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Comparative approaches to cortical microcircuits

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Recent trends in neuroscience have narrowed the scope of this field, notably through the progressive elimination of 'model systems' that were key to the development of modern molecular, developmental and functional neuroscience. Although the fantastic opportunities offered by modern molecular biology entirely justify the use of selected organisms (e.g., for their genetic advantages), we argue that a diversity of model systems is essential if we wish to identify the brain's computational principles. It is through comparisons that we can hope to separate mechanistic details (results of each organism's specific history) from functional principles, those that will hopefully one day lead to a theory of the brain.

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Brains, like all biological organs, are the result of long evolutionary processes. An evolutionary or comparative perspective on brain function can be informative on at least two levels: the mechanistic, by identifying inherited features (e.g., molecular components); and the algorithmic, by pointing to similar forms of solutions to common problems (e.g., circuit graphs, cellular operations, among others). Of particular interest are cases where common algorithms are not inherited, but rather result from evolutionary convergence. Those instances, clear evidence for which is still admittedly rare, may point to the essence of an operation, identifying both computation and algorithmic solutions, independently of implementation. A comparative approach to understanding brains as information processing systems thus meets David Marr's classical distinction between levels of understanding [1,2].

An evolutionary approach to brain function requires comparisons. One great practical difficulty in this exercise lies in defining the objects of these comparisons (Figure 1). Should they be gene or protein sequences, spatio-temporal gene expression patterns, cell morphologies, architectonics, connectivity graphs, gross structural features, biophysical and synaptic characteristics, emergent properties (e.g., travelling waves, consciousness), or functional consequences (e.g., gain control), to take but a few examples? In other words, what are the relevant dimensions? At a time when modern technology takes us from an artisanal to an industrial phase of neurobiological investigation, do we acquire all data that can be had, on the premise that any data are useful? If so, should we (and if so, how?) harmonize data acquisition, archiving and cataloguing? Or do we make some wise operational choices? If so, which ones? These questions are very important if we wish, for example, to cluster and compare datasets. The answers depend much on how we conceive of 'understanding the brain'. Understanding implies reducing the description, that is, throwing away. But what can we throw away? How do we know *a priori*? A comparative approach is thus useful also in that it forces us to identify, or at least be explicit about, the features and dimensions that should matter to reach a functional understanding.

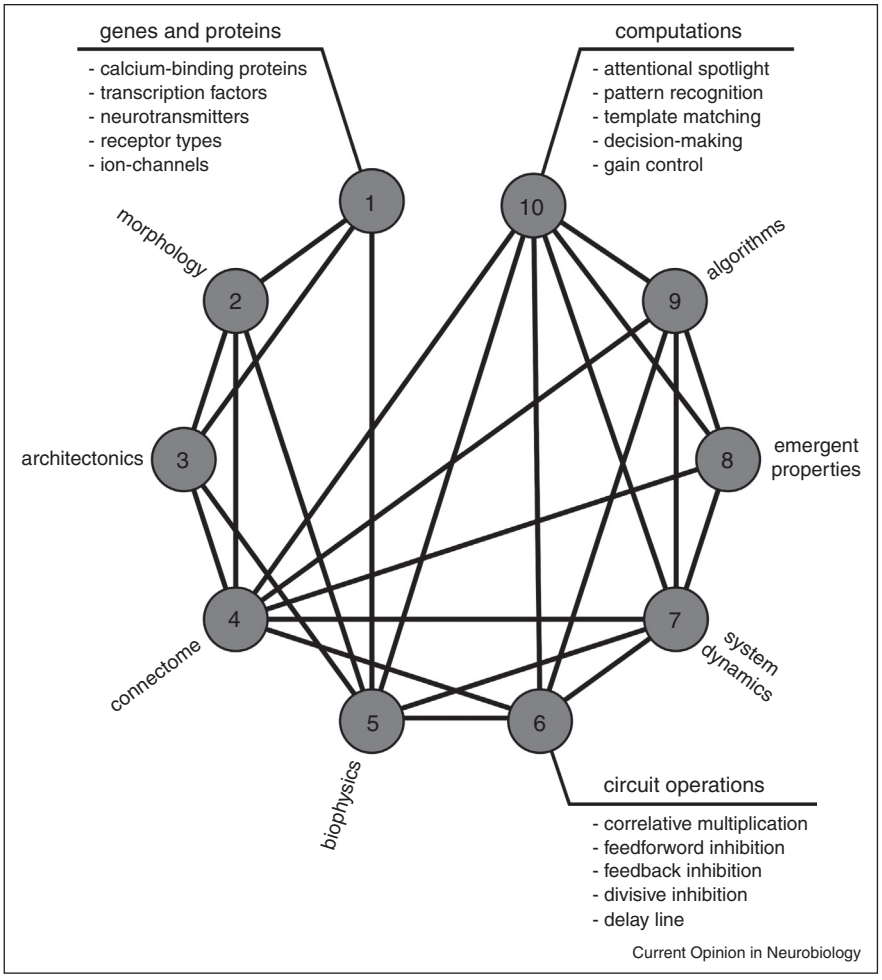
The complexity of multi-scale problems

The multi-level organization of the brain makes it difficult to define precisely meaningful entities for comparisons (Figure 1). The outcome of a comparison (e.g., across cell types or circuits) depends on the features selected and on their relative weightings. Results based on some features or dimensions may not map clearly onto classifications based on other dimensions. In addition, classification and feature profiles themselves may change with developmental time or brain state [3]. In some cases, these parametric variations may be linked to the homeostatic stabilization of some high-level set point, itself often unknown. If so, the parametric variations are only sets of solutions to a larger overarching goal [4,5], but not necessarily interesting in and of themselves. In other cases, they may underlie true state transitions, and thus be critical to a functional understanding. Finally, the variability of data collected across hundreds of laboratories using many finicky techniques makes comparability a central problem of neuroscience. How then do we deal with comparative outcomes that are based on these data? Industrial scale initiatives, such as those of the Allen Institute [6,7,8••], strive towards explicit standardization. But is the time ripe for worldwide standardization?

Harmonization of data and techniques, open-source

As the world neuroscience community engages in ambitious large-scale national or multi-national efforts,

Figure 1



Comparing brains or circuits is a challenging multi-scale problem. This circular diagram illustrates some important features of neural systems and some of the possible mappings between them. Nodes 1 to 10 are meant to represent different levels of analysis, from the molecular to the computational. Each node represents a large class of descriptors, that can be more or less independent of one another. A few examples are given for nodes 1, 6 and 10. (The nodes and links depicted are in no way exhausive.) Not depicted here is the fact that there usually exists many possible mappings between pairs of nodes. For example, a given computation may result from several biophysical or circuit implementations, which may themselves result from several molecular/developmental histories. The challenge is to encover, through these comparisons and linkages, some overarching principles of brain function.

discussions have been initiated on the topics of data formats (e.g., [9]), management and storage [10], on the need for standardization of techniques and of nomenclature (as with the bird brain consortium [11], the Petilla terminology for inhibitory interneurons [12,13] and newer efforts [14,15•]). The challenges posed are not linked only to the political/sociological difficulty of building a consensus in a large, widespread and heterogeneous community [16]. It is also linked to the complexity of the scientific questions (see Figure 1), their fuzziness sometimes, and thus to the absence of an agreed-upon ranking of the features that we should care most about. Other fields of biology in which large-scale efforts and standardization have been solved with success (such as sequencing or even functional brain imaging) are ones in which the scientific questions or goals were constrained and well posed. This led to targeted technological development, the spread of analysis routines and machines and consequently, the harmonization of these fields. Understanding the brain (from molecules to cells, circuits, behavior, perception and disease) is so multi-faceted that a push for harmonization may seem premature. Harmonization will likely happen *de facto* as soon as the questions are clearly posed, the methods well adapted, and the market of methodologies open and free. What seems increasingly important is therefore the open sharing of methods, the use of open-source platforms, the use of common test/

calibration datasets for method comparisons, and the posting of published datasets.

Comparing cortical circuits: details versus computational principles

Cortical microcircuits are particularly difficult to compare (across brain areas as well as across animal species), in great part because we still understand little about them and the coding principles that they express. (It is useful to remember here that we know the architecture of cerebellum in exquisite detail in many vertebrate species, but still understand little about its operations.) Cortical neurons probably have no single 'role' in a circuit, and defining precisely what a circuit consists of is, when one thinks hard about it, not at all clear. We are naturally drawn to the neuron as a scale for study and comparison, but is it always the right one? Add to these observations the fact that activity-dependent plasticity rules can constantly alter circuit constituents and one realizes the complexity of the challenge [17,18].

How then can we proceed? The synthesizing approach of certain anatomists led to the concept of a canonical circuit that, repeated throughout cortical areas, implements some computational primitive [19]. This is a powerful operational idea for it means that if we understood the canonical circuit, say of visual neocortex, we could understand the rest of the neocortical sheet. Recent work, however, highlights interesting differences across primary sensory cortices [20,21], raising some doubt about the prospect of identifying equivalent operations and circuits across cortical areas that process primary visual, auditory or somatosensory information (V1, S1, A1), recognize abstract visual objects (IT), plan- or execute eye movements (FEF, M1) or motivate behaviors (cingulate cortex). Furthermore recent work on orientation selectivity in visual cortex indicates profound inter-species differences in the organization of maps (pinwheels vs 'salt and pepper') in visual cortex [22–25]. Although these results raise some doubt about the idea of a 'canonical' cortical circuit, the different architectures recently uncovered may ultimately reveal even more powerful organizing principles, of which pinwheels and salt and pepper architectures would be only two examples [26].

A different style of comparative approach rather proceeds from the emergent functional properties back towards underlying mechanisms. For example, looming-sensitive visual neurons with similar response dynamics have been described in very distant species such as pigeons and locust [27,28]. This identifies these dynamics as a potentially key property in circuits that mediate collision avoidance, although these circuits are totally unrelated (thalamic nucleus rotundus in birds, lobula optic lobe in insects). Similarly, spike-timing-dependent plasticity rules have been found in insects [29] as well as vertebrates [17,30] and early visual pathways in the retinae of vertebrates and flies [31•,32,33] increasingly appear to operate according to similar principles. These examples confirm the essential value of a comparative approach, based on computation, as beautifully illustrated in the classical comparison of sound localization circuits in the barn owl and jamming-avoidance circuits in the electric fish Eigenmannia [34]. These studies all identify common computational principles that were reached through evolutionary convergence and thus, that may often rely on different mechanisms. Hence, while exhaustive mechanistic descriptions (e.g., [6,7,8••,35]) have undeniable value, it is not entirely clear that they are the most efficient path towards computational understanding. We believe that comparative computational work has an essential role to play in identifying those principles (without minimizing the importance of mechanistic detail).

Theta-band activity in mammalian navigation circuits

The hippocampus and entorhinal cortex offer an excellent case study for the value of a comparative approach. Although these brain areas and their role in spatial navigation have been studied for decades in rats [36], it is only recently that their operations have been examined in flying mammals such as the Egyptian fruit bat [37,38], an animal with long-range foraging behavior and challenging navigational requirements.

Place cells, grid cells, border cells and head-direction cells all appear to exist in both rats and bats [36,37], even though place fields are 2-dimensional in rats and 3-dimensional in flying bats. Interesting inter-species differences occur, however, in the collective neural dynamics that accompany these mapping properties. Whereas high-frequency ripple oscillations are seen in both rats and bats [37,39•], *theta* (8–12 Hz) range oscillations in bats are different from those seen in rodents: for example, they occur only in short (1–2 s) bouts during echolocation, their spectral peak is small and they are accompanied by a large *delta*-band (1–5 Hz) component. In addition, *theta* rhythmicity is absent in the firing patterns of place cells in the bat, during any mode of behavior examined [37,39•,40]. These findings are relevant for primate studies also, where intermittent *theta* oscillations have also been observed [41] and force us to reassess the role of *theta* as a fundamental or necessary phenomenon linked to spatial navigation. Stated differently, these results do not imply that *theta* oscillations are not relevant; they suggest, however, that alternative solutions not dependent on *theta* may exist.

Several computational models, developed for spatial representation by place and grid cells in rats, are impacted by these findings. Oscillatory interference models propose that interference between somatic and dendritic *theta*-band oscillations in single neurons transforms

a temporal oscillation into a spatially periodic grid [42–44]. Although this model received support from intracellular recordings of place cells [45], the recent results in bats suggest that it may not be a general model for representing space (or for the encoding and retrieval of memories) (though see [46]). Alternative models based on attractor dynamics [47], however, can account for the bat data. If the different roles of *theta* in rodents and bats are confirmed, one would like to know how they evolved, and when. These results emphasize the observation that solutions to fundamental and common computational problems are not necessarily unique, and that understanding the diversity of these solutions should also be an important goal of modern neuroscience.

Normalizing gain-control circuits

It is increasingly clear that microcircuits in the brain carry out a number of essential functions, such as gain control, filtering, amplification, exponentiation, association, and coincidence detection, to take but a few examples. They can also serve to constrain and define trajectories in neural space, a property now observed in sensory as well as motor systems [48,49].

Normalization is a special case of a gain control operation and is well illustrated by recent studies in invertebrates (*Drosophila* antennal lobe and locust olfactory system) [50], early vertebrates (zebrafish olfactory bulb) and mammals (retina and neocortex). Although these examples are all interesting, meaningful comparison between them is sometimes difficult. In *Drosophila* and zebrafish, the computation is essential and low-level (odor concentration normalization), and the algorithmic and mechanistic details very well understood [51,52•]. In mammalian V1, by contrast, details on implementation are still fragmentary, but the computations accomplished of greater operational scope [53].

The antennal lobe (AL) of *Drosophila* and olfactory bulb (OB) of zebrafish perform a normalization of responses to a range of odor concentrations, as well as normalizing single glomerular responses to global AL/OB activity. In mammalian V1, 'response normalization' [54] usually describes operations whereby responses to a particular feature of visual space (e.g., spatial position and orientation) are suppressed by stimuli with a broader feature range [55].

In V1 neurons, response normalization is not simply a function of light intensity but can depend on higher-level features such as orientation tuning and fractional receptive field activation. Normalization phenomena include, for example, two forms of response suppression: (1) cross-orientation suppression, which comes into play when gratings of preferred and non-preferred orientation are superimposed within the receptive field of a neuron [56]; (2) surround suppression, in which the part of a stimulus with a suppressive effect affects the summation (excitatory) field [57].

Algorithmic and mechanistic implementations are now well understood in the *Drosophila* and zebrafish early olfactory systems [58]. High gain for weak signals in *Drosophila* is implemented by high-quantal EPSPs, high basal release rate [59], and olfactory receptor neuron (ORN) convergence on projection neurons (PNs) [60,61]. Gain reduction for strong signals, by contrast, relies on fast vesicle depletion (hence strong short term depression) at the ORN-PN synapse [59]. Adaptive homeostatic mechanisms appear to be involved also, whereby unitary EPSCs are tuned to PN input resistance [59].

In both zebrafish and *Drosophila*, nonspecific 'lateral' inhibition is established via interneurons that receive inputs from many (in some cases almost all) glomeruli; thus, PN responses are controlled adaptively when other glomeruli are co-activated. The effect of this normalizing inhibition grows almost linearly with the magnitude of the entire network's activity [52•,62–64]. In both systems, one observes electrical coupling of interneurons to PNs/mitral cells, contributing to normalization by spike synchronization and shunting inhibition (reducing neuronal excitability locally via increased chloride conductance) [64,65]. Interesting differences exist, however, such as the site of interneuron action: presynaptic in *Drosophila* [63] but postsynaptic (on mitral cells) in the zebrafish olfactory bulb [64].

In mammalian V1, details on mechanistic implementation are less exhaustive and the evidence originates mainly from slice work [66]. It has been suggested that GABAergic inhibition plays little or no role in normalization such as contrast saturation or cross-orientation suppression [67], though it might be involved in surround suppression. Evidence for shunting inhibition is also unclear [68]. A recent study supports an alternative mechanism in the form of decreased excitation [69•]. Only the timing of the divisive signals involved in normalization offers some clues as to their origin: for cross-orientation suppression, they match that of LGN [70] suggesting a feed-forward arrangement. By contrast, signals from a broader region of visual space as in surround suppression resemble V1 responses [71], suggesting a feedback arrangement. Recent results nicely show that layer 6 modulates the gain of visual responses via intracortical disynaptic inhibition [72,73••].

Conclusion

Six hundred million years of metazoan evolution have generated many solutions to comparable neurobiological challenges, all constrained by the common physics of our environment. Comparative approaches, far from being quaint relics of musty 19th-century museum systematics, are essential to modern neuroscience in a number of ways.

For example, one can exploit them to gain historical or evolutionary insight into the progressive elaboration of complex circuits, such as cortical networks in amniotes [74••]. Alternatively, informed comparisons can help us separate implementation details — interesting in and of themselves and essential for practical applications, such as in human and animal medicine — from computational and algorithmic principles, those that will ultimately help us derive a theory of the brain. One added benefit of diverse experimental approaches is that they keep revealing surprises. For example, insects appear to possess a navigation system not without resemblance with the head-direction system of mammals [75,76]. Insects also probably generate internal models of prey motion and steering maneuvers [77], not unlike vertebrates do [78]. In short, comparative approaches may, in many cases, allow us to identify general principles of circuit function, just as they have in past decades with basic biophysical and synaptic functions.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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