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Chasing the Dreams of Early Connectionists

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ABSTRACT: Mapping and examining the wiring pattern of neural systems is a fundamental pillar of neuroscience. In this Viewpoint, we review a recently described mesoscale connectome map of the mouse brain. We underscore the map's high spatial resolution and discuss key organizational network attributes of the presented connectome, its potential impact on neuroscience, and the general importance of connectome maps to obtain insight in the workings of the brain at a system's level.

KEYWORDS: *connectome, mesoscale connectivity, mouse, neural networks, graph theory, brain*

Dating as far back as to the earliest days of neuroscience, anatomists have always been fascinated by creating maps of the brain's white matter. One of the early pioneers, Niels Stensen (1638−1686), envisioned in his 1665 essay that a fruitful way of studying the brain's white matter might be *"to follow the nerve threads through the substance of the brain to find out where they go and where they end"* (quoted from refs 1 and 2). Today, inspired by their vision, neuroscience is standing at the frontier of state-of-the-art technology capable of making a map of not just a subset, but *all* nerve threads that comprise the brain.

In a recent Nature paper,[3] the team of Hongkui Zeng from the Allen Institute for Brain Science describes the results of a high-throughput data acquisition and processing platform to systematically map and document the anatomical wiring of the adult mouse brain. Connection mapping involved the administration of anterograde recombinant Adeno-Associated Virus (AVV) tracers to 295 nonoverlapping anatomical regions, providing a complete coverage of the mouse brain, with axonal projections systematically traced from the source of the injections (cell bodies) to the synaptic termination sites of the infected axons using two-photon microscopy. With this technology, Zeng and colleagues provide a first brain-wide "connectome" map[4] of the neural wiring of a mammalian brain at a mesoscopic scale. Previous studies have provided macroscale wiring diagrams of, for example, the macaque and cat cortex, but all these maps have been based on a collation of tract tracing data across a large number of studies, resulting in relatively coarse and often incomplete connectome maps. Besides an unprecedented mesoscale resolution of spatial coverage, the Allen Brain mouse connectome map (Figure 1A) provides one of the first reconstructions performed by a single group following a standardized mapping protocol, which is another strong improvement over earlier pioneering endeavors.

Interestingly, going beyond "just" mapping connections, Zeng and colleagues also performed a first examination of the topological architecture of the presented mouse connectome. Several features of mammalian brain organization are reported. The wiring density ranged up to 38% between ipsilateral and 35% between contralateral regions, suggesting a remarkably high level of interhemispheric connectivity. Furthermore, connectivity strength—expressing the level of axonal connectivity between brain sites—is noted to span a 10^5-fold range, leading the authors to conclude that not only the presence of long-range neural projections but also the variety in strength of connection pathways forms a fundamental aspect of neural network architecture. Embracing network science as a mathematical tool for examining the topological organization of the presented neural network, the mouse connectome further revealed significantly elevated levels of local clustering (over 7 times higher than in a set of 1000 random networks, Figure 2) and community structure (showing 6 large-scale communities, Figure 1). These local organizational features are combined with short global paths between brain regions (Figure 2) which are just a fraction longer than the very short routes that appear in random networks, together indicating a "small-world" organization of the mouse connectome[4] (Figure 2).

The authors further note that the number of afferent and efferent white matter projections per brain site tends to follow a fat-tailed distribution, reflecting the presence of a set of high degree regions with an above average level of connectivity. Sparse additional examination reveals that these putative neural "hubs"[5] are widely distributed across the mouse brain (Figure 1B, red dots), cover the majority of anatomical communities and have a significantly denser level of mutual connectivity than expected based on their degree ($p < 0.001$). Interestingly, connections spanning between hub nodes tend to involve (on average) relatively long anatomical pathways ($p < 0.001$, as compared to other connections), a high number of bidirectional connections (67% in contrast to 37% for other connections) and higher ranked weights ($p < 0.001$), supporting the notion that neural hubs and their connections form a central high capacity, high cost "rich club" in the mammalian brain.[6] All together, the described network examinations provide converging evidence that the mammalian brain has a complex, nonrandom network architecture. However, as nicely put forward by Zeng and colleagues, neither a small-world nor a scale-free model could fully explain the topological organization

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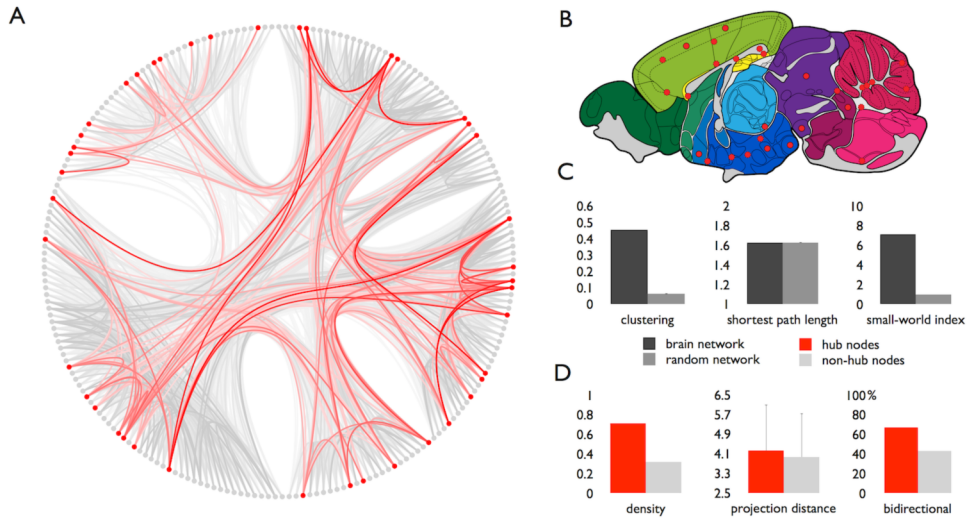

Figure 1. (A) Circular representation of the 25% strongest intrahemispheric connections of the mouse connectome as mapped by Zeng and colleagues, with nodes arranged according to community participation (6 main communities are observed). Hub-to-hub connections (red) are shown on top. (B) Schematic figure of a sagittal slice of the mouse brain taken from the Allen Brain atlas (www.brain-map.org). (C) The mouse connectome reveals a high level of topological clustering (> random level) and short communication pathways (~ random level), indicative of a small-world organization. (D) Preliminary findings suggest the presence of densely mutually interconnected hub nodes (red points in A and B, left histogram) with hub-to-hub connections (red edges in A) that span on average longer physical distances (middle), comprise higher ranked weights and are more often part of a bidirectional pathway (right) compared to the other pathways in the network (gray edges in A).

Figure 2. Neural networks can be described and examined as a set of nodes (e.g., neurons or mesoscale brain sites) and a collection of connections between nodes (e.g., reconstructed anatomical pathways) (most left panel). Within this mathematical framework, information on the local organization of the network can be, for example, provided by the level of network clustering, reflecting how strong the neighbors of a node are connected (left panel, orange), and the extent to which nodes form local subnetworks or communities (left panel, blue). Information on the global organization of a network can, among other measures, be examined in terms of the average number of steps that is needed to travel from one place to another place in the network (right panel, green). Due to their high level of connectivity and central embedding in the network, hub nodes and their connections often form a prominent structure within the overall network (most right panel, red).

of the mouse connectome, suggesting that the complexity of neural networks goes beyond that of simple wiring models.[7]

After the presentation of such an unprecedentedly detailed connectome map, what is next? Given the still growing interest in brain connectivity, it is certain that the open-access Allen Brain map will be heavily used in the most exciting years of connectomics yet to come. Among many other purposes, it may serve as a golden standard for studies elucidating key organizational features of anatomical neural systems, provide anatomical reference for studies that use the mouse as animal model for brain disorders, and/or function as data set for more computationally driven studies. However, despite its high spatial and sampling resolution, the presented map cannot provide answers to all connectome questions. For instance, similar to previously reconstructed connectome maps of other species, the adopted techniques do not allow the reconstruction of connectome wiring on the individual level. Data from a large number of different animals is required to obtain a complete connectome map, thus limiting the examination of potential individual variation in connectome wiring. Intriguingly, in a small subset of overlapping injection experiments, Zeng and colleagues report on intriguing high levels of consistency of connectivity across tested animal specimens, while connectome studies in human samples—with connectivity estimates derived from in vivo magnetic resonance imaging—often report individual differences in brain wiring to be related to individual variation in cognitive performance or aspects of personality. It therefore remains an open challenge for future studies to clarify on which scale, and to what extent, variation in brain wiring is linked to individual differences in behavior. And while connectome mapping is undeniably a crucial step in obtaining understanding of the workings of the mammalian brain, Zeng and colleagues rightfully mention that obtaining detailed insight into the functioning of neural networks may require a different approach. Providing a sneak preview of new advances to come, Zeng and colleagues discuss an extension of their framework to viral vectors that actively monitor and manipulate synaptic processes, potentially bridging the gap between anatomical connectivity and functional circuitry.

Pioneering anatomist Niels Stensen concluded: *"To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance, would be too low an opinion of nature's finest masterpiece. They [fibers] everywhere adopt a certain arrangement among themselves, created more or less according to the functions for which they are intended. If the substance is everywhere of fibers, as, in fact, it appears to be in several places, you must admit that these fibers have been arranged with great skill, since all the diversity of our sensation and our movements depends upon this."* (quoted from refs 1 and 2). With the presented mesoscale brain map (www.brain-map.org), the researchers of the Allen Institute for Brain Science have brought neuroscience one step closer to fulfilling the dreams of these early connectionists. And for that matter, those of today's connectomists.

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Notes

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