Establishing homology between monkey and human brains

Tor D Wager & Tal Yarkoni

Neuroimaging methods are beginning to provide promising ways of understanding the functional organization of the brain across species.

Recent decades have seen a massive scientific effort to identify the functional organization of the brain in both humans and non–human species. Work in humans and other species provides complementary insights: animal models provide unique opportunities for invasive study of biological mechanisms, but differences in brain organization across species are a major obstacle to the identification of functional homologies. As a result, human and animal work is all too often discussed in parallel, separate literature. In this issue of *Nature Methods*, Mantini and colleagues introduce a method for identifying cross-species homologies to the neuroscientist's arsenal[1].

Their technique, interspecies activity correlation (ISAC), uses functional magnetic resonance imaging (fMRI) to identify brain regions in which humans and monkeys exposed to the same dynamic stimulus—a 30-minute clip from the movie *The Good, the Bad and the Ugly*—show correlated patterns of activity[1] (**Fig. 1**). The premise is that homologous regions should have similar patterns of activity across species. For example, a brain region sensitive to a particular configuration of features, including visual motion, hands, faces, object and others, should show a similar time course of activity in both species—even if its anatomical location differs across species and even if the precise features that drive the area's neurons have not yet been specified.

Previously, homology has been established primarily based on anatomical and cytoarchitectural similarity[2] or on functional responses to specific stimuli (for example, motion in a particular part of the visual field[3,4]). However, such work is complicated by the absence of a simple 1:1 mapping across species, the great number of possible homologies and the laborious nature of such mapping experiments. The ISAC method is a sort of 'high-throughput' alternative that allows the simultaneous mapping of potential homologous regions across the brain. It does so without reference to particular classes of stimuli, identifying homologous regions that respond to as-yet undefined classes of neural processes, for example, regions that respond to complex combinations across multiple features (hands, objects, faces and others), interactions between visual features and other 'top-down' cognitive processes. In combination with established homologies, the ISAC method is a potentially valuable and important way of synthesizing findings across species.

As with any new method, there are challenges to be overcome. One important obstacle is that the ISAC method[1] requires that humans and monkeys engage the same psychological processes during stimulus viewing. For highly dynamic stimuli such as movies, this is often not the case: humans view a movie in the context of its narrative and meaning, which can influence the strength and quality of attention, eye movements and fMRI activity throughout the cortex and thalamus, including 'early' visual areas[5]. Consequently, some homologies may be missed and some false homologies may be identified.

Homologies will be missed when the same process is engaged at different times in each species—for example, if humans pay attention to facial cues that monkeys are oblivious to. False homologies could be identified when the same stimulus engages attention to different aspects of complex stimuli—for instance, Clint Eastwood's appearance on screen is associated with both low-level features (for example, faces and gross body movements) as well as multimodal and high-level ones (for example, speech and facial affect). Monkeys might attend primarily to Eastwood's gross movements, whereas humans might attend to his facial expressions and speech, causing the ISAC method

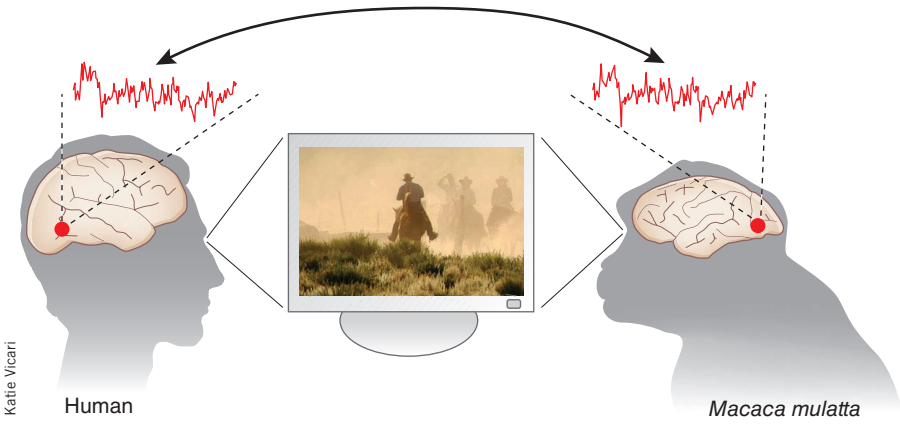

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Figure 1 | The ISAC method. Humans and monkeys watch the same film as their brains are scanned with fMRI. The time course of fMRI activity during viewing is extracted from 'seed' regions in human participants and correlated with the fMRI signal in monkeys, and vice versa, with an adjustment made for interspecies differences in vascular hemodynamics. After statistical thresholding, the resulting maps in each species show areas that are potentially homologous with the targeted seed region in the other species.

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to identify a spurious 'homology' between regions responsive to motion and body parts in monkeys and faces, prosody and social cognition in humans. This phenomenon provides a rival explanation for some of the putative homologies Mantini *et al.*[1] identify across anatomically divergent regions.

The susceptibility of the ISAC method to these pitfalls will no doubt be investigated in future studies, as will its ability to provide information on homology outside the visual system. Subsequent studies could replicate interspecies activity correlations across different types of stimulus sets, including those that monkeys and humans are more likely to perceive in similar ways. In addition, putative homologies could be corroborated by follow-up fMRI or electrophysiological studies attempting to find the critical features that drive regional activity across species.

Another exciting future direction is the hybridization of the ISAC method with established techniques for retinotopic and functional mapping so that candidate homologous regions may be jointly constrained by interspecies activity correlations and similarity in functional responses. Ultimately, this type of approach could be used to integrate other types of information as well, including patterns of gene expression and cytoarchitecture. This strategy may be supplemented by methodological developments. Multivariate methods[6] can be used to both bypass the need for a priori definition of 'seed' regions based on anatomy and simultaneously consider multiple sources of information. Pattern-based methods could be used to identify regions that code for similar types of information across species[4].

In sum, the ISAC approach will lead to new opportunities, new challenges and new conflicts to be resolved, as any new technique does. It comes at a crucial and exciting time in the neurosciences, as new techniques including fMRI can finally be used to directly map brain function in humans and other species, and this wealth of parallel information must be integrated to bring insights from animal models to bear on the human condition in increasingly precise ways.

COMPETING FINANCIAL INTERESTS
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Modeling cellular signaling: taking space into the computation

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In living systems, chemical reactions and the geometry of cells feed back on each other. Methods for computational modeling are beginning to take this complexity into account.

We often describe cellular signaling networks in terms of circuits or wiring diagrams, but that view is incomplete. In a computer, computation takes place on a static network of electric wires. In biological systems, computation takes place in networks of biochemical reactions. A key difference is that biochemical reactions actively change the shape of cells and organelles over time, directly affecting the spatial position of molecules and the possible biochemical reactions that can occur. In other words, cells and tissues constantly remodel the structure of the computing networks—the 'wires'—by altering the spatial organization of the reactants. Hence, in biology the remodeling of the network is as important to the computation as the reactions taking place. A new computational method described in this issue of *Nature Methods*[1] now makes it easier for biologists to model such feedback between chemical reactions and geometry.

Taking into account this feedback in computational models requires addressing two key challenges. First, one must track the effects of chemical reactions on the mechanics and geometry of cells and tissues[2]. Second the network of possible biochemical reactions must be locally reconstructed as the cellular geometry changes, a task that is computationally expensive because of the combinatorial complexity of signaling networks[3].

Angermann *et al.*[1] describe a new computational approach that addresses these challenges by combining advanced spatial simulation techniques with a rule-based description of molecular interactions (**Fig. 1**). They implement this hybrid approach in the general-purpose software platform Simmune[4], which provides a flexible graphical interface for constructing and simulating such models. Together, the new methods and graphical modeling environment of Simmune should expand the scope of spatial models of cellular signaling and accelerate the construction of new models.

One of the standard methods for modeling the spatial localization of biochemical reactions is partial differential equations (PDEs). With this approach, three-dimensional (3D) spatial compartments, such as cells and organelles, are subdivided into small volumes, called voxels. PDEs are then used to compute how the average concentration of every molecular species in each voxel changes over time. As the shape of the compartment changes, voxels can be deformed, added or removed. Some simulation tools are starting to provide these spatial capabilities, such as CompuCell3D (ref. 5) and Virtual Cell[6]. A fundamental limitation of PDE models is that a separate equation and variable is required for every potential molecular species. Taking protein complexes and post-translational modifications into account typically creates an overwhelming number of possible molecular species. This difficulty has been termed the problem of combinatorial complexity[3].

The new methods implemented in Simmune address the problem of combinatorial complexity by using an established rule-based approach[3,7,8] to define the biochemistry of the system. Rules describe only the minimal conditions required for a reaction to occur. Thus, a small set of interaction rules can succinctly represent, without approximation, a much larger reaction network composed of many

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