Cell

'Fore Brain: A Hint of the Ancestral Cortex

Lora B. Sweeney[1,2,3] and Liqun Luo[1,2,3,*]
[1]Neurosciences Program
[2]Department of Biology
[3]Howard Hughes Medical Institute
Stanford University, Stanford, CA 94305, USA
*Correspondence: lluo@stanford.edu
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By combining gene expression profiling with image registration, Tomer et al. (2010) find that the mushroom body of the segmented worm *Platynereis dumerilii* shares many features with the mammalian cerebral cortex. The authors propose that the mushroom body and cortex evolved from the same structure in the common ancestor of vertebrates and invertebrates.

The mammalian cerebral cortex underlies many higher-order processes, such as perception, memory, language, and advanced motor skills. With its intricate furrows and ridges (i.e., the sulci and gyri), the complexity of the cerebral cortex is evident even at its surface. Beneath the surface, the cerebral cortex is separated into layers of densely packed neurons with axons reaching deep into the white matter. These layers are divided further into functional regions that correspond to the body plan. How does such a complex structure develop such precise organization? Many researchers have approached this question from a developmental perspective by identifying and perturbing molecular components that contribute to the structure of the cerebral cortex (Hébert and Fishell, 2008). Alternatively, one can take an evolutionary approach and search for an ancestral precursor to the cortex. In this issue of *Cell*, Tomer et al. (2010) follow the latter approach and identify a brain region of the segmented worm *Platynereis dumerilii* (an annelid) called the mushroom body that shares the same "molecular fingerprint" as the developing mammalian cortex.

The cerebral cortex derives from the pallium. From the Latin for "cloak," pallium refers to the outer layer of the brain. The mammalian palium consists of the cerebral cortex, olfactory cortex, and the hippocampus. The evolutionary origin of the vertebrate pallium has fascinated biologists for centuries because our highest mental functions originate from it. To identify structures in the developing brain of *Platynereis* that are possibly related to the vertebrate pallium, Tomer et al. characterized the expression patterns of many genes at different stages of neural development in the worm. The standard methods for characterizing gene expression are in situ hybridizations and immunostaining with antibodies. However, these techniques are generally restricted to one or two genes at a time and thus are unable to provide direct comparisons of expression patterns for a large number of genes.

To overcome this technical hurdle, Tomer et al. use advanced image registration methods (including linear transformation and nonlinear warping), in which multiple microscopy images are aligned to one coordinate system, standardized to one size, and smoothed to correct artifacts due to stretches during sample preparation (Rueckert et al., 1999; Rohlfing et al., 2001; Kurylas et al., 2008). Specifically, Tomer et al. use the axon scaffold (i.e., bundles of axons in the developing brain) as a landmark to align individual gene expression patterns from multiple worms onto a standard brain template. This allows the simultaneous mapping of expression profiles for an unlimited number of genes during neural development. In this manner, the authors define the spatial relationship for the expression of more than fifteen genes in *Platynereis* that were previously shown to regulate the patterning of the cortex in mammals. These include many transcription factors such as Bf1 (brain factor 1, also known as Foxg1) and Pax 6 (paired box gene 6) (Hébert and Fishell, 2008).

With this technique, Tomer et al. identify a structure in *Platynereis* with gene patterns that mirror those observed in the vertebrate pallium. The authors then follow this structure during the development of *Platynereis* and find that its neurons develop into the mushroom body, a brain region in insects and worms involved in sensory processing and memory (Figure 1). Moreover, this embryonic structure in the worm gives rise to similar types of neurons as found in the pallium (e.g., glutamatergic and GABAergic neurons).

Similarities between the mammalian cortex and the invertebrate mushroom body have been noted previously, but such clear parallels in their gene patterning have not been observed (Strausfeld et al., 1998; Farris, 2008). Why not? Mushroom bodies are well characterized in insects, especially in the fruit fly *Drosophila*, and choosing to study an annelid was critical to making this new connection.

Based on the arrangement of the axon fibers and the function of its neurons, the mushroom body of insects has been loosely compared to the mammalian cerebral cortex, the hippocampus, or the cerebellum (Strausfeld et al., 1998). However, insects are fast-evolving invertebrates and thus may deviate quickly from their ancestors. By contrast, annelids evolve slowly and therefore make excellent organisms for comparing the

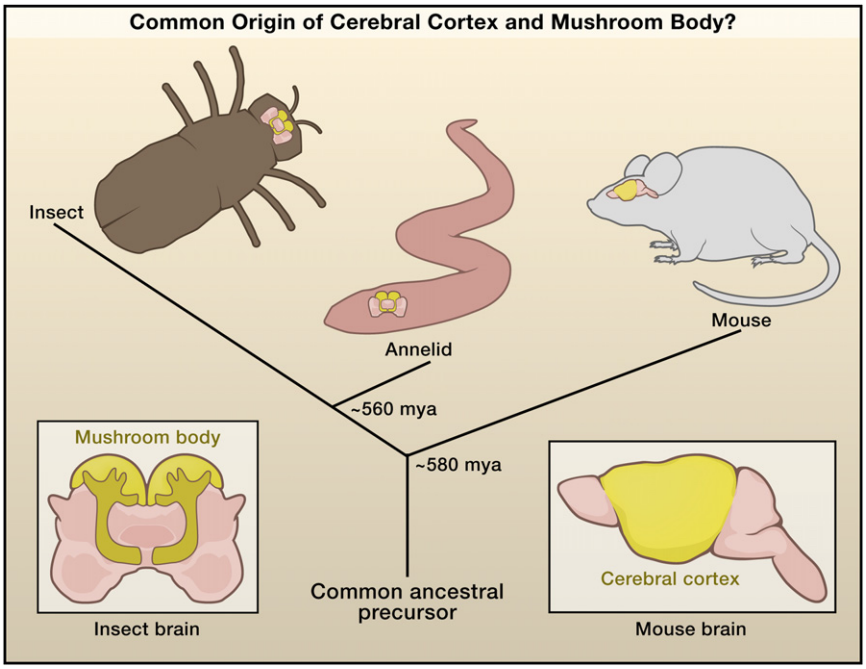

Figure 1. A Common Origin for the Mushroom Body and Cerebral Cortex?
In mammals, the pallium develops into the cerebral cortex, olfactory cortex, and hippocampus. Gene expression profiling combined with image registration in the developing brain of the segmented worm *Platynereis dumerilii* identified a brain region with gene expression patterns similar to that of the mouse cortex (Tomer et al., 2010). This region in the worm develops into the mushroom body, which is involved in sensory processing and memory formation in insects and likely worms. These results suggest that the mushroom body and the cerebral cortex evolved from the same structure in a common ancestor of vertebrates and annelids ~600 million years ago (mya). The estimates of divergence follow Peterson et al. (2004).

evolution of invertebrates with that of vertebrates. For example, an analysis of intron abundance across the entire genomes of vertebrates, annelids, and insects found that two-thirds of the human introns were also present in annelids but were largely absent from insects, confirming that insects have evolved faster than annelids (Raible et al., 2005). Moreover, annelids are extremely amenable to experimental analysis because they are easy to breed and observe in vivo. Further, they develop with highly stereotyped structures that vary little between individuals.

Given the similarity in the gene expression patterns of the developing annelid mushroom body and the mammalian cerebral cortex, do these structures share similar functions? The cerebral cortex transforms sensory information into action. The mushroom body of annelids also processes sensory information, receiving input from chemosensory cells on their mouthparts. In insects, the analogous structure is best known for processing olfactory inputs and for memory formation (Heisenberg, 2003). Indeed, Tomer and colleagues found that a subset of genes that share similar expression patterns in the annelid mushroom body and the mammalian cortex are also expressed in the *Drosophila* mushroom body.

Two distinct mechanisms can explain the molecular similarities of the invertebrate mushroom body and the vertebrate cerebral cortex. They could arise independently through convergent evolution, or they could evolve from the same structure in a common ancestor. Tomer and colleagues present a statistical analysis indicating that the similarities in gene expression that they observed are unlikely to occur by convergent evolution. Although these arguments suffer from the caveat that expression patterns of different genes may not have evolved independently, the number of genes studied by Tomer and colleagues do indeed favor the possibility of a common origin. Together, their data suggest that the vertebrate pallium and invertebrate mushroom body evolved from the same structure in the last common ancestor of these organisms (Figure 1). Moreover, this structural precursor may also have processed sensory information, as the cortex and mushroom body do.

That said, however, the vertebrate pallium and invertebrate mushroom body are considerably different. First, they have different shapes (Figure 1). This may result in part from considerable differences in neural developmental programs in vertebrates and invertebrates. Second, it is unclear whether the mushroom body exhibits the same type of layering and functional specialization as the cortex. Third, gene expression patterns appear to remain constant over time during development of the annelid mushroom body, but the patterns are quite dynamic during the development of the mammalian cortex. This temporal variation complicates the interpretation of the homologous gene expression patterns detected for the two structures. Finally, the expression profiles are not identical for the two structures. For example, expression of *Wnt3a* was present in the vertebrate pallium but not in the developing mushroom body. Such differences are probably not surprising, given that vertebrates and annelids diverged from a common precursor ~600 million years ago (Figure 1).

In summary, the data presented by Tomer and colleagues provide a tantalizing hint that one of the highest-order processing centers of the human brain shares an evolutionary origin with the mushroom body of worms and insects. In principle, the techniques presented by the authors for profiling expression patterns of numerous genes simultaneously can be used in other organisms to garner further support for this hypothesis. Furthermore, comparative structure-function analyses may also provide additional insights into the function of this ancestral structure, including how its form has adapted over the last 600 million years.

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