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Review

Comparing brains by matching connectivity profiles

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ABSTRACT

The great promise of comparative neuroscience is to understand why brains differ by investigating the relations between variations in the organization of different brains, their evolutionary history, and their current ecological niche. For this approach to be successful, the organization of different brains needs to be quantifiable. Here, we present an approach to formally comparing the connectivity of different cortical areas across different brains. We exploit the fact that cortical regions can be characterized by the unique pattern of connectivity, the so-called connectivity fingerprint. By comparing connectivity fingerprints between cortical areas in the human and non-human primate brain we can identify between-species homologs, but also illustrate that is driving differences between species. We illustrate the approach by comparing the organization of the frontal cortex between humans and macaques, showing general similarities combined with some differences in the lateral frontal pole.

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Comparative neuroscience can provide crucial insights into *why* our brain is organized the way it is. Knowing about the organization of the brains of species related to us constrains how we interpret maps of our own neuroanatomy and theories on the function of particular brain areas. In recent years, a number of large-scale projects have been launched aimed at mapping the organization of entire brains across different species. These projects focus on different modalities, ranging from anatomical measures such as cytoarchitecure, receptor distribution, and the architecture of connections to functional activation profiles and genetic expression patterns, and they hold the potential to provide comparative maps across a wide phylogenetic range (Striedter et al., 2014). In primate comparative neuroscience, the increasing availability of magnetic resonance imaging-based techniques has the potential to

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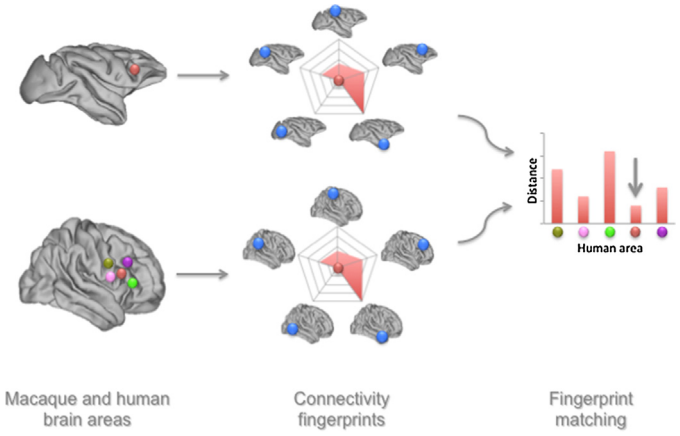

Fig. 1. Schematic example of the connectivity fingerprint matching approach. A macaque brain region (in red) is compared to multiple human brain regions (various colors in the left panel). For each of these regions, the connectivity with a predefined set of brain regions (in blue) for which the homology between the macaque and human has already been established, is determined. A difference measure between the macaque connectivity fingerprint and each of the human fingerprints is then determined. In this case, the human red area is the least dissimilar to the macaque brain region and thus the most likely candidate for homology.

substantially ease the acquisition of large volumes of data, allowing more diverse species to be studied at a higher rate than was previously possible (Mars et al., 2014). One of the main next challenges in this endeavor is to find formal methods to turn these diverse datasets into measures that can be meaningfully compared between brains.

The study of the architecture of connections between brain areas is one fruitful avenue for comparative neuroscience, especially in larger animals such as primates. This is mainly due to two reasons. First, connectivity has been proposed as one of the main mechanisms through which phenotypic diversity is realized (Krubitzer and Kaas, 2005). Second, the availability of connectivity is increasingly widespread. Apart from established connectivity databases such as the CoCoMac for the macaque (Bakker et al., 2012) and the Allen atlas for the mouse (http://connectivity.brain-map.org), diffusion MRI tractography and other MRI-based techniques now allow the acquisition of whole-brain connectivity data in a short time period. Such approaches have become increasingly popular in primate comparative neuroscience, leading to a flurry of studies with sometimes quite different goals and approaches. For instance, a number of studies have qualitatively compared human MRI data to macaque tract tracing results (Thiebaut de Schotten et al., 2012; Margulies and Petrides, 2013). Others have used connectivity-based clustering approaches to infer whether the human cortex follows similar organizational principles to that of the macaque (Tomassini et al., 2007; Beckmann et al., 2009). Finally, a growing number of studies has used diffusion MRI in multiple species to investigate the extent or projections of major white matter fibers across species (Rilling et al., 2008; Hecht et al., 2015).

Encouraging though these results are, the variety of approaches has meant that the results, or even the goals, of the different studies are often difficult to reconcile. Connectivity studies often yield very high-dimensional data that can be difficult to summarize. The purpose of the current paper is to provide a simple framework for comparing brain connectivity between species. The approach we present is based on matching connectivity fingerprints. Connectivity fingerprints were proposed by Passingham et al. (2002) as a way to summarize the important connections of a single cortical area with a selected set of other areas (Fig. 1). They observed that the set of connections of each area is a unique identifier of a brain region. Importantly, the connections of an area give vital clues about its function by demonstrating the type of information an area has access to and the other brain regions it can influence. In their original paper, Passingham and colleagues used the example of macaque areas F3 and F5 which, although both premotor areas, not only differ substantially in their connections to the rest of the frontal cortex, but also show very distinct neuronal responses in various motor tasks. The goal of the fingerprint is thus to provide a diagnostic measure of an area that summarizes its most important anatomical features and has direct implications for the area's functional relevance.

Here, we will provide three examples of how connectivity fingerprints can be used as a tool to compare various aspects of brain organization across and within species. Using a unified framework of permutation testing, we will demonstrate (1) how the anatomical homologs or most similar areas can be selected from a set of candidate areas, (2) how putative homologs can be identified across the whole brain in an unbiased manner, and (3) how the specific connections that drive the differences between species can be uncovered.

1. Materials and methods

A comparison of connectivity profiles lies at the core of the proposed framework. Accordingly, the creation of a connectivity fingerprint is a crucial step aimed at summarizing the high-dimensional, often whole-brain, connectivity profile by a few 'arms' of the fingerprint (Fig. 1). We refer to the area whose connectivity profile is displayed as the 'seed' area and to the areas on the arms of the fingerprint as the 'target' areas. The number of target areas should be sufficient to clearly demonstrate the diversity of connections of the seed area, but care should be taken to not include too many arms or the contribution of each arm will be too small and there will be a risk of overfitting the fingerprint. Importantly, the goal of the fingerprint is not to show only those areas with which the seed region is connected. Rather, the fingerprint should show a range of connection strengths, including the absence of a connection. As with any statistical test, it is important to have some variance to explain. Importantly, the fingerprint should be diagnostic for the seed areas under investigation (cf. Preuss, 1995).

Following the definition of the fingerprint, one needs to decide on the measure of comparison. Such a 'distance measure' will determine whether different fingerprints are either 'close' or 'far' from each other. Some measures emphasize the largest differences even further, while others actually downweight outliers. Importantly, if the target areas of a connectivity profile are carefully selected even simple distance measures often suffice, promoting interpretability, interchangability, and reproducability of the results. We have mostly used the city block or Manhattan distance

$$\sum_{i=1}^{n} \left| p_i - q_i \right|,$$

where p and q are two vectors representing the connectivity fingerprints to be compared and i indexes the n elements of the vectors, i.e., the n target areas of the fingerprint. Alternatively, sometimes it is more intuitive to use a measure of similarity, such as the cosine similarity:

$$\frac{\sum_{i=1}^{n} p_i \times q_i}{\sqrt{\sum_{i=1}^{n} (p_i)^2 \times \sum_{i=1}^{n} (q_i)^2}}.$$

In the following examples, we created connectivity profiles using either resting state fMRI data or diffusion MRI data, but the approach is not limited to such data. The approach could in theory be used to compare fingerprints created using different types of data, for instance when comparing, on the one hand, a template derived from a database of connectivity studies using tracers to, on