A common space approach to comparative neuroscience

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Abstract (150 words)

Comparative neuroscience is entering the era of big data. New high-throughput methods and data sharing initiatives have resulted in the availability of large, digital data sets containing many types of data from ever more species. Here, we present a framework for exploiting the new possibilities offered. The multi-modality of the data allows vertical translations, comparisons of different aspects of brain organization within a single species and across scales. Horizontal translations compare particular aspects of brain organization across species, often by building abstract feature spaces. Combining these two types of translation allows for more sophisticated comparisons, including relating principles of brain organization across species by contrasting horizontal translations, and making formal predictions of unobtainable data based on observed results in a model species through a combination of vertical and horizontal translations.

Keywords (6)

Translational neuroscience, mouse, macaque, connectivity, anatomy, model species

Introduction

Evolution provided comparative neuroscience with a compelling natural experiment in brain diversity. But understanding how the organization of the brain of a species is similar and how it is different to that of other species is challenging. It requires integration and synthesis of data from disparate fields, often lacking common references and terminologies. Neuroscientific data are difficult to obtain from outside of one's field and often require specialised training. By necessity, many researchers therefore focus on a particular data type in a particular model species, leaving interpretation of the usefulness of their data to understanding other species, including the human, to their colleagues. This has led to numerous confusions in the literature about anatomical translatability (van Heukelum et al. 2020) and even about the terminology used to describe behavioural tasks (Laubach et al. 2018). Alarmingly, these confusions might contribute to the failure of many clinical trials in neuropsychiatry (Hay et al. 2014).

The emergence of various high-throughput methods for neuroscience has the potential to change this. Where previously various types of data were only available for parts of the brain, in a few species, and only to a few labs, high-quality data of various species' entire brains are now acquired and, crucially, made available to the community in a digital format. Multi-modal high-quality human neuroimaging databases including those of the Human Connectome Project (Van Essen et al. 2013) and the UK Biobank Imaging (Miller et al. 2016) have set new standards for data availability. Now, for comparative neuroscience, MRI databases of non-human data are increasingly available thanks to initiatives such as the PRIMatE Data Exchange (Milham et al. 2018) and multicentre mouse MRI projects (Grandjean et al. 2020). Outside MRI data, transcriptomic databases from various species are increasingly becoming available (Keil et al. 2018), including the well-established Allen Institute databases for the human and mouse (Hawrylycz et al. 2012; Lein et al. 2007).

Comparing such data obtained from different species comes with challenges. A number of recent studies have focused on the issues of standardizing analysis pipelines and quality control, including comparisons of SNR (Mandino et al. 2019; Milham et al. 2020; Xu et al. 2019b). However, what has been largely absent is a framework to address the next stage in the analysis: the comparison of brain organization across scales and species. To make sense of brain differences we need to be able to understand the data in the context of a shared frame of reference. Here, we synthesize the approaches presented in the literature into a coherent framework that allows just that.

The common space approach in brief

Brains can differ in many respects, including global or local size, the number and size of cortical fields, the connections between brain areas, and cortical folding pattern (Krubitzer & Kaas 2005; Mars et al. 2018a) (Fig. 1A). These features interact. For instance, a change in size of the cortical sheet is often accompanied by an increase in the number of areas, which in turn can be accompanied by a change in areal connections. In fact, in anthropoid primates, brain diversity may be better characterized by brain reorganization than by changes in relative brain size (Smaers & Soligo 2013). Any framework for comparative neuroscience has to be

able to account for these considerations. We propose a 'common space approach' that satisfies these requirements and can point the way to future advances. The proposed framework relies on three ingredients.

To visualize the issues the framework has to address, let us imagine we want to compare brain organization between two brains (Fig. 1B). Identifying how the various aspects of brain organization that can differ between these brains manifest requires multiple types of information. Thus, rather than focusing on data of one particular modality in great detail, as was done by many of the great anatomists of the early 20th century, the challenge for modern comparative neuroscience is to integrate information from multiple sources. This gives rise to the first ingredient, that of *multimodality* of the data.

The next question is at which scale the comparison should be made. By necessity, many large comparative neuroscience studies were previously done at the scale of whole brains or large sections of the brain. Although this has led to very fruitful insights (Barton 2007; Dunbar & Shultz 2007; Jerison 1973), it has also led to great controversies due to differences in regional definitions (Barton & Venditti 2013; Passingham & Smaers 2014). Moreover, local effects may be better reflections of the types of changes we outlined above. Thus, the second ingredient is that one works with *local* data that is ideally of subregional resolution.

The final challenge is to provide a meaningful way to compare such local and multimodal information. This is particularly important when the brains under study are of vastly different size and morphology. Given that changes at one level, such a local expansion of brain size, can have dramatic effects at other levels, such as the location of brain areas, it is essential to find a way in which similar features can be meaningfully compared across species. In other words, we need to ensure that we compare like with like. One way to solve this problem is to describe the local organization of brains in terms of an abstract feature space, rather than physical x, y, and z coordinates. For instance, we previously showed that peak activations during functional tasks have seemingly arbitrary spatial arrangements in physical space but cluster together meaningfully when described in a space that encodes similarity in their connectivity (Mars et al. 2018b). The connections, rather than spatial dimensions, form a common space in which activation peaks can be meaningfully compared (Fig. 1C). The third ingredient is thus that of *feature-based comparisons in a common space*.

Armed with these three ingredients—multi-modal, local, and feature-based--we can now address the questions of how brains differ. Using the multimodal data at each locality of the brain, one can investigate how the different aspects of brain organization relate to one another within a given species. We term this *vertical translation* (i.e., comparing brains column-wise in Fig. 1B). Second, one can investigate how a given modality differs between the species, using an abstraction into features of interest that allows meaningful comparisons. We term this *horizontal translation* (i.e., comparing row-wise in Fig. 1B). Finally, one can investigate how the relationship between different modalities differs between species by combining insights from both translations.

Figure 1D shows the generalized framework in four example species of which various types of data are available (or, in some cases, missing). Vertical translation within a species follows the dotted lines, horizontal translation across species follows the striped lines. One can

compare species according to increasing phylogenetic distance by following the striped lines from the human to the macaque, marmoset, and mouse brain, or make more direct comparisons, such as a translation from the mouse directly to the human. In what follows, we illustrate cases of these possible translations and discuss how thinking about comparisons within this framework helps structure the debate and inspire novel questions.

Vertical translation

One of the central tenets of neuroscience is that the brain is hierarchically organized: cells form areas that form networks that perform computations that produce behaviour (Churchland & Sejnowski 1992; Mars 1987). Current high-throughput methods allow whole-brain measurements that span across all these scales (Lerch et al. 2017). Thus "vertical translation" not only means integrating across different sources of information, but also integrating across different scales. The traditional approach is to compare such measurements within specific parts of the brain. For example, early work looking at subdividing the brain into multiple functional areas centred around cytoarchitectonic features. Differences in cytoarchitecture between adjacent cortical fields was taken to be an indication of a change in function. Later these changes in cytoarchitecture were found to coincide with changes in density of certain receptor types (Geyer et al. 1998) and changes in extrinsic connections (Passingham et al. 2002). More recently, multimodal MRI combining microstructure and functional measures allowed for the definition of areal borders in vivo and in individual brains (Glasser et al. 2016).

Alternative approaches to comparing features of areas within a given species have emerged in recent years. Importantly, the advantage of whole-brain data of these different modalities is that they allow us to move beyond lining up areal borders to investigate *principles* of organization across different levels. An impressive example of this is provided by Burt and colleagues (2018), who investigated whether the hierarchical organization of cortical areas originally proposed based on laminar patterns of interareal connectivity (Barbas & Rempel-Clower 1997) is reflected at multiple levels of brain organization. As a proxy for anatomical hierarchy, they used an MRI-derived T1w/T2w map of the human cerebral cortex. This map is thought to reflect regional variation in grey matter myelin content, with high values in primary sensory areas and low values in association cortex (Glasser & Van Essen 2011). They then compared the T1w/T2w map to spatial maps reflecting the expression of layer-specific genes, showing a positive correlation of cortical hierarchy with supra- and infra-granular layer genes and a negative correlation with granular layer 4 genes (Fig. 2, left). Hierarchical gradients in gene expression were also reported for genes coding for specific neural cell types. Moreover, they found that the T1w/T2w map topography corresponds strongly with the first principal component of spatial gene expression profiles.

The study by Burt and colleagues (2018) demonstrates the use of the ingredients of a comparative approach that we outlined in the previous section. Using data from different high-throughput methods, in this case aggregating data from multiple subjects to create a group map, with high spatial resolution allowed them to compare the results from different modalities in a common space. As the brain under consideration is the same at each level, this common space can be a simple two-dimensional space representing the cortical sheet.

However, their final analysis of performing, in effect, a spatial principal component analysis demonstrates how the topographic information can be effectively reduced to a lower level space.

This idea of abstracting a complex spatial map to a low dimensional space reflecting its essential features is present in numerous recent works looking at so-called cortical gradients (Blazquez Freches et al. 2020; Haak et al. 2018; Vos de Wael et al. 2020). In addition to linear dimensionality reduction techniques such as principal components analysis, other techniques such as diffusion embedding translate relationships between data points – such as connectivity strengths between brain areas – into distances in an embedding space. In one prominent example of this approach, Margulies and colleagues (2016) used diffusion embedding to describe the human brain in terms of connectivity gradients. The first gradient runs from primary sensory and motor areas to the transmodal areas that together form the default mode network; a second gradient differentiates the different primary areas, thus dissociating different sensory modalities. The authors argue that the principal gradient provides an organizing spatial framework for large-scale cortical networks and suggest it underlies the role of the default mode network in higher-level information processing that is unrelated to immediate sensory input.

The approach of lower-dimensional embedding to demonstrate principles of brain organization is well suited for comparisons across data modalities. Indeed, following the principle of vertical translation, Huntenburg and colleagues (2018) explore the idea that the principal primary-to-transmodal gradient is reflected in connectivity, tissue properties such as myelin, and function, referring to it as an intrinsic coordinate system for the cortex. Paquola and colleagues (2019) formally test this notion, showing that the different modalities indeed display a similar hierarchy, but also that they become increasingly dissociated in transmodal cortex. Importantly, this demonstrates how vertical translations can be used to discover dissociations between scales as well.

Horizontal translation

The vertical translations discussed in the previous sections had the advantage that they all worked in the same brain space. This is clearly not true for horizontal translations, where brains can differ strongly in size and morphology. Before any comparison can be done, we must solve a correspondence problem and describe each part of the brain in terms of features that are shared between the different brains (Fig. 1C).

A first solution to this problem is to describe homologous spatial landmarks that can be reliably identified on the brains of different species and to use these to guide a registration algorithm. An early version of this approach was pioneered by Van Essen and colleagues. As a prime example, Van Essen and Dierker (2007) defined a series of homologous locations, such as the primary sulci, on the cortical sheet of the macaque monkey and the human. These homologous features in effect formed the common feature space between the two brains. A surface-based registration algorithm was then used to find a spatial warping that best matched the locations of these landmarks, whilst interpolating between them. Once a transformation was found, they could then ask which parts of the cortical sheet had to be

particularly distorted to allow alignment of the homologous landmarks. They found that association cortex in lateral frontal, inferior parietal, and middle temporal cortex showed particularly strong distortions. Subsequent work showed similar effects in comparisons between marmoset, capuchin, and macaque monkeys (Chaplin et al. 2013). A more recent variant on this approach has been proposed by Auzias and colleagues (2013), who parameterized the cortical sheet in terms of a rectangular plane where different sulci run either mostly horizontally or vertically. Defining homologous sulci across species under this parameterisation greatly simplifies the correspondence problem (Coulon et al. 2018).

An alternative approach to spatially matching cortical sulcal landmarks has emerged in recent years. The idea still relies on defining corresponding landmarks, but rather than matching their spatial location, this approach uses the landmarks to describe different brains in terms of a common connectivity space. This builds on the notion that brain areas have a unique 'connectivity fingerprint' with the rest of the brain (cf. Passingham et al. (2002); Mars et al. (2018b)). For example, subdivisions within premotor cortex may be more or less strongly connected with another given region, but what distinguishes them most clearly is the overall profile of connections that they have with other areas (Tomassini et al. 2007). The same is true in cingulate and parietal cortex (Beckmann et al. 2009; Mars et al. 2011). Thus, if one can identify a suitable number of homologous areas between two brains (landmarks), one can describe other areas in terms of their connectivity profiles with those areas (Mars et al. 2016). The homologous areas form the dimensions of a connectivity space in which all areas of the brains under comparison can be described.

This 'connectivity fingerprint matching' approach has been used to systematically compare most parts of human and macaque association cortex (Mars et al. 2013; Sallet et al. 2013; Xia et al. 2019). Importantly, it allows one to show not just whether a region is 'the same' or 'different' across species, but to provide a more continuous assessment. For instance, Neubert and colleagues (2014, 2015) demonstrated that some areas of human anterior prefrontal cortex show a connectivity profile that is slightly different from any pattern found in the macaque. In a similar vein, Balsters and colleagues (2020) extended the approach to much more phylogenetically distant species by comparing striatal organization across mouse, macaque monkey, and human, and showed that parts of human striatum have no homolog in the mouse.

The main determining factor for the validity of such a horizontal translation using a common space is whether a sufficient number of well-established homologous features can be defined. In the case of macaques and humans many homologous areas are well defined, but as one moves outside of the common model species the definition of homologous areas becomes more problematic. An alternative approach is to base the common space not on grey matter areas, but on white matter tracts. For instance, a connectivity fingerprint of human medial and lateral frontal pole can be defined based on their differential connectivity with the frontal association tracts (Hartogsveld et al. 2017). This approach can be generalized by describing the entire cortical sheet in terms of its connectivity with each of the major white matter tracts, creating a cortex $\times$ white matter 'connectivity blueprint' for each species in which the tracts form the common space (Mars et al. 2018c). This is an attractive approach since the bodies of many major white matter bundles can be identified reliably across different primate species, whereas the branching patterns of these tracts as they approach the cortex provide

the key species differences. Thus one can define automated and robust standardized protocols to reconstruct major tracts across species based on the tract bodies and then use tractography to investigate how each tract reaches the cortex in each brain. Protocols for all major white matter tracts have now been defined for the human, chimpanzee, and macaque (Bryant et al. 2020; Mars et al. 2018c; Warrington et al. 2020) and partial reconstructions are available for several additional species (e.g., Schaeffer et al. (2017); Roumazeilles et al. (in press); Barret et al. (2020)).

A full horizontal translation between two brains opens up a realm of possibilities (Mars et al. 2018c) (Fig. 2, right). One can investigate relative similarities on an area by area basis, but one can also take the connectivity fingerprint of a particular part of one brain and search for similarities across the entire brain of another species. This was done first to search for an area in macaque temporal cortex similar to the human temporoparietal junction area (Mars et al. 2013). Having established a whole-brain to whole-brain mapping, one can then use this to predict how a cortical map, such as a map of cortical myelin or a functional activation map should look in another brain. For example, the white matter tract blueprint mentioned above was used by Mars and colleagues (2018c) to transform a human myelin map onto the macaque brain geometry, and the resulting map showed strong resemblance to an empirical map based on macaque MRI. This approach arguably has great potential for comparative neuroscience, allowing one to make quantitative predictions about how a map should look in one brain based on knowledge of another. Finally, having established cross-species similarity across entire brains, one can investigate which parts of the brain match least across species. For macaque-human comparisons, this shows areas in human lateral frontal and particularly some other parts of temporal association cortex that have a connectivity fingerprint that cannot be matched to any in the macaque brain (Mars et al. 2018c). These areas thus have access to a combination of information that no macaque brain area has.

As in the vertical translation, the common space can be used to create a low-dimensional embedding space where different species brains can be concurrently projected. This approach was taken by Xu and colleagues (Xu et al. 2019a) in a comparison of macaque-human connectivity. They defined a common space based on homologous areas, established the areas' connectivity fingerprints, and then used a gradient approach to define a low-dimensional joint embedding space. This joint space can then be used to describe each part of the two brains, showing how homologous areas occupy a similar place, and showing areas of low similarity in—again—frontal and temporo-parietal association cortex, as well as parts of the default mode network on the medial wall of the hemispheres. Since the gradients are defined in the joint embedding space, their surface representation can be used to guide a surface-based registration between the two brains, simplifying the brain-to-brain translation.

The common spaces that we have described thus far have always been anatomical, based on known areal homologs, sulci, or grey or white matter connectivity. However, the common space can also be formed at a higher level of abstraction. For instance, in an approach that shares some similarities to the connectivity fingerprint matching approach, Caspari and colleagues (2018) used a 'functional fingerprint' matching approach to investigate human/macaque similarities in areas involved in attentional processing. They required human subjects to perform various conditions of an attention shifting paradigm and characterized the functional profiles of an area in the medial superior parietal lobule that

shows activation when subjects shift their locus of attention. They then required macaque monkeys to do the same task and searched across the brain for voxels that match the human functional profile, showing significant similarity in macaque areas V6 and V6a.

Another approach to defining an abstract common space is to describe brain areas in terms of neural representation. One particularly powerful example is given by representational similarity analysis. This method describes multivariate brain signals in terms of the geometry of the activity, i.e. how the collective multivariate response to different stimuli or conditions changes. Thus, it abstracts away not only spatial location, but also the nature of the measured signal. This means that such methods can equally be applied to fMRI signals or to electrophysiological recording, making it a powerful tool for cross-species comparisons (Barron et al. 2020) or even explicit comparisons between biological and artificial brains. As an example, Kriegeskorte and colleagues (2008) used a representational similarity approach to compare macaque extra-cellular recordings and human functional MRI. They found strikingly similar neuronal representations in inferior temporal cortex of the two species, suggesting a similar representational code in the two brains. Similarly, Hunt and colleagues (2015) found similar single-trial indices of internal decision making state in dorsolateral prefrontal cortex in local field potentials recorded from the macaque and human MEG.

Comparing common spaces

Using a common space allows one to build a brain-to-brain translational map that in turn can be used predict how any particular feature map from one brain might look in the other. If different modalities are used to construct the common spaces, an obvious question is whether the results obtained are consistent. As a case in point, Fulcher and colleagues (2019) were interested to see whether the vertical relationship observed in primates between cortical hierarchy evident in T1w/T2w maps and spatial gradients evident in other modalities are also present in the mouse. As one piece of evidence they were able to show significant spatial correlations between the gene expression maps of a number of receptor subunit and cell type marker genes and the T1w/T2w map. They then focused on genes that have a known human ortholog and compared the gene-T1w/T2w correlation values between the mouse and the human. This resulted in a significant correlation of correlations, suggesting that the relationship between the modalities was preserved across species. In effect, whether one uses the T1w/T2w or the gene expression maps as a common space between the mouse and human brain, the results should show significant similarity.

Such a similarity between the T1w/T2w and gene expression maps as common spaces between the mouse and the human is comforting. The fact that the principles of organization—operationalized here as the relationship between different levels of the biological hierarchy—are comparable across the two species mean that knowledge of multiple areas in the mouse can be used, in some cases, to make inferences about the nature of an area that is only found in the human and not in the mouse itself. However, it would be wrong to assume that horizontal translations using data from different modalities should always line up. Indeed, in discussions of homology in the context of the biological hierarchy a number of authors have pointed out that homologous high-level characteristics can be due to low-level non-homologies and vice versa (Sommer 2008; Striedter 2019). As an example of

the former, Striedter and Northcutt (1991) discuss the example of the grasshopper *Calliptamus italicus* that produces similar songs to other grasshoppers and in similar circumstances, but does so using a different part of the body. A parsimonious interpretation of grasshopper phylogenetic relations suggests that the behaviour is homologous, but the way it is produced diverged. The so-called neural recycling hypothesis, which suggests that homologous anatomical regions contribute to highly species-specific behaviour such as reading in the human brain (Dehaene & Cohen 2007), can be interpreted as an example of the opposite situation. The key message from this for the present framework is that in order to fully understand differences across brains, one needs to investigate how different horizontal translations line up. In fact, exploring differences between horizontal translations using different common spaces is a suitable way of investigating the type of changes that have occurred between brains.

Motivated by this line of thinking, Eichert and colleagues investigated whether various differences observed in the white matter organization of the human temporal lobe compared to that of other primates were all due to the same type of change. One of the hall-mark results of primate comparative neuroscience using neuroimaging is the observation that the arcuate fasciculus projects much more ventrally in the human temporal lobe than in the macaque monkey and chimpanzee great ape (Rilling et al. 2008). However, the horizontal translation based on homologous areas suggest that temporal and inferior parietal territory close to the grey matter projection areas of the arcuate has vastly expanded in the human brain (Van Essen & Dierker 2007). This has, among others, led to area MT+ moving from a dorsal superior temporal sulcus location in the non-human primate to a much more ventral location in the human (Huk et al. 2002). This means that the ventral projections of the arcuate can be explained both by an expansion or relocation of its existing grey matter projections or, as suggested by Rilling and colleagues, by invasion by the arcuate of new cortical territory (Mars et al. 2018a). Comparing horizontal translations based on multiple modalities can resolve this question.

In two studies, Eichert and colleagues used a common space based on one modality to determine expansion and relocation of areas and then investigated whether the resulting horizontal translation could account for differences between species in the cortical projections of the arcuate fascicle. In the first study, they used the Van Essen and Dierker (2007) translation based on cortical homologs and showed that this map could not predict changes in arcuate projections between the macaque monkey and the human (Eichert et al. 2019). In a second study, they used surfaced-based registration to align macaque, chimpanzee, and human T1w/T2w maps (Eichert et al. 2020). The resulting translations were able to account for some of the major relocations of cortical areas in occipitotemporal cortex, including the lateral-to-medial shift of primary visual cortex and the dorsal-to-ventral relocation of MT+ (Fig. 3, left). When applied to projection maps of certain cortical tracts, including the ventral inferior fronto-occipital fascicle, these translations could account for some between-species differences in cortical projections. However, this was not the case for the arcuate, whose ventral temporal projections far exceeded those predicted by the translations based on the T1w/T2w common space. Applying this approach to a range of temporal tracts showed a variety of degrees in which between-species differences in cortical projections were driven by cortical relocation or expansion of projections.

Comparing common spaces thus allows one to investigate how the relationships between different levels of brain organization have diverged across species. This, in turn, allows a better understanding of 'homology' of features across species. An interesting example is the default mode network of the brain. This network was originally identified as a 'task negative' network of areas that tends to be more activated when the brain is not engaged in a specific task (Shulman et al. 1997), but is now more generally interpreted as a network involved in generic high-level cognition through dynamic interactions with more task-related networks (Vatansever et al. 2015). As discussed above, Margulies and colleagues (2016) describe the default mode network as situated at the extreme end of a gradient ranging from primary to transmodal cortices. A default mode-type network was been reported now in many different species, including other primates such as the chimpanzee, macaque, and marmoset (Barks et al. 2015; Liu et al. 2019; Vincent et al. 2007), but also carnivores and rodents (Lu et al. 2012; Szabó et al. 2019). At one level, one might interpret these networks as equivalent across the species, as they are suggested to fulfil the same role of dealing with the most abstract information a brain is capable of processing. On the other hand, at a lower level the anatomical regions that form these networks need not be homologous. In the human, for instance, the default mode seems to involve regions in middle temporal cortex that might not have clear homologs in other species, especially outside the primate order (Bryant & Preuss 2018). Indeed, the default mode seems to have the connectivity fingerprints that differ the most between the human and macaque monkey (Xu et al. 2019a). Therefore the default mode network's function might be homologous across species, but the areas of which it is comprised might not be.

Combining translations

Arguably the greatest potential for comparative neuroscience lies in combining various translations. We already saw an example of this in the translation of cortical myelin maps in a common space of white matter connections (Fig. 2B; Mars et al. (2018c)). In essence, this corresponds to a vertical translation (myelin to connectivity space), followed by a horizontal translation (based on common connectivity space), followed by another vertical translation (connectivity back to myelin). This type of explicit prediction of how a particular data type would look in one brain based on another is the true goal of translational neuroscience.

Depending on what types of data are available for each species, we can dissociate two scenarios. In the first, the data from the species under investigation share at least one modality in common that can be used to build a common space for the horizontal translation, but other data modalities are only present in one of the species. Measurements of anatomical (axonal) connectivity are a good example. In animals, we can use neuroanatomical tracers to very accurately map the origin, termination, and sometimes the entire trajectory of axons. These techniques are not available in humans. Diffusion MRI tractography is a technique that can provide information about anatomical connections in humans, but it is a rather indirect probe of connectivity and that makes it error-prone. But diffusion MRI tractography is available for use in animals. Having this same technique in both humans and animals is a great opportunity for horizontal comparisons, as differences between the species cannot trivially be attributed to differences in measurement techniques.

Combined translational approaches of this type have been possible for some time. Croxson and colleagues (2005), for instance, used diffusion-weighted imaging estimates of white pathways and their probabilities of interconnection with frontal cortical areas to compare humans and macaques. However, this approach has become increasingly refined. For example, Follloni and colleagues (2019) defined a protocol to reconstruct the amygdalofugal tract in the macaque monkey in a way that captured its course and projections as known from invasive tracers (vertical translation) and then used these protocols to study this tract in the human using tractography (horizontal translation) (Fig. 3, right). A similar approach has shown it is possible to identify similar connectional hubs in anterior cingulate cortex based on tracers and tractography in the macaque and tractography in the human (Tang et al. 2019). By comparing tractography to tracers in the macaque monkey, we can also learn a great deal about the errors made by diffusion tractography (Jbabdi et al. 2013). We can then use this knowledge to predict or correct errors made in human tractography, and obtain more anatomically faithful results despite the unavailability of neuroanatomical tracers in humans (Haber et al. 2020).

In the second scenario, all modalities might be present in both species, but we want to use one particular modality for the common space. This is the scenario discussed above translating the myelin map based on a connectivity common space, but it can be extended to validate and improve the use of model animals to understand human brain function. An interesting example case is the use of rodents in the study of the neural basis of social behaviour (Grimm et al. 2020). The rodent has a much less encephalized neocortex, many of whose subdivisions are implicated in social information processing in the human (Olsson et al. 2020; Rushworth et al. 2013). However, using a rodent model allows a much wider range of vertical translations, including the use of genetic mutants, optogenetics, and invasive tracers (Bicks et al. 2020; Velez et al. 2010). Horizontal translations based on connectivity or expression of orthologous genes can be used to first validate the model. For instance, one can predict brain morphological changes in individuals with particular genetic alleles based on changes observed in mutant mice models. If successful, the horizontal translations can then be used to predict effects that cannot be studied directly in the human, formalizing the link between preclinical and clinical research. Such an approach would usher in a more quantitative approach to the use of model species, allowing finer predictions in the human, but also—using the reverse translation—by tailoring the model better to the questions arising from any human case. This would help refine the use and reduce the number of animals in research.

Conclusion

We have presented a framework for comparative neuroimaging. By exploiting multi-modal data providing local detail and constructing feature-based common spaces we compare both across scales within a species through vertical translations and across species through horizontal translations. Importantly, this framework helps understand the different principles of brain organization across species through comparisons of horizontal translations and make formal predictions even when data are available in only a subset of species by combining translations. Ultimately, such a formal framework benefits both translational neuroscience

using model species and large-scale comparative neuroscience investigating diversity along larger sections of the evolutionary tree.

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Author contributions

R.B.M. conceived of the idea and wrote the first draft; S.J. and M.F.S.R. edited the draft; all authors approved the final manuscript.

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Figure legends

Figure 1. The common space approach. (A) Brains can differ in many respects. Blue spheres indicate cortical regions, grey lines connections. Brain changes compared to an ancestral or reference state (top) can include overall and local expansion, increased arealization, and changes in connectivity (based on Krubitzer and Kaas (2005); Mars et al. (2018a)). (B) Many data types are now readily available across species, allowing vertical translations within species and horizontal translations across species. Myelin maps adapted from Eichert et al. (2020); white matter tracts redrawn from Thiebaut de Schotten et al. (2012). (C) By describing the brain in terms of a particular feature that has clearly defined homologs between species, it is possible to compare the brains in the same common space. (D) This framework can be generalized across multiple species and levels or data types (indicated by the different colors), even when not all data types are available in all species. For example, when we compare the human brain (bottom right) with the brains of other species we might be able to compare data from some modalities directly (for example, resting state based estimates of connectivity and diffusion weighted imaging based estimates of connectivity might be indicated by yellow and green colors) but other data modalities, such as tract tracing data (indicated by blue color), might not be available for the human brain.

Figure 2. Vertical and horizontal translations. (left) Example of a vertical translation. A human T1w/T2w map (top row) shows high values in primary areas and low values in association cortex. This pattern is similar to that of expression of layer 4 genes and the inverse of layer 1-3 and 5/6 genes (middle row). The first principal component of spatial gene expression also matches this pattern (bottom row). Adapted from Burt et al. (2018). Reprinted by permission from: Springer Nature, Nature Neuroscience, Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography (Joshua B. Burt, Murat Demirtaş, William J. Eckner, Natasha M. Navejar, Jie Lisa Ji, William J. Martin, Alberto Bernacchia, Alan Anticevic and John D. Murray), (2018). (right) Horizontal translations allow one to (A) quantify the similarity between a region in one species and areas across the entire brain of another, (B) create whole-brain to whole-brain maps, and (C) quantify which regions in any brain have lowest similarity to the comparison brain. Adapted from Mars et al. (2018c).

Figure 3. Extending translations. (left) A horizontal translation between macaque, chimpanzee, and human brains based on T1w/T2w maps can be used to predict the projection pattern of white matter tracts across species. If the predicted and actual projection map (red

on bottom brain) do not match, as is the case here for the human arcuate fasciculus predicted from the macaque (green) and chimpanzee (blue), reorganization across levels has occurred between the brains. Adapted from Eichert et al. (2020). (right) Combining translations allows one to make predictions for modalities that are not present in one of the species. For instance, a horizontal translation from macaque tracers to the human is not possible, as tracer data cannot be obtained in humans. Therefore, one can compare macaque tracers to macaque diffusion MRI tractography in a vertical translation and then compare tractography across species in a horizontal translation. Figures adapted from Folloni et al. (2019) (right top) and Tang et al. (2019) (right bottom).

Figure 1

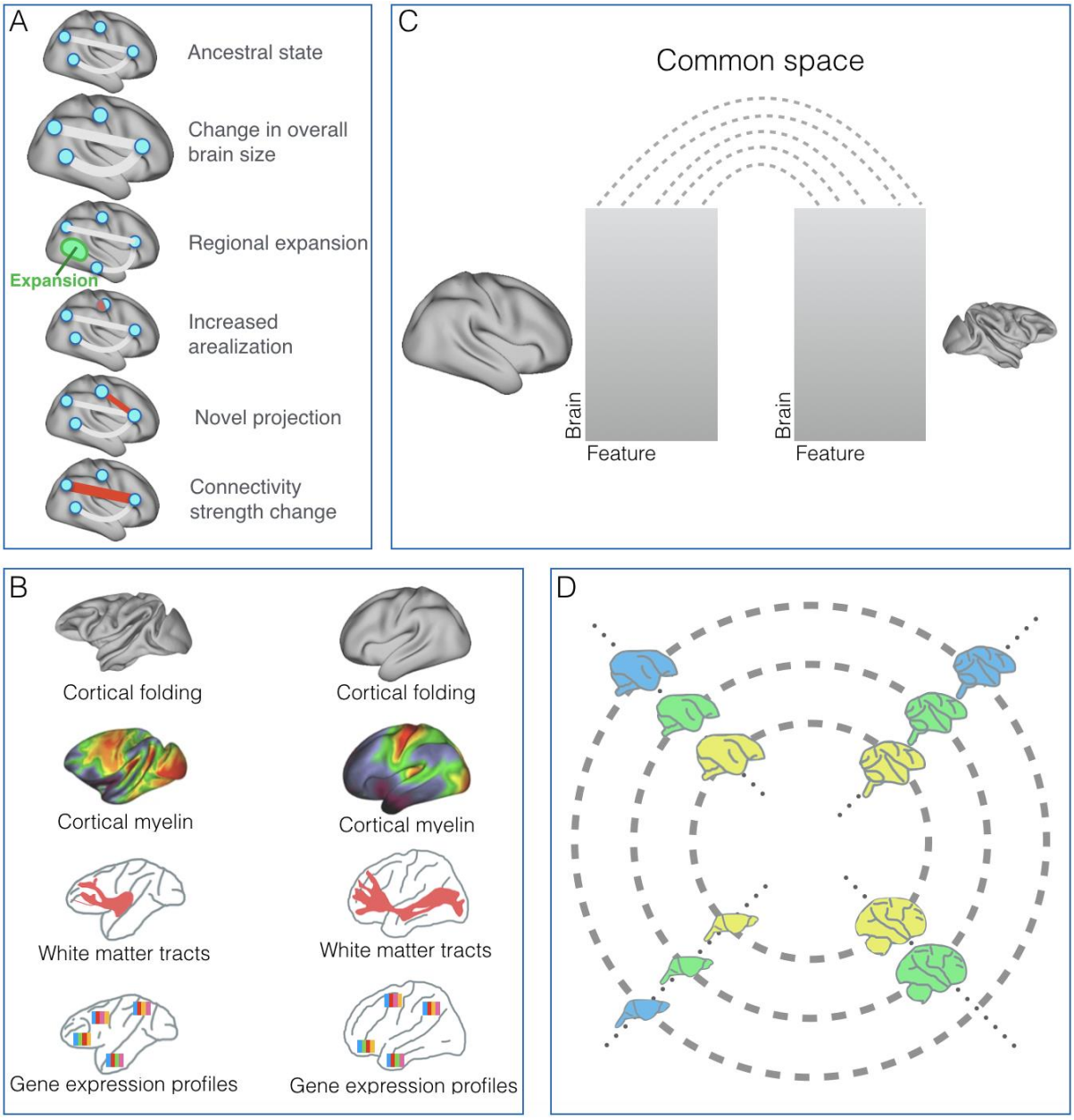

A
Ancestral state
Change in overall brain size
Regional expansion
Expansion
Increased arealization
Novel projection
Connectivity strength change
C
Common space
Brain
Feature
Brain
Feature
B
Cortical folding
Cortical folding
Cortical myelin
Cortical myelin
White matter tracts
White matter tracts
Gene expression profiles
Gene expression profiles
D

Figure 2

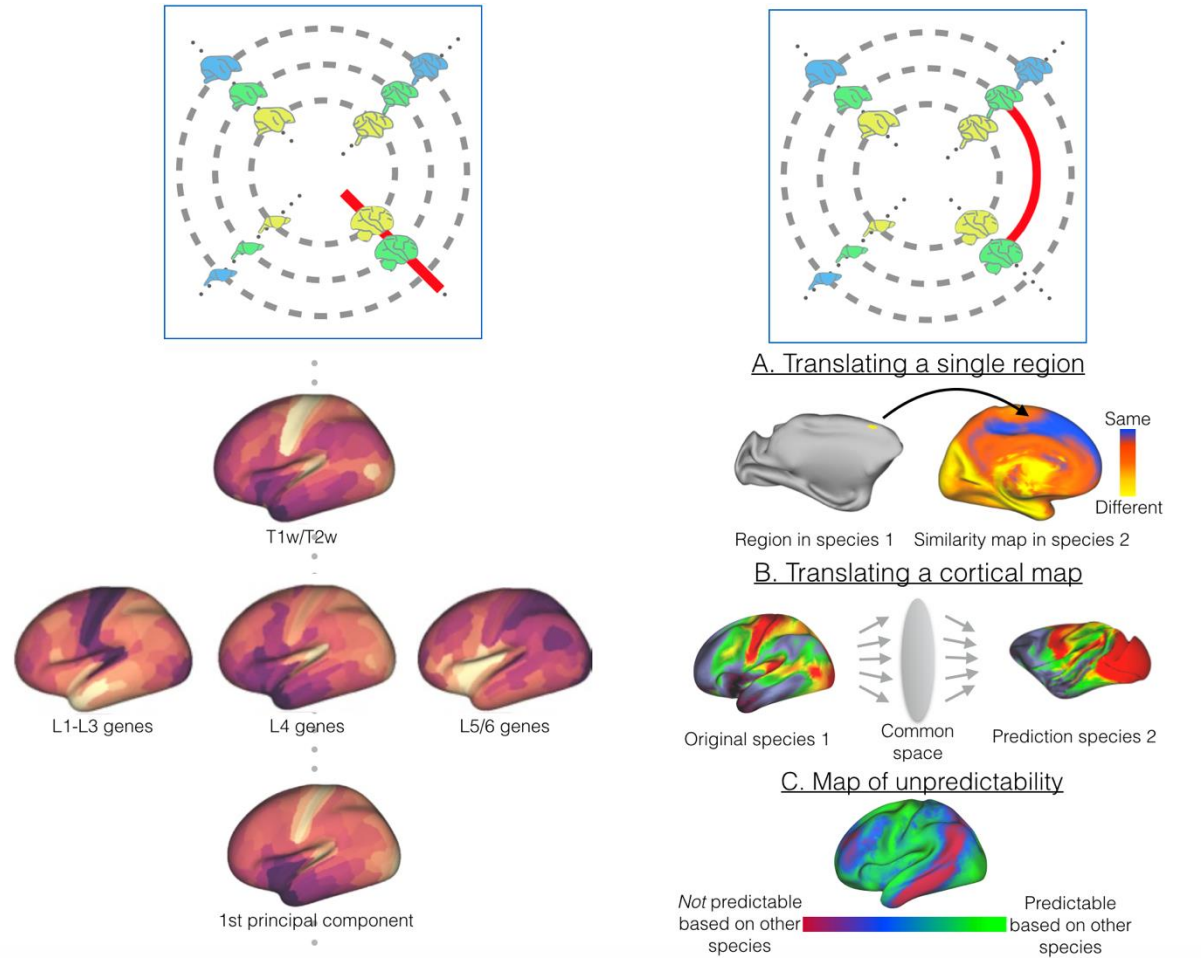
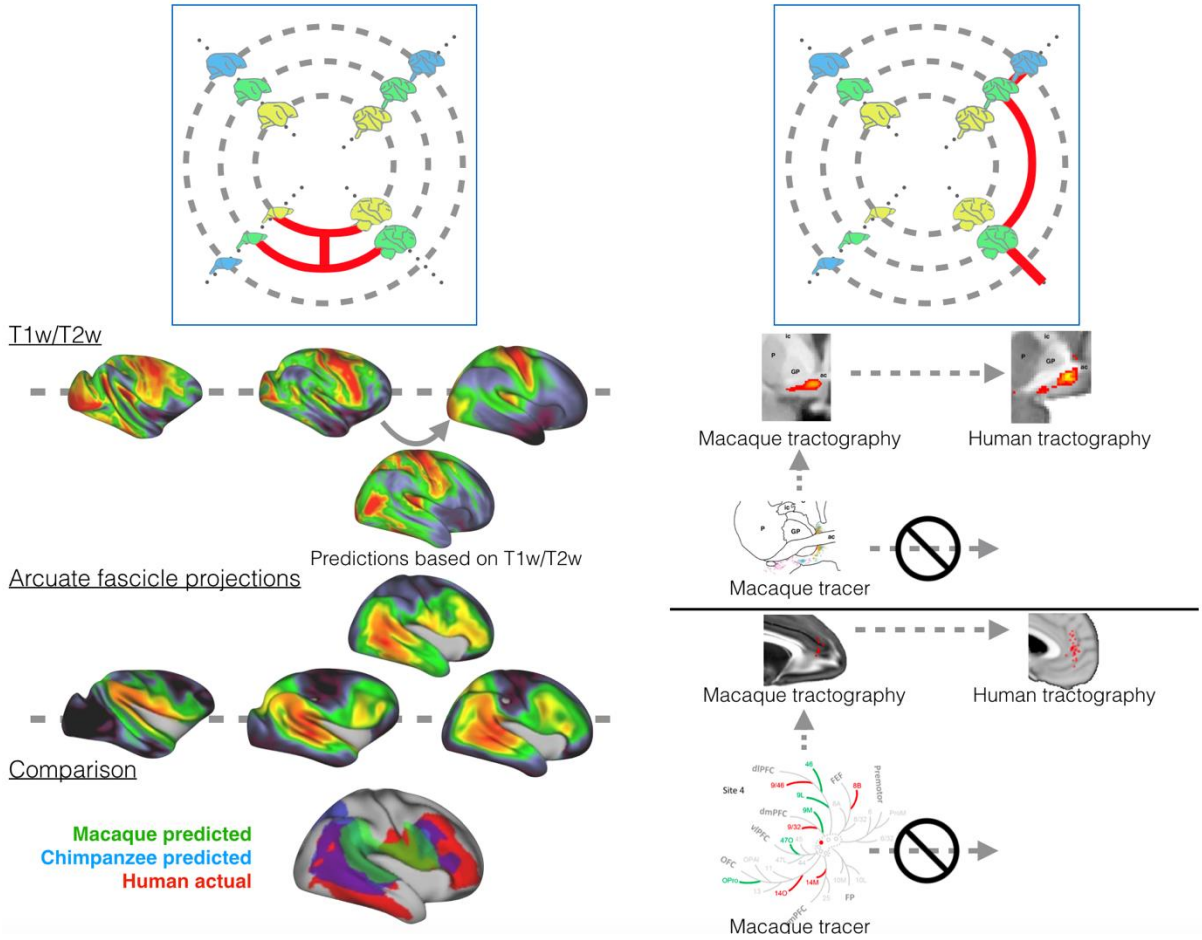

T1w/T2w
L1-L3 genes
L4 genes
L5/6 genes
1st principal component
A. Translating a single region
Same
Different
Region in species 1
Similarity map in species 2
B. Translating a cortical map
Original species 1
Common space
Prediction species 2
C. Map of unpredictability
Not predictable based on other species
Predictable based on other species

Figure 3


T1w/T2w
Predictions based on T1w/T2w
Arcuate fascicle projections
Comparison
Macaque predicted
Chimpanzee predicted
Human actual
Macaque tractography
Human tractography
Macaque tracer
Macaque tractography
Human tractography
Macaque tracer