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Grand challenge: finding similarities and differences in mammalian brain organization

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Introduction

There are over 6,000 currently recognized species in the class Mammalia (Burgin et al., 2018). Biodiversity is the enduring result of past events and presents environmental and ecological conditions (Jones and Safi, 2011). The ability to interact with the environment and display a range of behaviors depends on the coordinated interaction of different structures of the nervous system with specialized functions, from sensory receptors to higher sensory and motor processing centers. Thus, it is crucial to understand how these circuits operate in order to understand mammalian behavior.

Over the years, neuroscientists have been searching for organizational principles underlying mammalian brain function. From classical studies to advanced modern techniques, significant efforts have been made to understand the brain circuit organization. The first diagrams of brain circuits were created in the late 19th century, primarily by Cajal, using the Golgi method (reviewed in DeFelipe, 2002). This technique allows for a detailed study of the morphology of neurons and their connections, marking a significant milestone in understanding brain architecture. Since then, the introduction of new methods and techniques has enabled researchers to progress the study of brain organization to better understand brain function and its role in cognition and behavior. Nowadays, big interdisciplinary international projects (e.g., Human Brain Project, Blue Brain Project, Brain Initiative, Human Connectome Project, Allen Institute Human Program, and The China Brain Project) are making use of advances in imaging, artificial intelligence, and computational neuroscience, with the aim of fully mapping brain connections. However, despite the outstanding progress made by these projects, the vast majority of neuroscientific studies in mammals have traditionally focused on investigating only a few species (mainly rodents and non-human primates). These species have primarily been chosen because of their suitability for standardized laboratory studies or their genomic similarities to humans (as with monkeys). Nevertheless, many mammals exhibit unique capabilities that have not yet been characterized in these species. Thus, one of the major challenges in mammalian neuroscience is to support the study of a broad range of species in order to reveal both conserved and species-specific features, ultimately leading to a better understanding of mammalian brains and their role in inducing behavior.

The importance of studying a broad range of species

Since the very early studies of brain organization, neuroscientists have been trying to understand how features such as brain size, the number of brain regions, cell lamination patterns, and interconnections between areas are organized in different brain regions, and how they relate to cognitive abilities. There has been a long-standing debate regarding the uniformity versus non-uniformity of brain organization, with some researchers emphasizing the similarities, while others highlight the differences (reviewed in DeFelipe, 2002). For example, the cerebral cortex has been traditionally divided into a number of cytoarchitectonic fields that can be distinguished from their neighbors based on differences in the overall density, size, and shape of the cells and their arrangement in cortical layers, which supports the idea that differences in cortical organization would give rise to a distinct and specialized neural architecture (e.g., Brodmann, 1909; von Economo and Koskinas, 1925; von Economo, 1927; for a review, see Amunts and Zilles, 2015). Other researchers have proposed that functional differences between areas are mostly due to connections (Szentágothai, 1978; Creutzfeldt, 1977; Rockel et al., 1980; Douglas and Martin, 2004). Supporters of this view affirm that during evolution, the complexity of the neocortex increased in larger brains due to the addition of microcircuits with the same basic structure. However, when a range of species other than those commonly used (mouse, rat, cat, monkey, and human) were considered, new arrangements were found (Haug, 1987; Glezer et al., 1988; Reep et al., 1989; Stolzenburg et al., 1989; Hof et al., 2000; DeFelipe, 2002; Defelipe, 2011; Chengetanai et al., 2020; Manger et al., 2021). Thus, new insights can be obtained by examining species diversity. For example, analyzing brains that are larger than the human brain can be of great interest, such as the brains of African elephants, in which it has been revealed that there are three times more neurons than in the average human brain; however, the majority of these neurons are found in the cerebellum, showing that it is the larger absolute number of neurons in the human cerebral cortex (but not in the whole brain), which correlates with the superior cognitive abilities of humans (Herculano-Houzel et al., 2014).

Alternative methodologies have also allowed for the study of new aspects of circuitry, and comparative studies are becoming more common. Indeed, there is increasing evidence that each species has unique molecular, anatomical, and physiological features (Preuss and Coleman, 2002; Oberheim et al., 2009; Defelipe, 2011; Sherwood et al., 2012; Geschwind and Rakic, 2013; Hawrylycz et al., 2012; Kaas, 2013; Eyal et al., 2018; Sousa et al., 2017; Verendeev and Sherwood, 2017; Molnár et al., 2019; Elston et al., 2001; Marchetto et al., 2019; Hodge et al., 2019; Kalmbach et al., 2021; Lee et al., 2023; Galakhova et al., 2022; Luria et al., 2023; Benavides-Piccione et al., 2024; Kanari et al., 2024). In this regard, the concept of species-specific types of neurons is a matter of debate because the definition of a cell type depends on its morphological, physiological, molecular, and genetic composition (e.g., Ecker et al., 2017). Consequently, it is important to examine the diversity of species from different perspectives and encourage anatomical, physiological, and molecular researchers to reach consensus on current controversial terms and issues (preferably by meeting in person) in order to clarify brain organization in different species (e.g., PING, 2008; Nelson, 2002; DeFelipe et al., 2013; Molnár et al., 2019; Yuste et al., 2020).

Learning from the comparison of brain features

The study of different brains allows for the comparison of features across brain regions and species. If a particular brain microcircuit shows specific patterns responsible for information processing in a particular brain region, it can be investigated whether such patterns can serve as a foundation for comparing organizational principles across various brain systems, aiming to uncover both shared principles and region/species-specific adaptations (reviewed in Shepherd and Grillner, 2010). Taking pyramidal cells (the basic building block of the cerebral cortex) as an example, it is possible to analyze the extent to which these cells have parallel morphologies in different cortical regions and species by comparing distinct anatomical features, which have important functional implications. Pyramidal cells are composed of distinct dendritic apical and basal compartments that receive and integrate information from functionally diverse areas (DeFelipe and Fariñas, 1992; Spruston, 2008; Aru et al., 2020). These cells have been shown to be characterized—among different areas and species—by markedly different dendritic structures, which are directly related to function (reviewed in Elston, 2003; Elston et al., 2011). For example, certain areas of the prefrontal cortex of various primate species, including humans, have larger pyramidal cells, which are more branched and spinous than their counterparts in the occipital, parietal, and temporal lobes (Lund et al., 1993; Elston et al., 2001; Jacobs et al., 2001; Luebke, 2017; Benavides-Piccione et al., 2024). In addition, there is a trend towards increasing pyramidal cell complexity with anterior progression in the occipitotemporal cortex (reviewed in Elston, 2003). Regional variation in pyramidal cell structure has also been observed in mice, albeit to a lesser degree (Benavides-Piccione et al., 2006; Ballesteros-Yáñez et al., 2010). Briefly, the size of dendritic arbors influences their sampling geometry and the mixing of inputs; the patterns of dendritic branching may determine the degree to which the integration of inputs is compartmentalized within their arbors; and the density of dendritic spines influences various aspects related to the integration and co-operativity of inputs (e.g., Koch et al., 1982; Shepherd et al., 1985; Malach, 1994; Elston, 2003; London and Häusser, 2005; Spruston, 2008). Specifically, human pyramidal cells show greater, but not scalable, dendritic computation complexity in certain regions compared with pyramidal cells in other species, which accounts for the demonstrated singularity of the biophysics of these neurons (e.g., Jacobs et al., 1997, 2001; Jacobs and Sheibel, 2002; Elston et al., 2001; Zeba et al., 2008; Anderson et al., 2009; Hutsler and Zhang, 2010; Beaulieu-Laroche et al., 2018; Eyal et al., 2016, 2018; Gidon et al., 2020; Benavides-Piccione et al., 2020, 2021, 2024; Mertens et al., 2024; Kanari et al., 2024; Masoli et al., 2024).

Nevertheless, there are relatively small and simple human pyramidal neurons, such as those in the visual cortex (Elston et al., 2001; Benavides-Piccione et al., 2024). Interestingly, in brains that are larger than human brains—such as those of the African elephant—longer dendritic segments are found, but there is less intricate branching than that observed in human pyramidal cells. In addition, African elephants show regional variation similar to other rodent and primate species (Bianchi et al., 2011; Jacobs et al., 2011).

Thus, through detailed analyses of the particular features of pyramidal neurons across regions and species, it is possible to find some common dendritic organizational patterns. Examples of such patterns that have so far been determined as conserved are as follows: pyramidal cell dendritic diameter values decrease as the branch order increases; the length of dendritic segments increases with higher branch orders; intermediate segments are thicker and shorter than terminal segments; terminal segments of pyramidal neurons exhibit similar widths; and the main apical dendritic diameter correlates with axonal diameter and soma size—whereas there are other features whose variation is found to contribute to the region/species-specificity, such as the dendritic diameter, number of primary dendrites, branching complexity, and spine density (Benavides-Piccione et al., 2024; see also Elston and DeFelipe, 2002; Benavides-Piccione et al., 2020, 2021; de Kock and Feldmeyer, 2023). Thus, some features reflect a general trend in the structural organization and design of pyramidal neurons, whereas other features represent specific morphological parameters that contribute to the existing diversity within pyramidal cell structures across different areas and species. In addition, by identifying the distinct and conserved features between regions and species, it is possible to hypothesize via which steps pyramidal cell complexity may have increased during cortical expansion: (1) an increase in dendritic diameter, followed by further dendritic width enhancement of apical main and basal dendrites, along with an increase in axonal diameter; and/or (2) an enlargement in neuron size, involving a) extension of distal dendritic segment lengths; b) increase in dendritic complexity (e.g., number of nodes and dendrites); and c) an increase in the number of dendritic spines (Benavides-Piccione et al., 2024).

In addition, because morphological features highlight significant variations in the processing of information, it is possible to build models that demonstrate the biophysical and computational distinctiveness of neurons in different regions and species (e.g., Eyal et al., 2016, 2018). Furthermore, since the relationship between microscale cytoarchitecture and macroscale connectome organization has been established in several species, including humans (e.g., Scholtens et al., 2014; Barbas, 2015; van den Heuvel et al., 2015, 2016; Beul et al., 2017; García-Cabezas et al., 2019; Wei et al., 2019), the more elaborate the identification and extraction of the features of pyramidal neurons, the more comprehensive the characterization of macroscale organization. Therefore, it is essential to identify and extract features that capture the functional properties of pyramidal neurons in different cortical regions and species. Moreover, the study of the human brain in health and disease will not only help to better understand the mechanisms underlying human brain function but will also provide new insights into the underlying disease mechanisms of neurodegenerative and neurodevelopmental brain disorders.

Extrapolation of data matters: the case of the prefrontal cortex

A main concern regarding comparisons between species is the extrapolation of data between regions and species. The prefrontal cortex (PFC) is particularly relevant in this regard because its function is still poorly understood, and potential inter-species differences remain the subject of much debate, as demonstrated by a recent workshop that brought together experimental and computational scientists to discuss this matter (https://www.humanbrainproject.eu/en/education-training-career/workshops/pfc/). Here, we focus on only a few of the most pertinent points debated at this workshop. The granular prefrontal cortex (gPFC) is involved in a variety of high-level cognitive processes, particularly those involving executive control, attention, memory, and social behavior. It has undergone dramatic expansion in primates and is composed of diverse regions that vary in terms of the size, density, and distribution of their components, displaying a complex set of connections and diverse gene expression repertoire (reviewed in Povinelly and Preuss, 1995; Goldman-Rakic, 1996; Kaas, 2013; Fuster, 2001; Kolk and Rakic, 2022; Preuss and Wise, 2022). Nevertheless, the long-standing question alluded to above remains, that is, it has not yet been defined the extent to which it is possible to extrapolate from the whole PFC to specific regions of PFC, or species, to make comparisons (e.g., Preuss, 1995). For example, rodents have homologs of the agranular areas found in primates but lack homologs of the granular cortex, which constitutes the largest part of the PFC in most primate species. Likewise, the connectivity observed in primates as a result or consequence of the new areas generated in primates cannot be studied in mice. Thus, it could be agreed that the delimitation of the PFC across species is based on the presence of a gPFC. Similarly, the overall homology of areas between species should be revised to define a more appropriate extrapolation of the data. Similarly, the extent to which the same behavioral task can be applied to different species should be better defined, highlighting potential limitations when comparing tasks across species. In particular, inferring from animal models to humans requires even more careful evaluation—not only due to species specificity, but also because there are technical and ethical constraints that limit the methods that can be used to study the human brain. Consequently, understanding the human brain requires the direct analysis whenever possible and there is a clear need for more strategic tools to achieve this. Similarly, it is important to outline the types of experiments or strategies that should be employed to examine each brain species. Finally, interindividual variability should also be considered, particularly in humans and the PFC region, which exhibits greater variability than that reported in other species (e.g., Jacobs and Scheibel, 1993; Peng et al., 2019; Benavides-Piccione et al., 2021).

Concluding remarks

In summary, it is essential to support the study of a broad range of species—rather than focusing solely on mice, rats, and other primates—to reveal the diversity of the animal kingdom. Identifying both conserved and species-specific features will help uncover the neural mechanisms underlying differing mammalian behaviors. The human brain has several unique features since every species has its own particular traits. Promoting research on the human brain is crucial to ensure a better understanding of its structure and function, which will ultimately help explain human behavior. Multidisciplinary approaches and collaboration between experimental and computational scientists are necessary to establish a consensus on the key issues related to brain organization across species.

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