from the noisy movements of the dancing bee. This is a significant conceptual leap towards understanding this enigmatic behavior. The big task ahead will be to take this immensely elegant proposal and put it to the test. It is now up to the united forces of electrophysiologists and two-photon microscopists to finally solve "the most astounding example of non-primate communication that we know"[1].

DECLARATION OF INTERESTS

The author declares no competing interests.

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Evolutionary neurogenomics: Lengthy resolutions for complex brains

Leonid L. Moroz
Department of Neuroscience, College of Medicine and the Whitney Laboratory for Marine Biosciences, University of Florida, FL 32080, USA
Correspondence: moroz@whitney.ufl.edu
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Genomic blueprints underlying unique neuronal organization are enigmatic. A new study reveals the recruitment of ancient, larger genes for synaptic machinery, providing evolutionary constraints and flexibility, with increasing gene sizes being found in animal lineages that led to cephalopods and vertebrates.

The astonishing complexities of neural systems can only be understood through the lens of evolution. However, the paths that led to extant diversities of neural systems are elusive, with numerous, mostly unresolved, hypotheses. The current reconstructions indicate either single or multiple origins of neurons and synapses[1,2], highlighting the chimeric and modular nature of neuronal genealogies[1] with genetically different cellular lineages comprising nervous systems as we know them today[3]. Uncertainties are high, however, because 25 of 33 extant metazoan phyla are practically untouched by modern neuroscience[3]. The six most investigated phyla (nematodes, arthropods, chordates, molluscs, annelids, and cnidarians) are only the tip of the iceberg of neuronal diversity. A few model organisms, with numerically simpler nervous systems and compact genomes, are predominantly used for mechanistic deciphering of neural circuits. But what makes a neuron or a synapse? Admittedly, there are no pan-neuronal and pan-synaptic genes[4], although various markers specify diverse neuronal phenotypes. What are the genomic mechanisms underlying neuronal identity and plasticity? Are there any 'grand designs' or constraints of neuronal evolution? In this issue of *Current Biology*, McCoy and Fire[5] addressed one of the most fundamental questions in gene evolution: how does the size of genes affect their usage and recruitment in neural architectures? The authors found that many genes expressed in nervous systems are oversized, ancient, and sequence constrained, having undergone parallel gene size and isoform expansion across the animal kingdom. The shorter genes and transcripts, however, tend to be

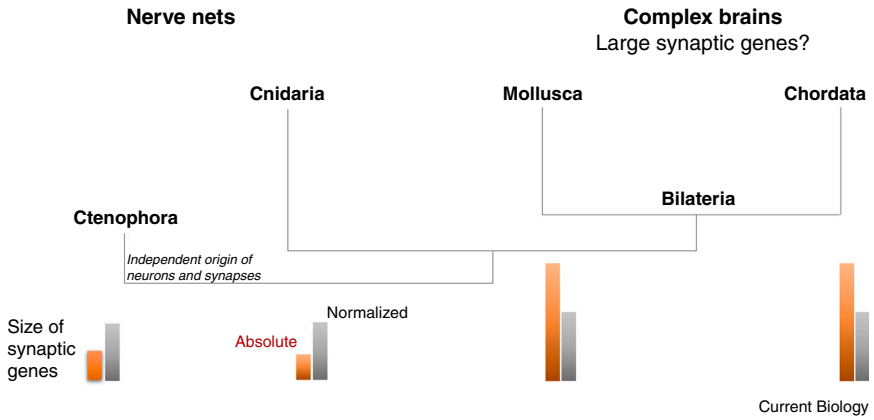

Figure 1. Parallel evolution of synaptic gene sizes in representative metazoans.
The bars at the bottom illustrate the absolute (orange) and relative sizes of synaptic genes (see details in McCoy and Fire[5] for medial sizes of the top 10% largest genes across phyla). Ctenophores represent an outgroup with likely independent origins of neurons and synapses compared with the rest of metazoans[2]. Cephalopod molluscs and chordates are exceptional examples of independent increase and diversification of large-sized neuronal and synaptic genes.

expressed in the skin, testis, and immune system[5,6] and can be associated with rapid stress responses.

McCoy and Fire[5] identified more than 35,000 orthogroups across 13 representative species; each orthogroup is a set of genes from multiple species that all descended from a single gene in the last common ancestor. The results of these unbiased genome-wide comparisons suggest that: first, most evolutionarily young genes are small, whereas the majority of larger genes have deep ancestry with premetazoan origins; second, these larger genes are predominantly expressed in the nervous system; third, large synaptic genes are evolving under strong purifying selection as demonstrated by low ratios of non-synonymous to synonymous substitutions (dN/dS) in mammals; and finally, these synaptic genes have concurrently grown larger and gained the most isoforms in distantly related animal lineages that led to cephalopod molluscs and vertebrates[6] (Figure 1). Cephalopods evolved one of the most complex brain architectures (with ~500 million neurons in *Octopus*[3]) independently of birds and mammals. In a previous study, McCoy and Fire also showed that gene size expansion occurred predominantly through net gains in intron size, with a positional bias toward the 5′ end of each gene[7], highlighting additional regulatory sites in these non-coding regions and expanding the adaptive space for gene evolution.

Transcription and translation of large-sized genes

The quantitative aspects of transcription and translation make this study interesting and important. Neural systems constantly change transcriptional outputs as results of learned behaviors, but large-size genes need a lot of time to be transcribed. The speed of RNA polymerase II (RNA Pol II)-mediated transcription in animal cells can range from 0.6 kb/min to 4.3 kb/min[8] (although the highest speed reported is up to 80 kb/min). RNA Pol II speed is also highly regulated: a fourfold variation in transcription velocity has been measured between identical copies of the same gene. Still, most data point to ~1 kb/min as the average rate of RNA synthesis in vertebrates and *Drosophila*[8].

The largest human gene reported in the McCoy and Fire study[5], *RBFOX1*, has ~2.5 million bases (equivalent to a whole bacterial genome). *RBFOX1* regulates tissue-specific alternative splicing and is involved in multiple psychiatric disorders[9] and neurodevelopmental phenotypes across vertebrates[10]. It might take about one day to transcribe the entire length of *RBFOX1*! Consequently, other large genes with enriched expression in neural tissues and ranging in size from 1.5 to 2.2 million bases can be transcribed within 5–10 hours.

The largest genes in humans are not necessarily the same as those in *Octopus* or other metazoans, but the reported trends of recruiting oversized genes for neural and synaptic machinery are convincing[5]. The largest identified gene orthologs in *Octopus* encode dopamine receptors (*DRD3*/*DRD2*) or are associated with cilia, flagella and signal transduction (*CCDC39*, *CFAP65*, *FUZ*, and *BAIAP3*) and range from 1.3 to 1.5 million bases. It would likely take hours, if not days, to transcribe them (direct experimentally measured data on transcriptional kinetics are much desired for most invertebrates).

In contrast, intron splicing is unexpectedly rapid, occurring within 5–10 minutes[11] or even faster (less than 30 seconds[12]), irrespective of intron length. Finally, ribosomes translate mRNAs at a time scale of 3–6 amino acids/second[13,14], with cell-, tissue-, and age-specific elongation rates. Dystrophin (3,685 amino acids (aa)), neurexin (1,468 aa), and ionotropic glutamate receptors (900–1,000 aa), encoded by some of the largest-sized human synaptic genes, could be translated within just 3–10 mins.

Transcription–translation coupling in learning and memory

McCoy and Fire's findings[5] and the above-mentioned kinetics of transcription and translation raise two questions. First, how is the transcription–translation coupling of large-sized synaptic genes coordinated in a highly polarized neuron as it learns and encodes memories? Second, by recruiting the largest genes, what constraints (or benefits) exist for neuronal transcription–translation and overall adaptability in evolution?

Most neurons in vertebrates and cephalopods are post-mitotic, terminally differentiated cells. Hence, these cells have 'sufficient time' to transcribe the largest genes and maintain their respective proteins. Indeed, many of these genes encode adhesion molecules with potentially extended lifetimes, dynamically contributing to long-term memory storage as structural modulators of the synaptic, neuronal, and glial microenvironments. However, environmentally induced neuroplasticity requires rapid expression of genes encoding scaffolding synaptic proteins and receptors — the inherent components of learning and memory[15]. In other words, there might not be enough time to transcribe these genes on demand.

The potential solution is that these larger genes can be transcribed in advance but kept 'dormant' (for example, by RNA-binding proteins) and then transported to distant synaptic sites to support localized protein synthesis following appropriate stimulation. This paradigm is known as the dialog between genes and synapses[15]; however, the underlying mechanisms are still elusive. In sum, speed is the key constraint for transcription from bacteria to neurons[8], with neurons being more sensitive to kinetic perturbations, especially during learning and memory, which enforce perfect timing of synaptic inputs for transcription–translation coupling within a network and a 'window of opportunity' for efficient adaptive responses.

The intron delay hypothesis and comparative data[5] provide a mechanistic framework for how intron size might contribute to the orchestration of gene expression patterns in development. Genes with long introns are preferentially affected by a slow RNA Pol II in differentiated neurons[16] and disruption of dynamic coupling of cell-type-specific genes, and might lead to genotoxicity and neuropathologies[17]. Slowing the RNA Pol II velocity might increase longevity[18] and ameliorate age-related memory loss, possibly due to better coordination of the expression of multiple genes and a reduction in genotoxicity. The evolutionary implications of gene-size-dependent kinetics are far-reaching.

Larger genes for complex brains

McCoy and Fire draw two key conclusions that inspire future directions for exploration: "Most young genes are small, while virtually all larger genes are ancient" and the largest genes have "the most potential to gain novel functions and expression patterns"[5].

Why did genes become larger, especially in cephalopods and vertebrate lineages? Possible hypotheses[5] include the rise of regulatory capabilities, tolerance, and accumulations of beneficial mutations by expanding both sequence and adaptive space for the accelerated evolution of neuronal, locomotory, and circulatory systems, all of which led to convergent innovations in two animal groups competing in the same ancestral marine ecosystems. Achieving better homeostasis for brains and other organs in cephalopods and vertebrates may support their larger gene and genome sizes, enabling more flexible and dynamic 3D genome architectures and therefore more interactions at the scale of the genome, neurons, and eventually the entire brain. Notably, larger genes often encode adhesion molecules, biopolymers, or multi-domain, multi-functional proteins that form and maintain molecular scaffolds and interactions at all levels of the biological organization. In other words, chemical and multicellular connectomes within the complex brain must be supported by enigmatic intra-genomic connectomes, facilitating the genome operation in 3D space and time (4D genomics).

Exaptations for multicellularity

Molecular adhesion is the universally crucial trait enabling cell–cell interactions and multicellularity at the dawn of metazoan evolution. The Precambrian establishment of the dynamic functional adhesome, in terms of the larger genomes and more oversized gene products in ancient holozoans, served as the exaptation[19] (or pre-adaptation) that paved the way to the rapid radiation of early animals during the Cambrian explosion.

Early multicellular organisms co-opted larger genes for integrative functions, enabling novel molecular connections in the forms of multimeric receptors, scaffolds, and adhesion molecules that physically brought together primordial neural-like secretory cells, eventually forming unique synapses. These events might have occurred independently in the early-branched groups of ctenophores, cnidarians, and bilaterians with different genes but similar kinetic constraints and exaptations provided by increased gene sizes. The largest adhesion and scaffolding proteins are ideally suited to form expanded adaptive space from which many synaptic functions were derived convergently, as in molluscs and chordates or ctenophores[2,3].

In conclusion, large, isoform-rich genes enabling exaptations and neo-functionalization are inherent evolutionary preconditions for establishing assemblies with new emerging properties that ultimately give rise to neurons connected by synapses. This generalized molecular adhesome continues to shape all levels of biological organization, starting with the rise of early ontogenesis and the injury/regenerative responses (as the prelude to long-term memory mechanisms) at the dawn of multicellularity in the common metazoan ancestor.

DECLARATION OF INTERESTS

The author declares no competing interests.

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Ant evolution: Amber revelations of extinction, survival and recovery

Brendon E. Boudinot
Senckenberg Gesellschaft für Naturforschung, Senckenberganlage 25, 6035 Frankfurt am Main, Germany
Correspondence: brendon.boudinot@senckenberg.de, boudinotb@gmail.com
https://doi.org/10.1016/j.cub.2024.03.008

Ant fossils from the Cretaceous are rare but critical for understanding the early evolution of this incredibly successful group of animals. New amber fossils fill important gaps, revealing patterns of death, survival, and radiation around the end Cretaceous extinction.

Earth is teeming with mammals and birds, but constantly underfoot are "the little things that run the world"[1] — the ants. While the evolutionary histories of vertebrate groups have been worked out in great detail, the evolution of ants is still largely shrouded in mystery. Despite their diversity (>14,000 living species), numerical preponderance (≥20 quadrillion individuals alive today), ecological importance and complex social organization, there have been to date only ~60 fossil ant species recovered from Cretaceous deposits[2–5], mostly in amber. The scarcity of fossil ants is due to the rarity of fossil-bearing amber inclusions, the limited popularity among fossil hunters and simply the small size of these otherwise globally widespread animals. Amber fossils of ant ancestors date back to ~99 million years ago and record a lost fauna of intermediate linages of wasp-like ants, the extinct 'stem ants', as well as 'crown ants', which are those species descended from the common ancestor of the living ants. It is likely that despite their morphological antiquity, the stem ants were eusocial, as winged and wingless females (most likely representing 'queens' and 'workers') have been found for several species, and there is preserved evidence of brood care, and therefore overlapping generations and possible reproductive altruism[6]. Because these stem ants are known almost exclusively from deposits that far predate the end-Cretaceous mass extinction, it is unknown whether the stem lineages died out partway through the Cretaceous, or whether they survived until the end of the era of dinosaurs. Two new studies in this issue of *Current Biology*, one by Christine Sosiak and colleagues[7] and one by Elyssa Loewen, Micheala Balkwill and colleagues[8], as well as a third study[9], shed new light on this problem and that of ant survival, radiation and ecological recovery.

Stem ants differ from crown ants in several features that suggest less refined social organization. Most of the stem groups have long and unwieldy antennae, without the characteristic 'elbowing' that allows for trail following and fine motor control around the mouth[5,10]. Their worker thoraxes were more complex, hinting at a lack of skeletomuscular reorganization for running on the ground, and they had less sophisticated pumping mechanisms in the head compared to modern ants, suggesting a less developed ability to feed on liquids[5,10,11]. Two of the primary lineages of stem ants were apparently ecological specialists, likely being top predators at this small scale[12]. These ants had highly modified heads and mouthparts for gripping prey — the so-called 'hell ants' and 'iron-maiden ants'[13,14]. Sosiak and colleagues[7] demonstrate that two of the main stem groups survived over 10 million years longer into the Late Cretaceous than had been previously recorded (Figure 1). This considerably strengthens the case that the end-Cretaceous event was the cause of stem-ant extinction, although a substantial fossil gap for this lineage of 10 million years before the Mesozoic doomsday remains. Sosiak and colleagues[7] also found that the body size of worker ants has been stable for ~100

