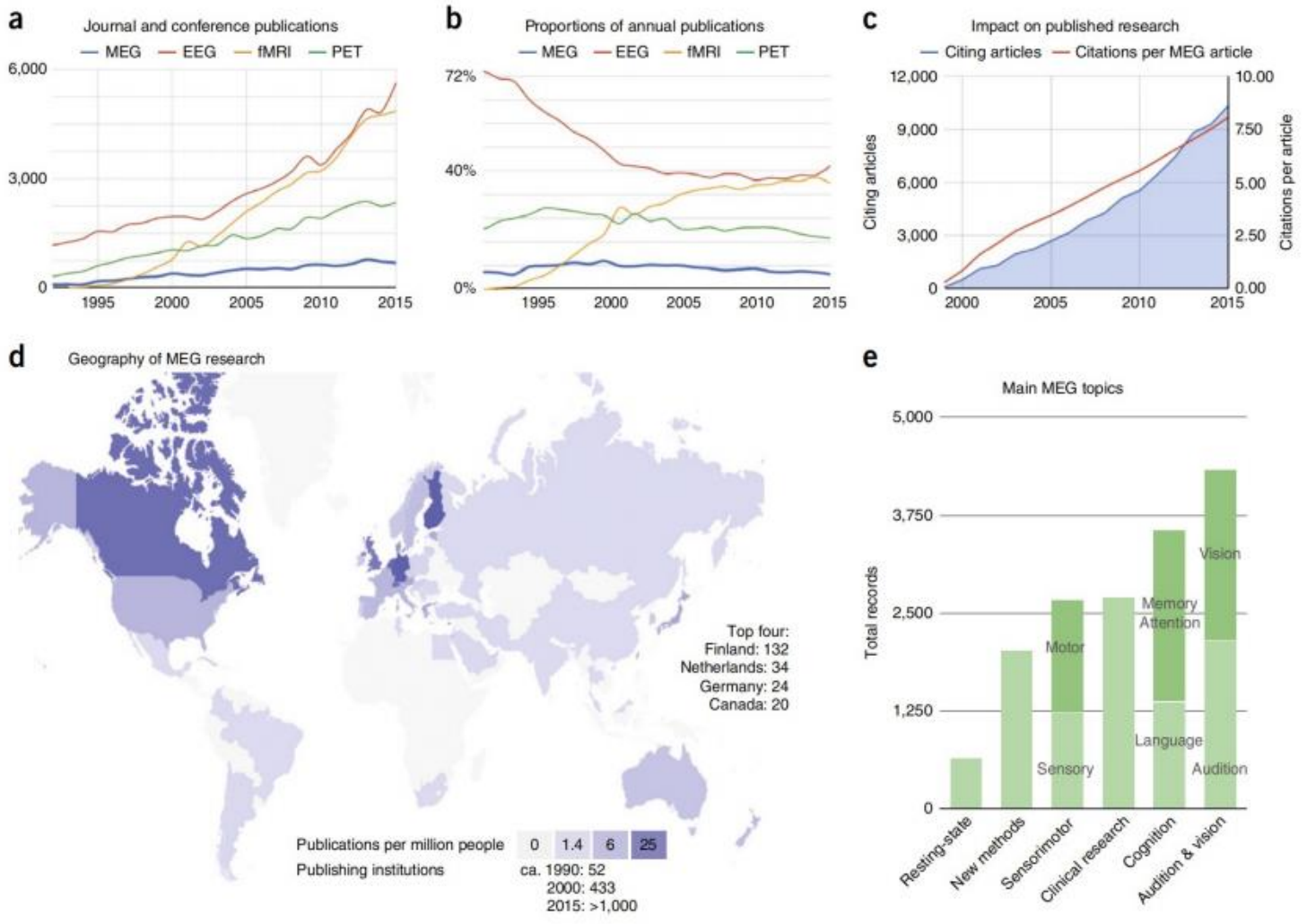
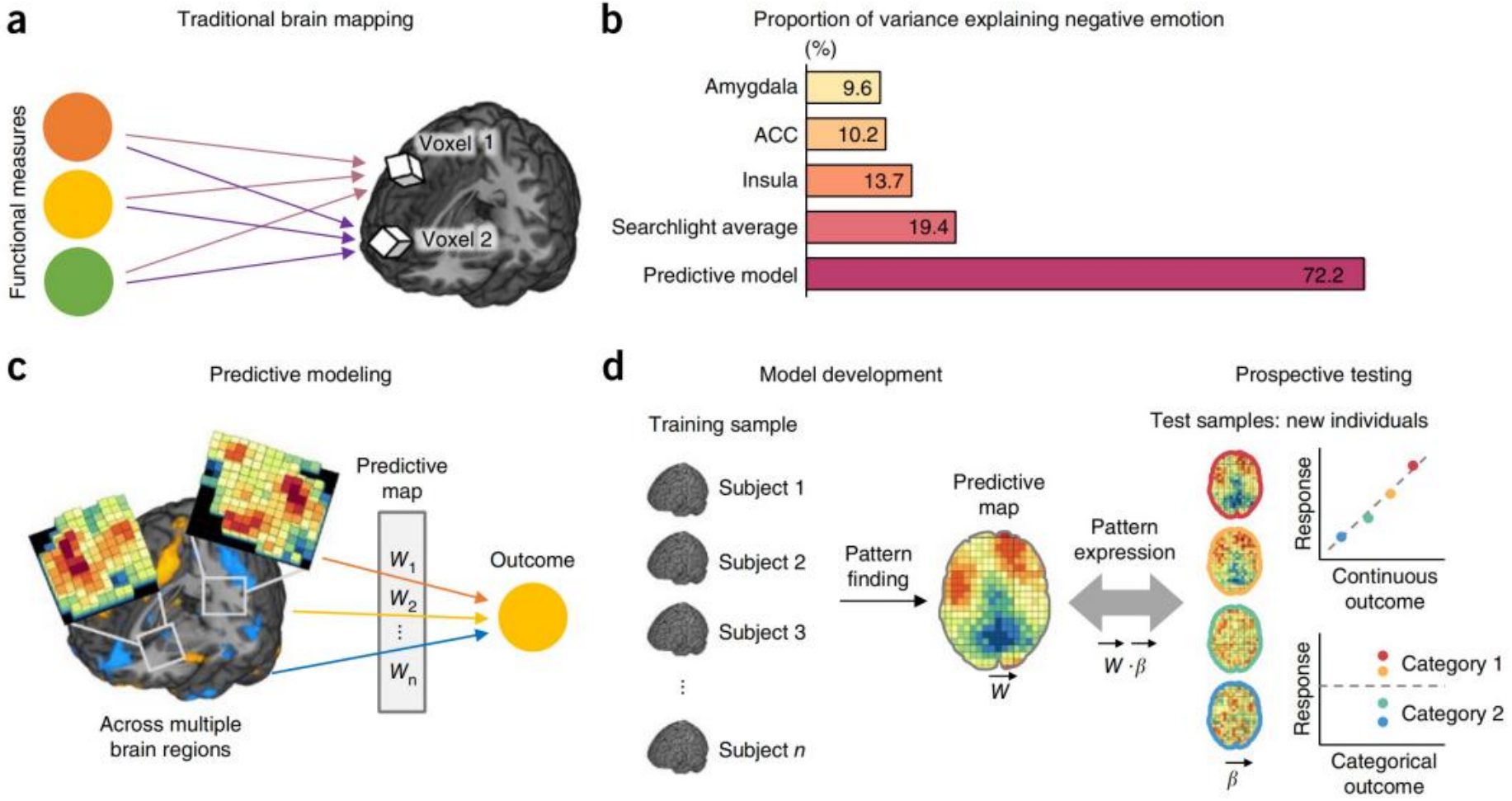


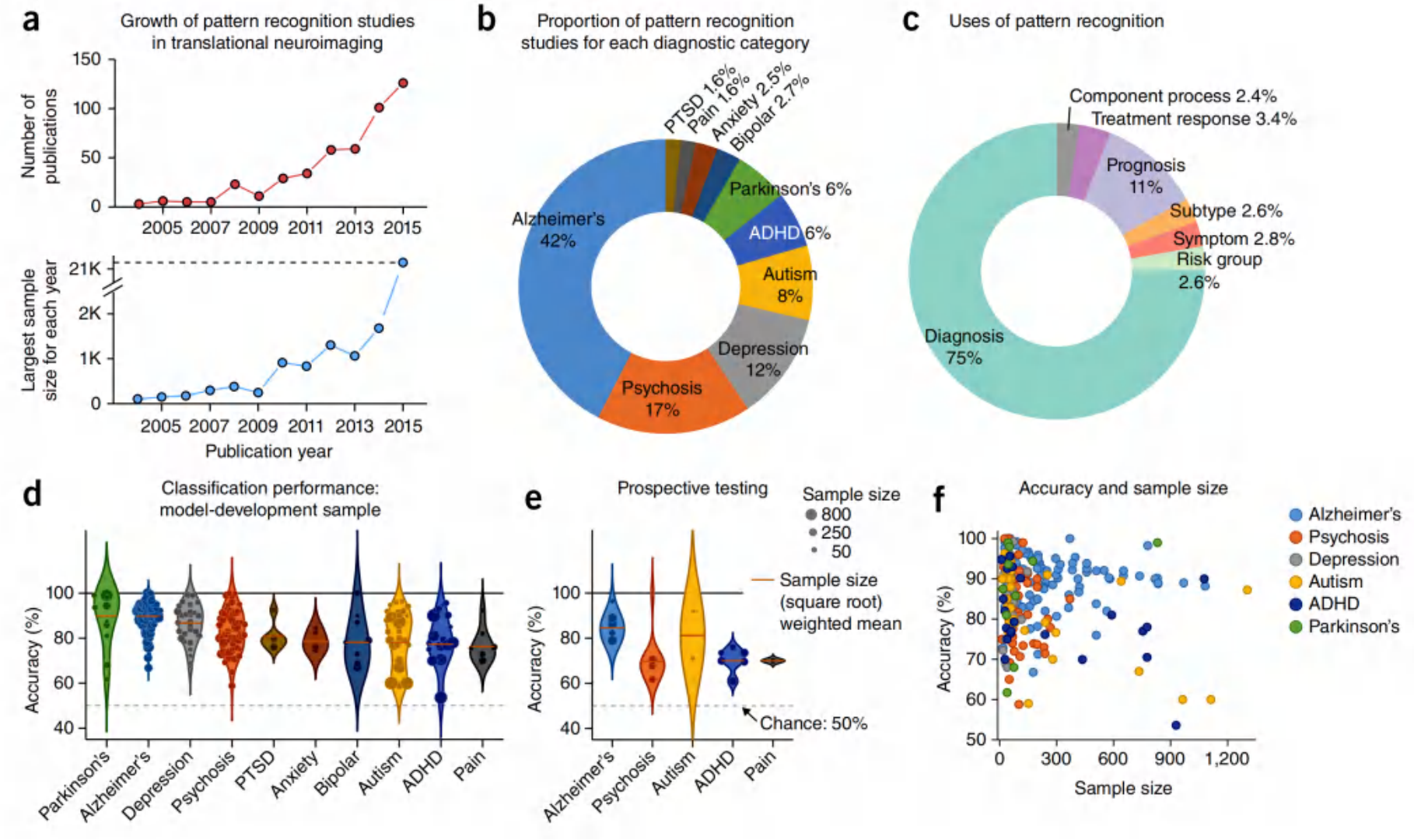
Baillet (2017) *Nature Neuroscience*, 20:327-338

Building Better Bio-Markers



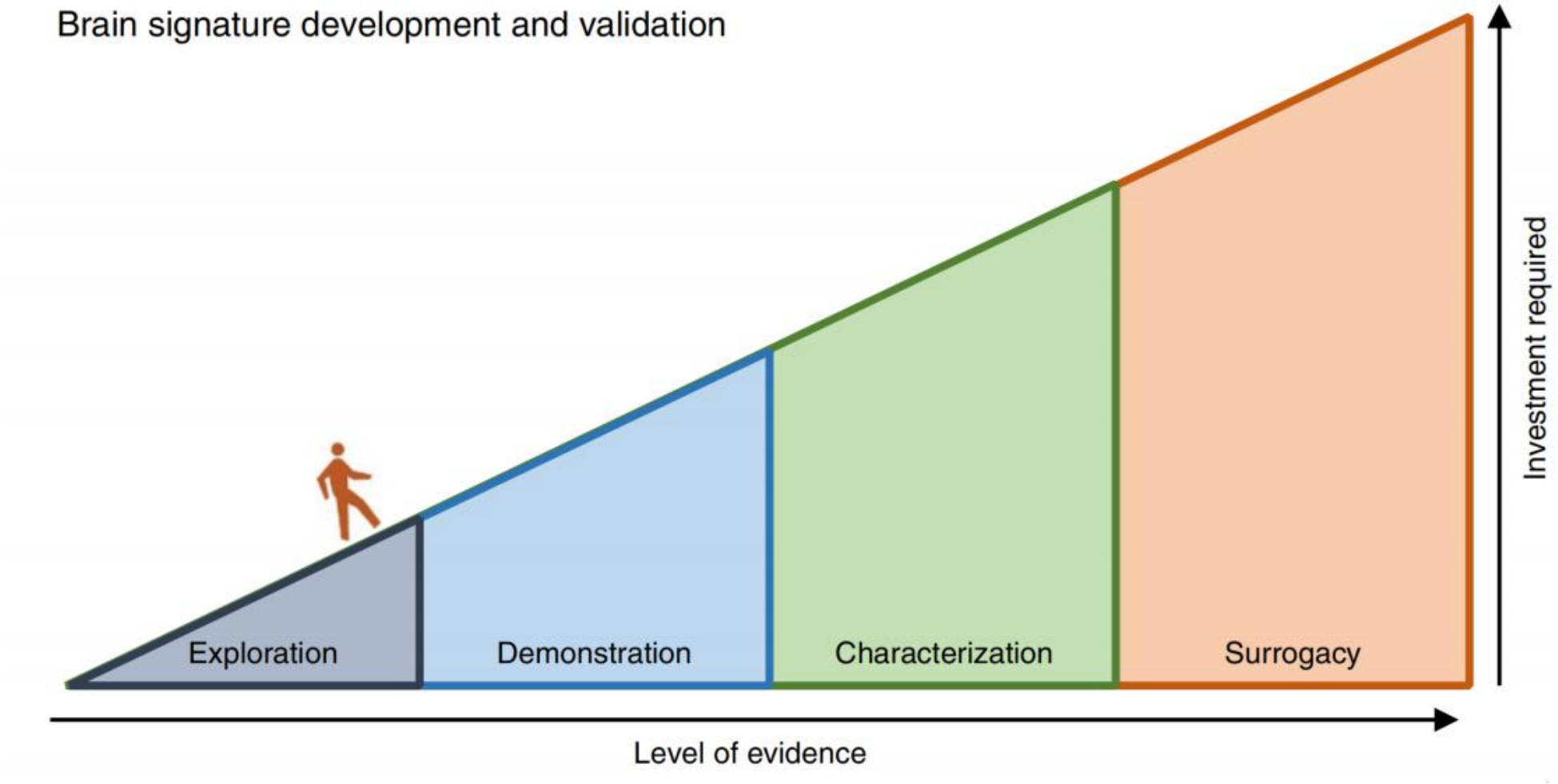
Woo et al. (2017) *Nature Neuroscience*, 20:365-377

Building Better Bio-Markers



Woo et al. (2017) *Nature Neuroscience*, 20:365-377

Building Better Bio-Markers



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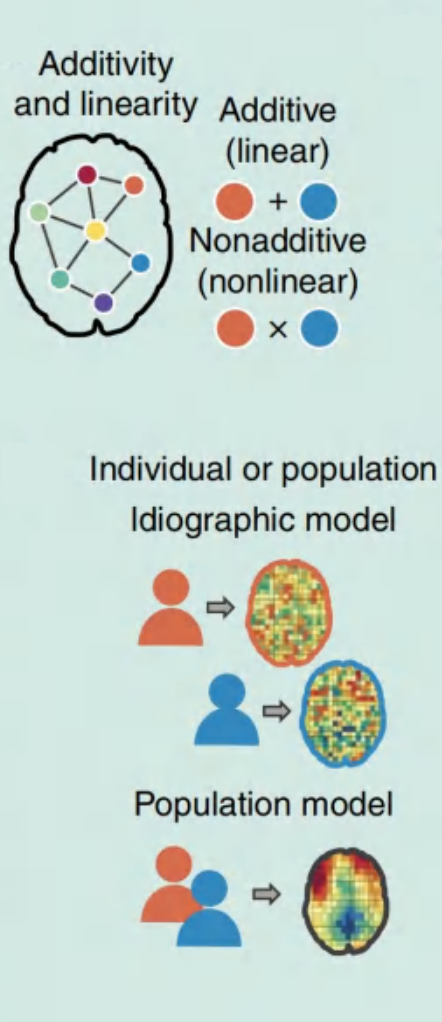

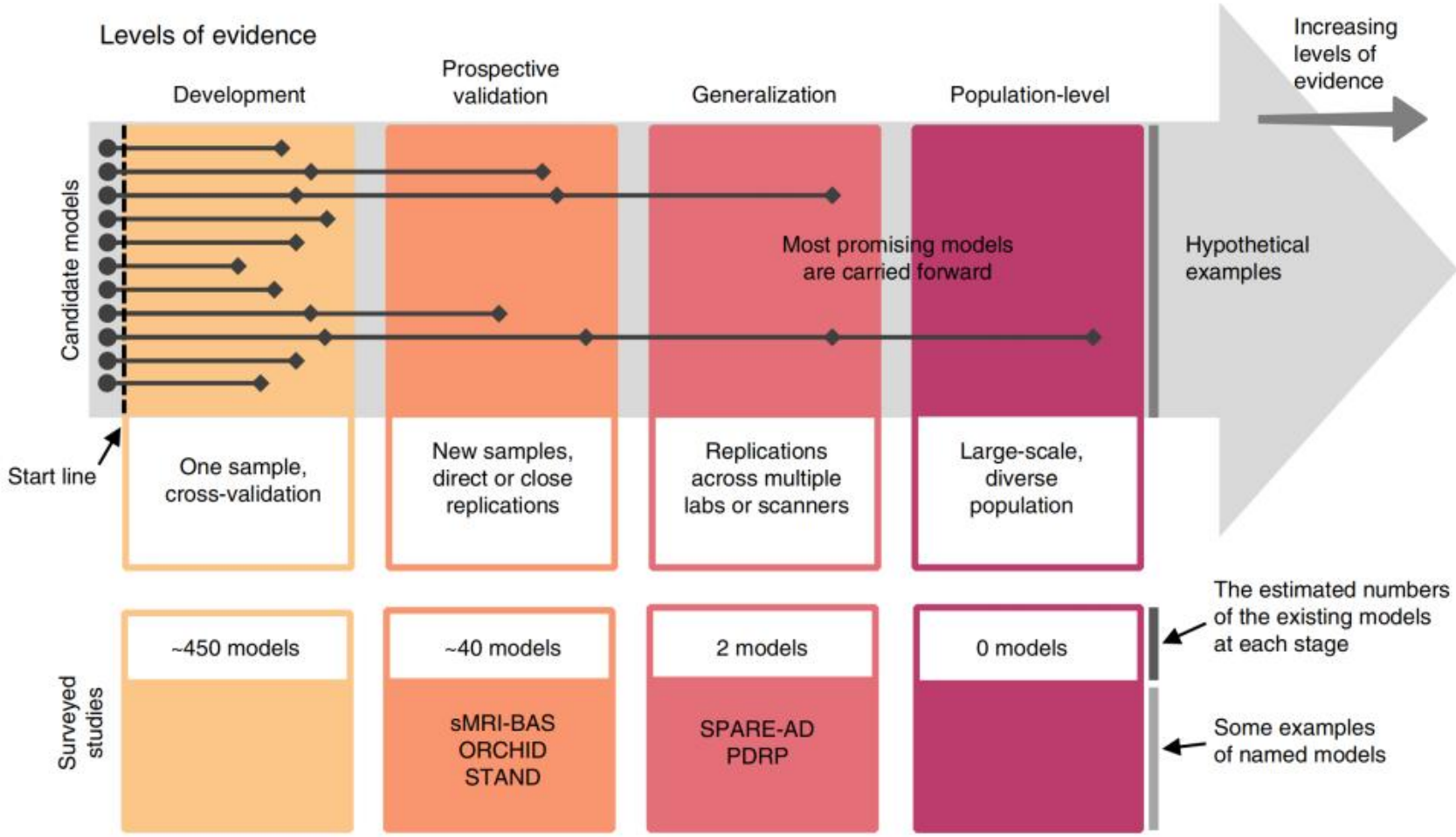

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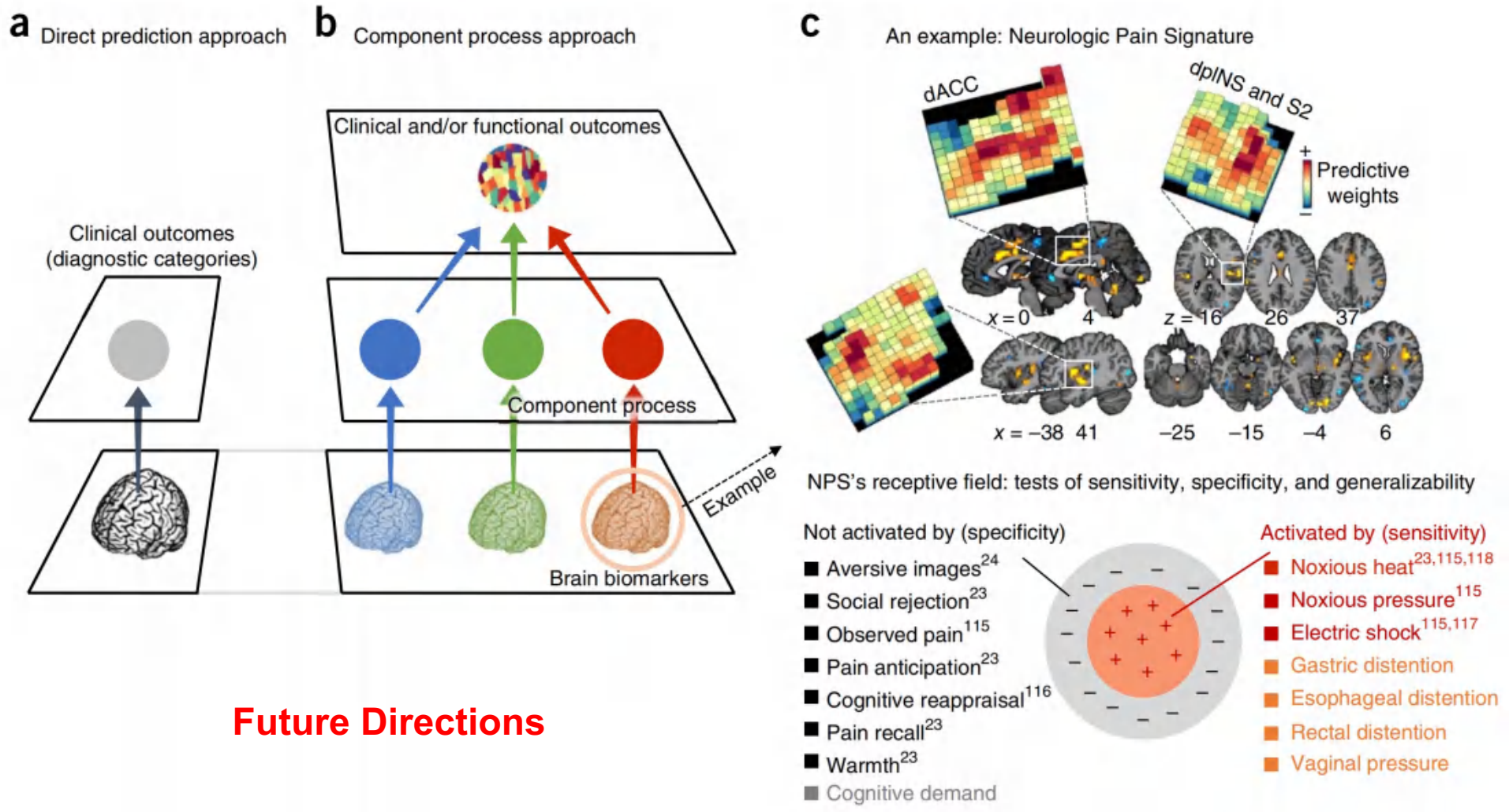
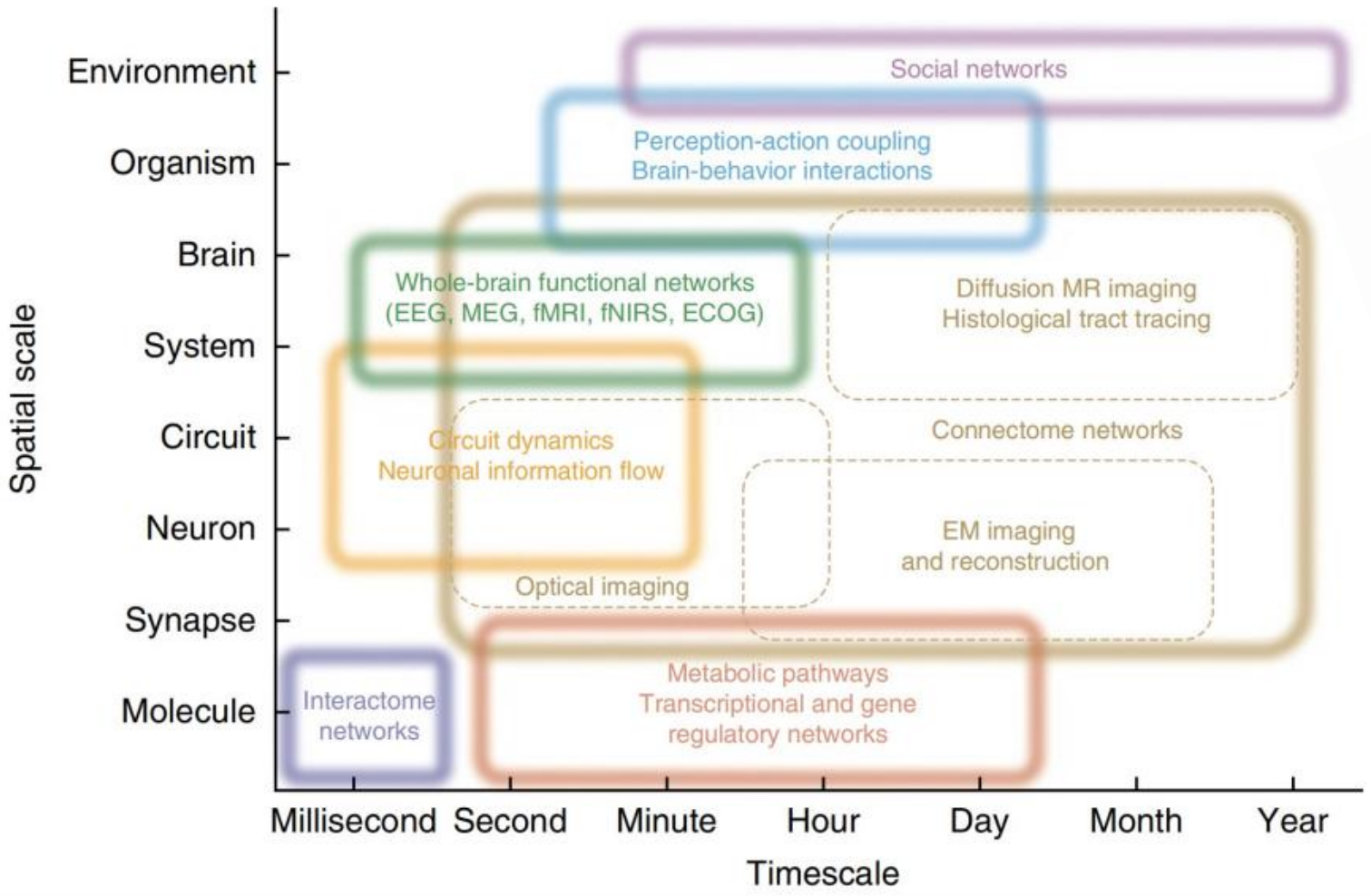


Future Directions

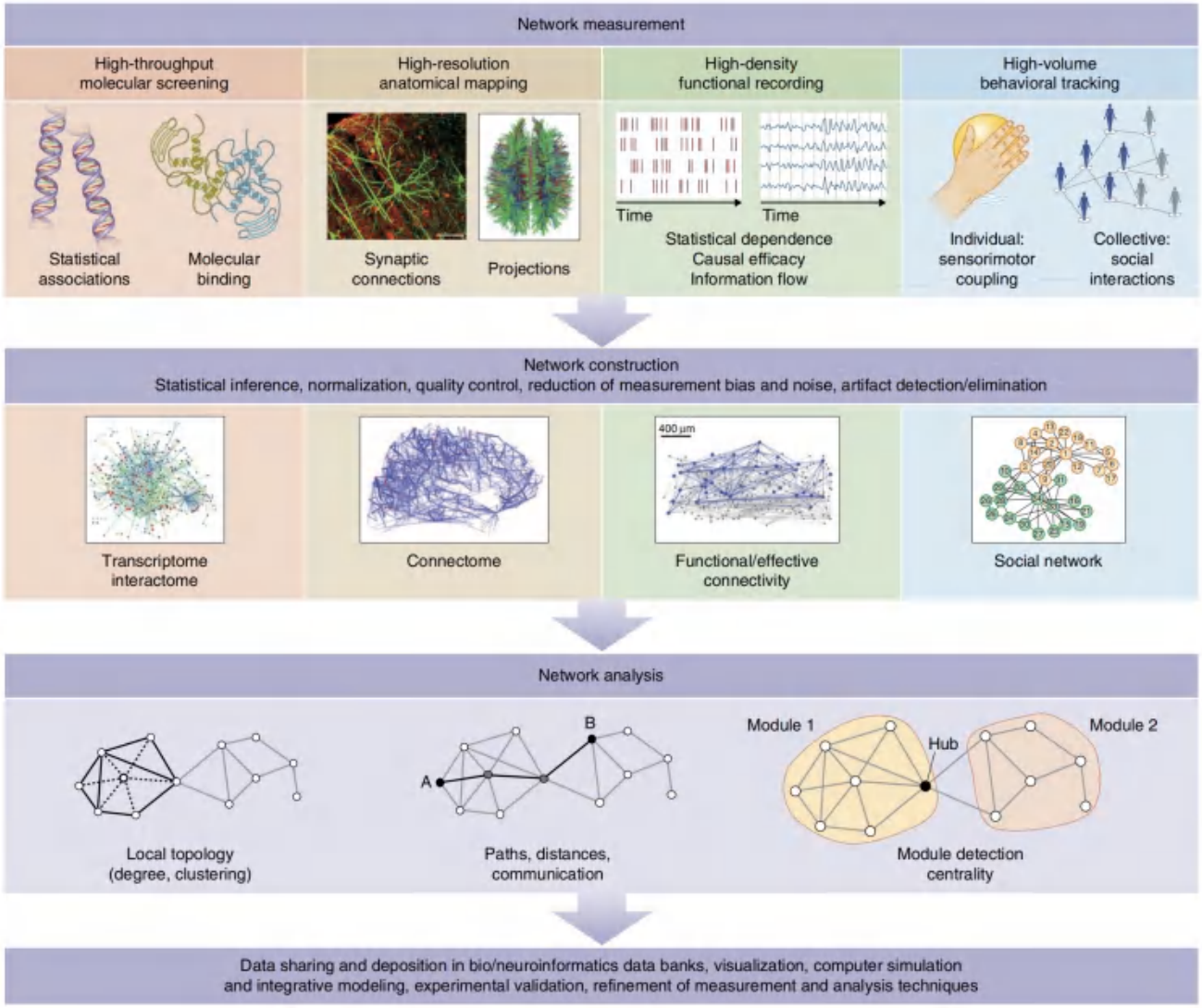
Woo et al. (2017) *Nature Neuroscience*, 20:365-377

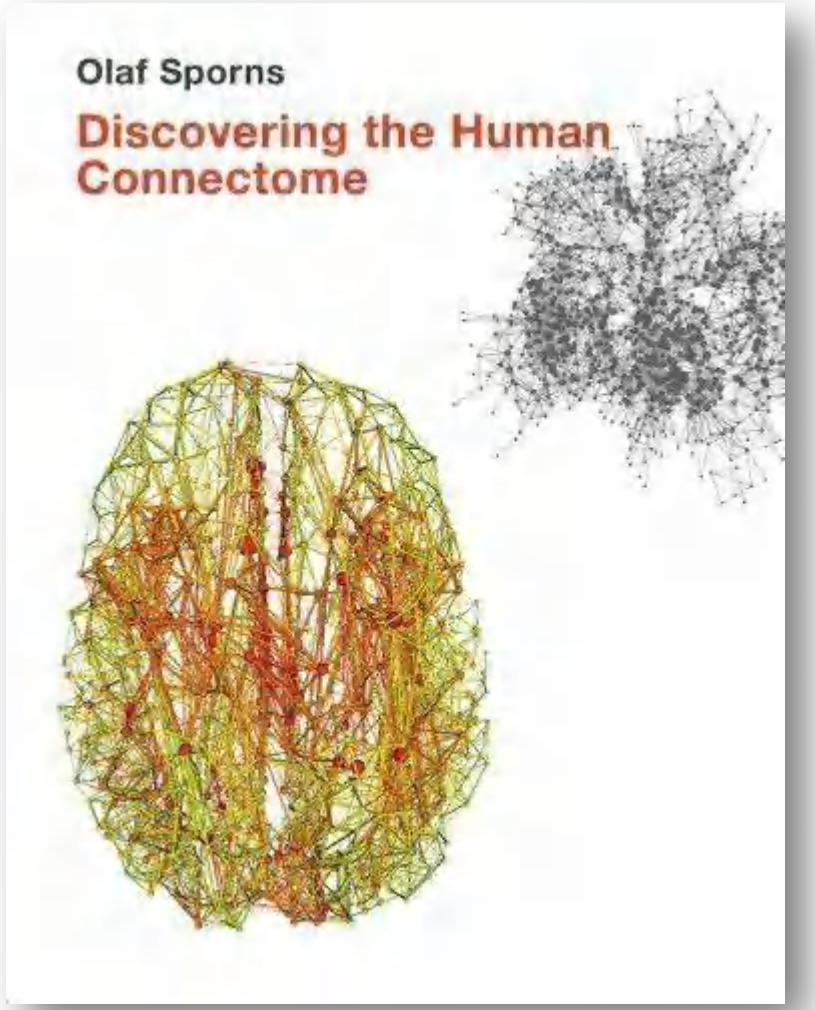
Network Neuroscience



Bassett & Sporns (2017) *Nature Neuroscience*, 20:353-364

Network Neuroscience





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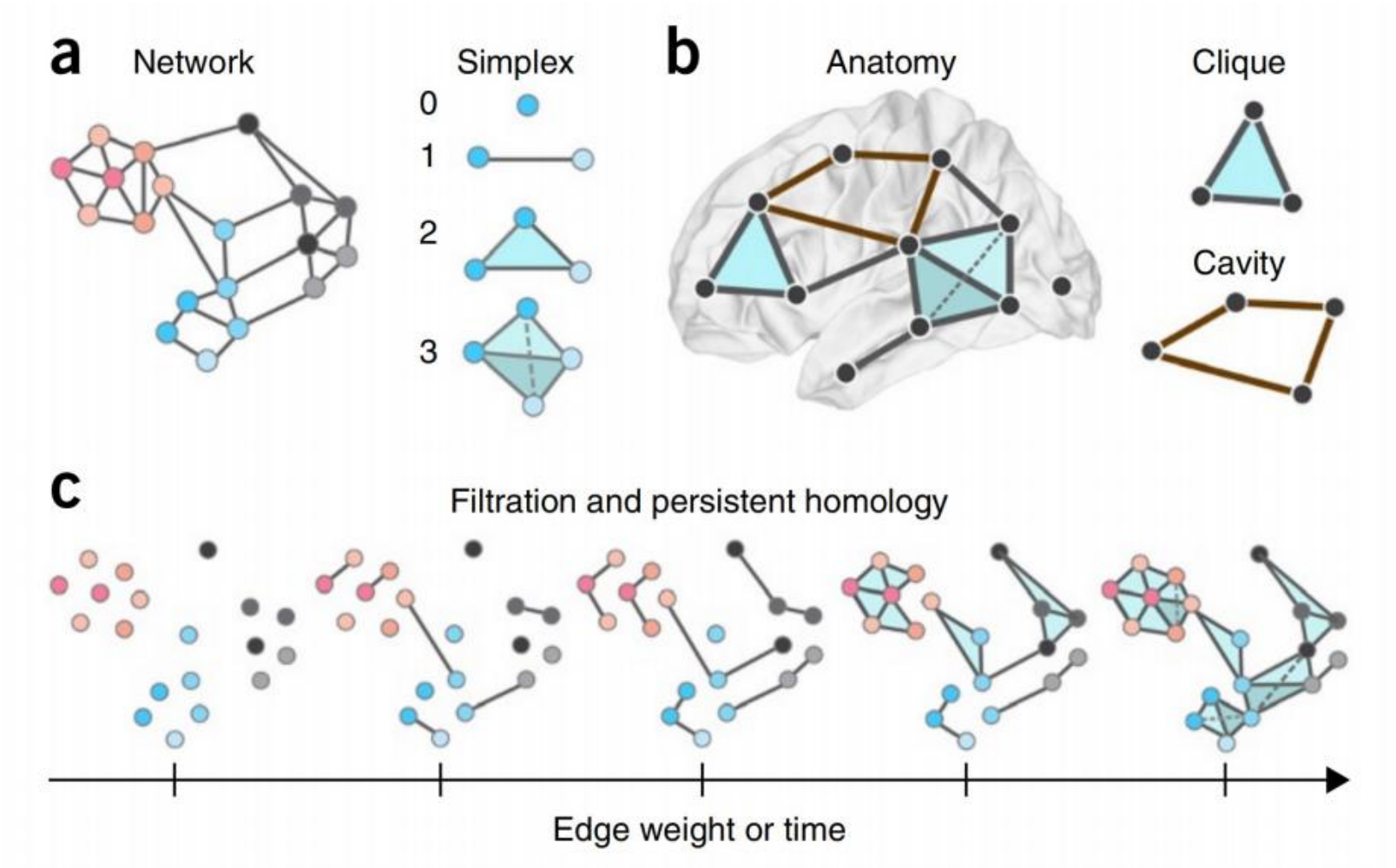

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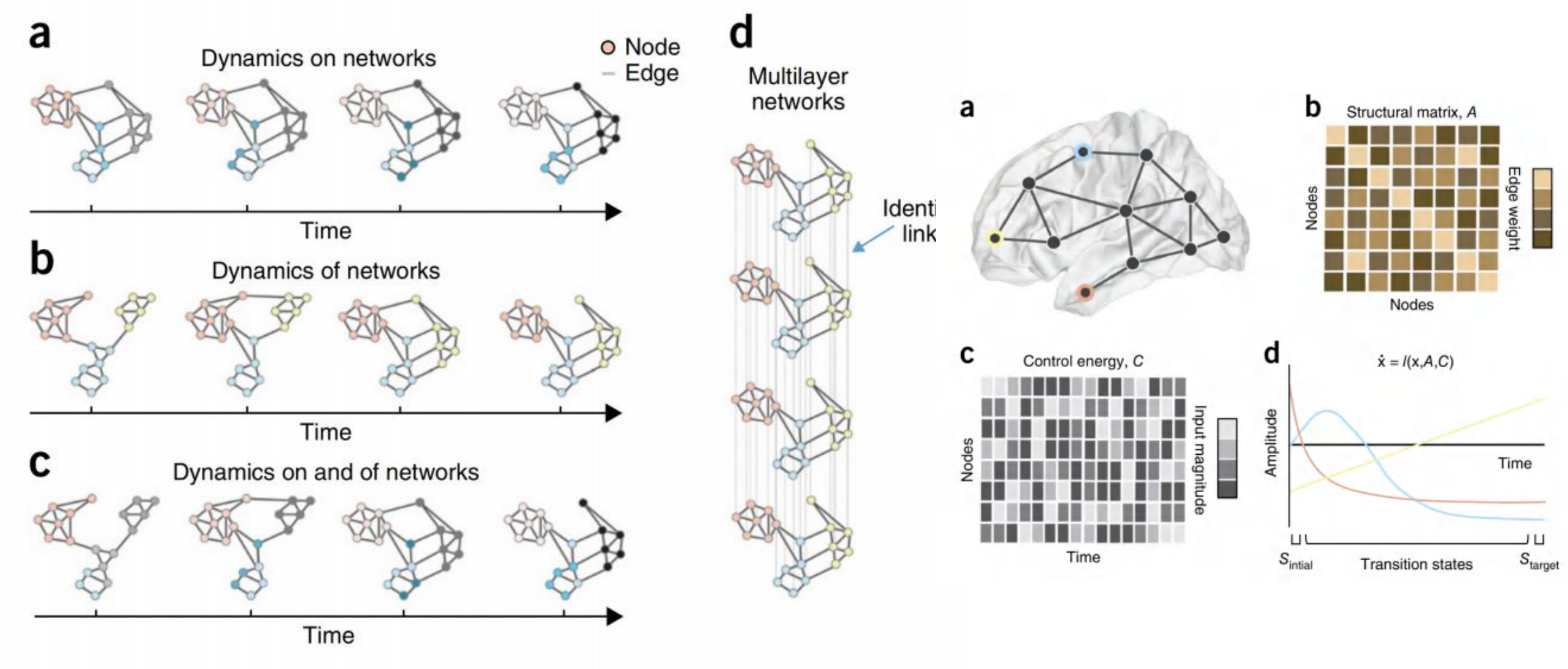

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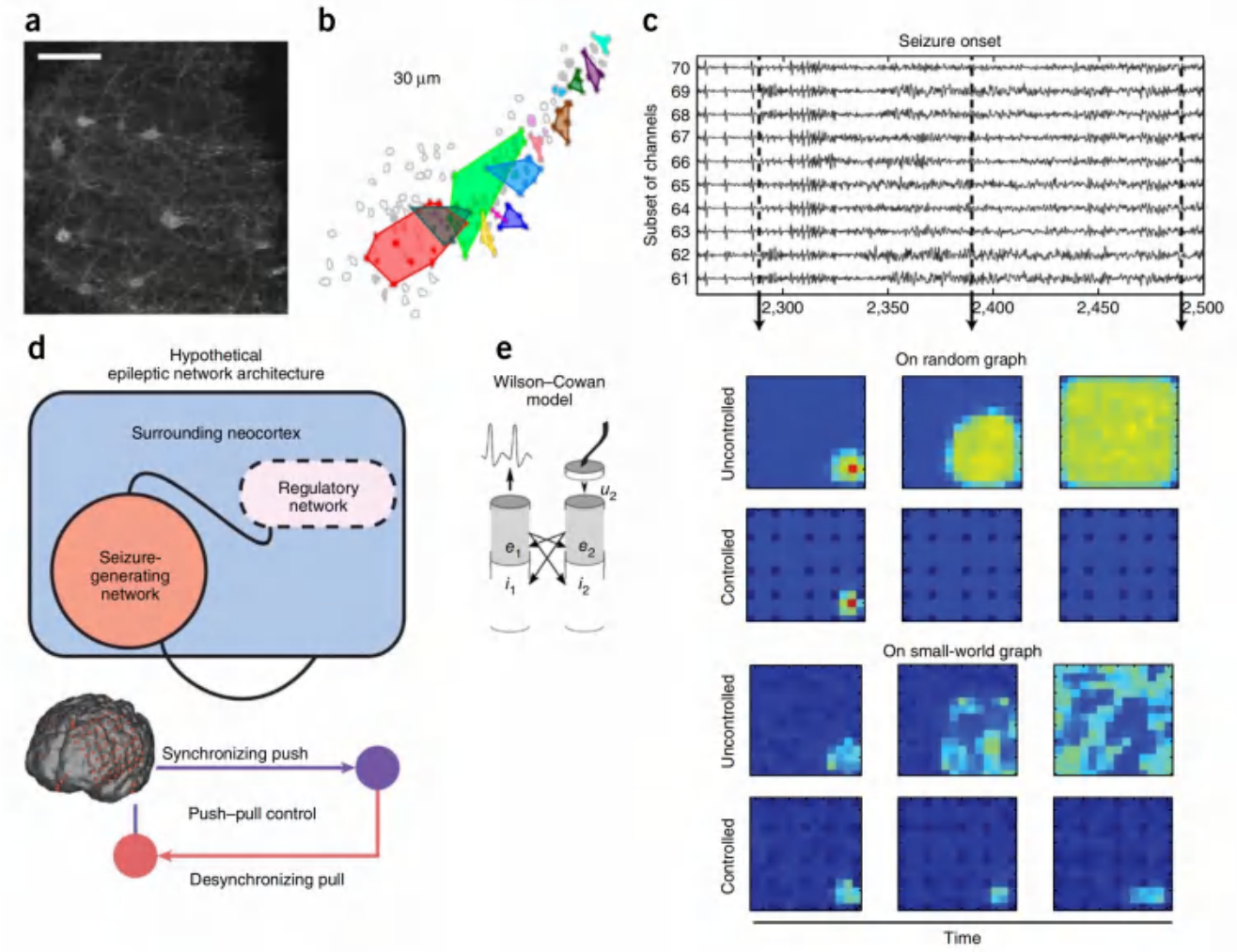

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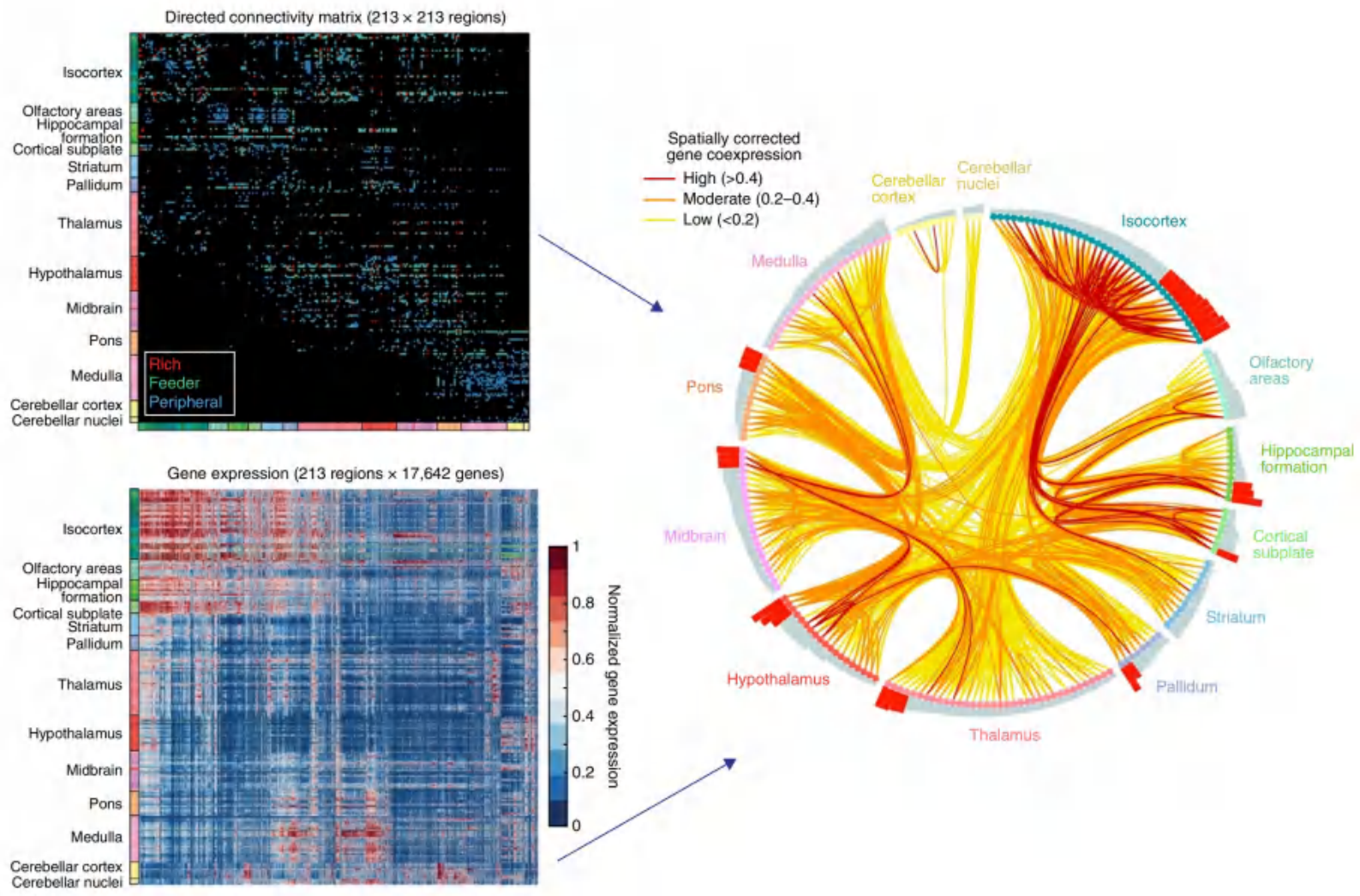

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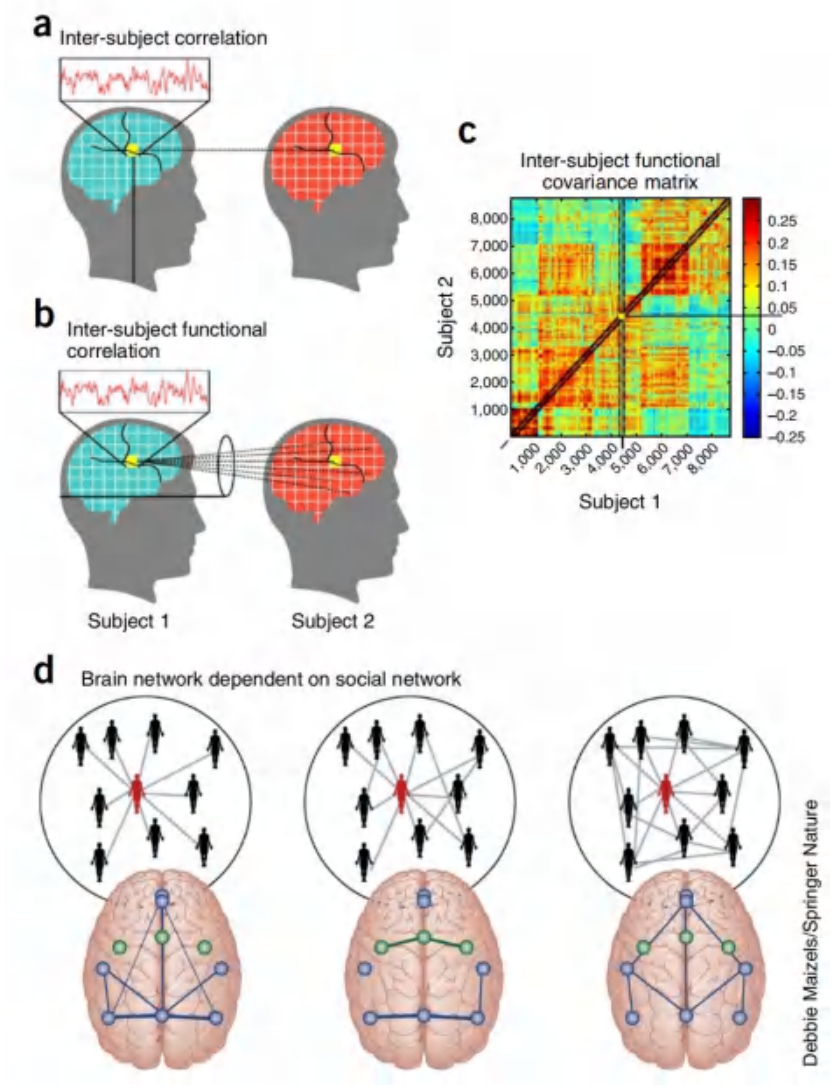


Figure 8 Crossing scales from brain networks to social networks. (**a**–**c**) As we interact with one another, our patterns of brain activity can track together, whether in a single voxel (**a**; inter-subject correlations), from a single voxel to other voxels (**b**; inter-subject functional correlation) or from any voxel to any other voxel (**c**; inter-subject functional covariance). These patterns can be studied from a network perspective using the tools of graph theory to better understand how relationships between individuals affect the similarities and differences in our patterns of brain activity. Taking the idea one step further, we can study how the patterns of brain activity in a person who is central in their social network differ from the patterns of brain activity in a person who is less central to their social network. Indeed, how our brains respond to or can be predicted from our social networks is a critical open question with direct import for health interventions at the large-scale of neighborhoods, cities, countries, and cultures (see also ref. 137). **a**–**c** adapted from ref. 149, Springer Nature, and **d** adapted from ref. 150, R. Schmaelzle, M.B. O'Donnell, J.O. Garcia, C.N.C. Cascio, J. Bayer, D. Bassett, J. Vettel and E.B. Falk.

Bassett & Sporns (2017) *Nature Neuroscience*, 20:353-364

The Most Recent Wave of Brain Connectivity

REVIEW

Atlas-based data integration for mapping the connections and architecture of the brain

Trygve B. Leergaard* and Jan G. Bjaalie

REVIEW

Solving brain circuit function and dysfunction with computational modeling and optogenetic fMRI

Jin Hyung Lee[1,2,3,4]*, Qin Liu[1]†, Ehsan Dadgar-Kiani[1,2]

REVIEW

Scale matters: The nested human connectome

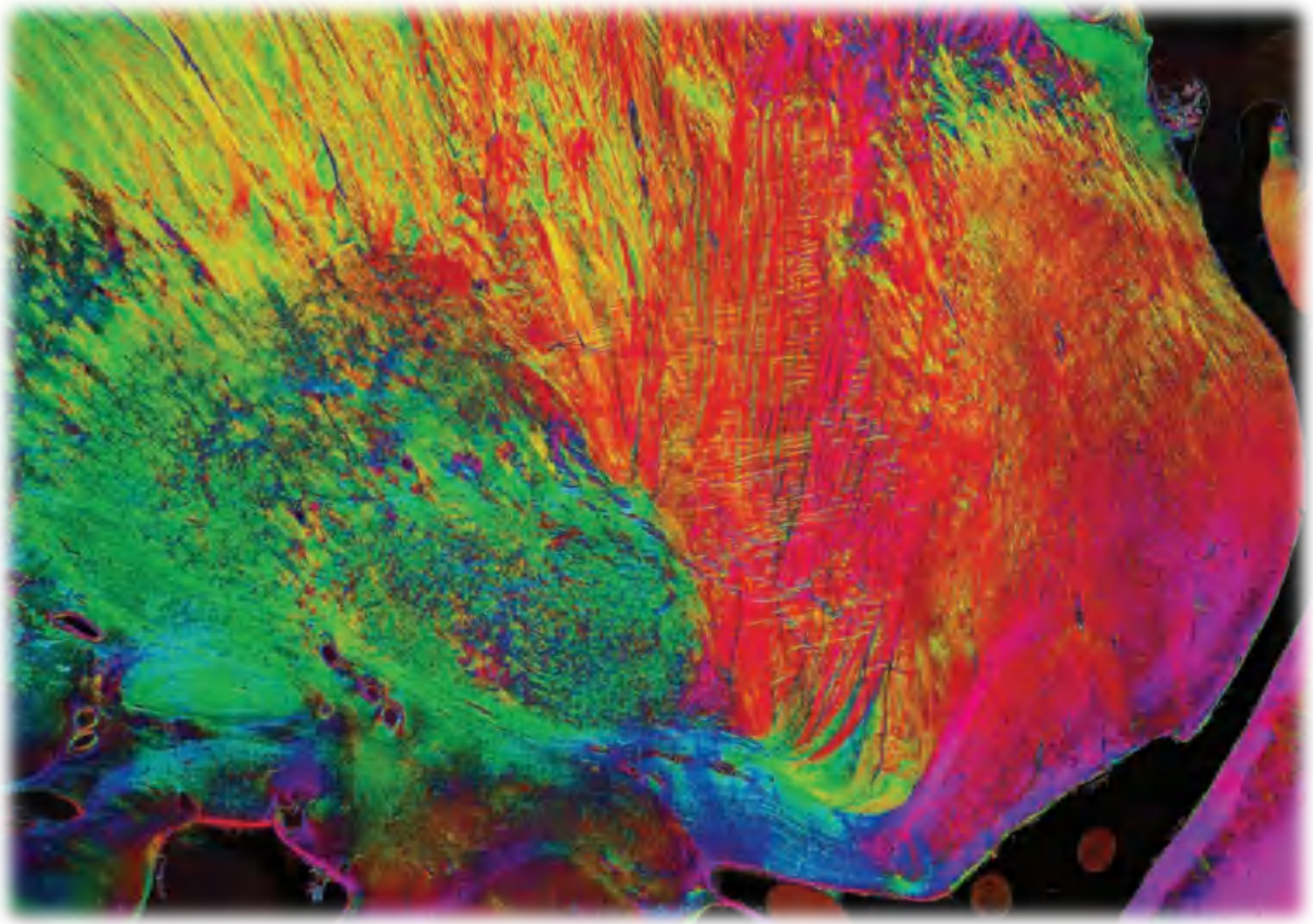
Markus Axer[1,2]* and Katrin Amunts[1,3]

REVIEW

The emergent properties of the connected brain

Michel Thiebaut de Schotten[1,2]* and Stephanie J. Forkel[2,3,4,5]

No Neuron is An Island



SPECIAL SECTION

REVIEWS

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Solving brain circuit function and dysfunction with computational modeling and optogenetic fMRI p. 493

Scale matters: The nested human connectome p. 500

The emergent properties of the connected brain p. 505

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RESEARCH ARTICLE p. 514

NO NEURON IS AN ISLAND

By **Peter Stern**

The brain is so much more than its constituent cells. Each neuron in the brain connects with thousands of other neurons—but instead of a cacophony of connections, we have a synchronized symphony.

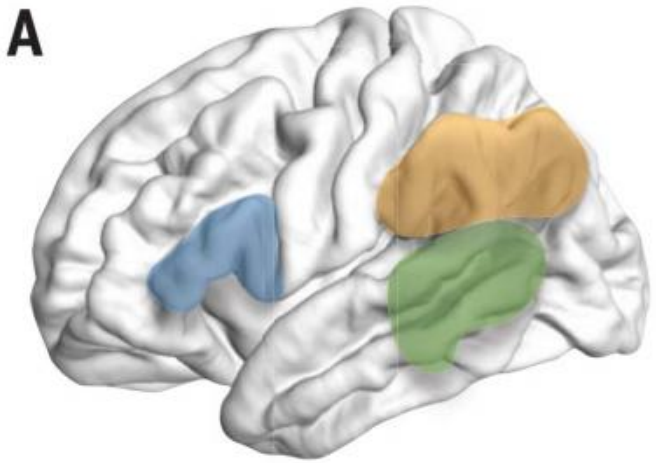
Coordination of the body's myriad functions, behaviors, and thoughts requires large numbers of neurons to act cooperatively and not as isolated entities. The outcomes are driven by the connections between the neurons, whether that involves communicating with a neighboring nerve cell or sending and receiving signals to and from distant areas of the brain.

Innovative neuroscientific techniques allow researchers to specifically stimulate select groups of neurons in animals and noninvasively measure how they activate other parts of the brain, whether near or far. Advances in brain imaging reveal anatomical projections and functional connectivity patterns, allowing us to see their activation in real time. The first digital brain atlases of the mouse and rat, for example, provide astonishing insights into the connectivity of cells.

With a better understanding of the complexity of normal brain connections, we learn more about what goes wrong when they are disrupted. And the view of connectivity patterns in various organisms begins to reveal the steps involved in the evolution from the simplest neuronal nets to the multilayered, multinucleate mammalian brain.

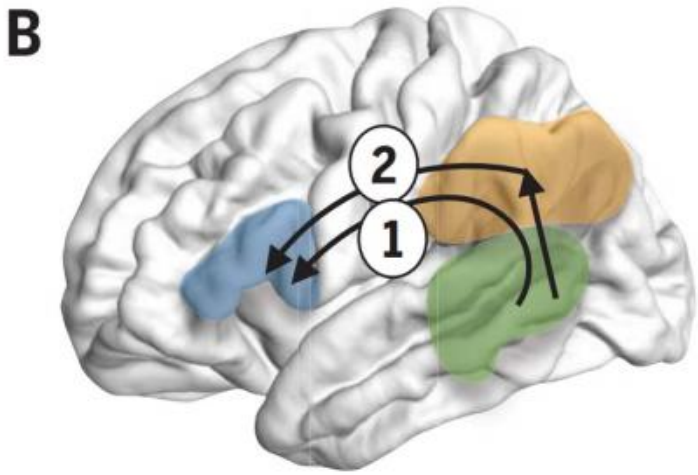
Without connections that run smoothly, the brain is nothing more than a pile of neurons.

The Emergent Properties of The Connected Brain



Modular language model

- Broca's area for articulation
- Geschwind's area for concepts
- Wernicke's area for comprehension



Hierarchical language model

1. Direct processing route
2. Indirect processing route

The Emergent Properties of The Connected Brain