during development, and how those patterns are revised during sensorimotor learning in adulthood.

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Special Issue: Time in the Brain

Forum

Evolution of Locomotor Rhythms

Jeremy S. Dasen[1,*]

Nervous systems control locomotion using rhythmically active networks that orchestrate motor neuron firing patterns. Whether animals use common or distinct genetic programs to encode motor rhythmicity remains unclear. Cross-species comparisons have revealed remarkably conserved neural patterning systems but have also unveiled divergent circuit architectures that can generate similar locomotor behaviors.

In both simple and complex nervous systems, the speed and pattern of locomotion is regulated by oscillatory neural circuits that direct rhythmic contraction of muscle. Our understanding of the evolution of locomotor networks has benefited from comparisons of genetic pathways that specify neuronal classes in diverse species (a 'bottom-up' approach) [1], as well as through dissection of locomotor circuit designs in mature organisms (a 'top-down' approach) [2]. Recent studies provide insights into how motor rhythmicity is encoded at a molecular and circuit level and reveal clues about the origin of locomotor behaviors.

Conserved Developmental Patterning in Animal Nervous Systems

All motor behaviors rely on the generation of functionally diverse neuronal cell types; therefore, cross-species comparisons of developmental programs can shed light on the composition of the hypothesized 'urbilaterian' ancestor that gave rise to all bilaterally symmetric animals. While the cellular organization of the earliest nervous systems is still under debate [3], studies of neural patterning in invertebrates suggest that it was fairly complex and likely relied on the expression of homologs of genes essential for neural progenitor patterning in modern vertebrates (Figure 1A). An important unanswered question is how ancient gene networks were utilized to shape the architecture of circuits that control basic motor functions.

Because neuronal identity can be defined by which sets of genes are uniquely expressed within a given cell type, many studies have focused on conserved expression domains of transcriptional regulators. However, whether conserved transcription factor expression within a progenitor domain generates similar neuronal classes across species is less clear. The most thoroughly studied neuronal class essential for locomotion are motor neurons (MNs). Studies in flies, worms, and vertebrates have revealed sets of conserved transcription factors essential for specifying MN progenitors, as well as postmitotic fate determinants including Lim- and Mnx homeodomain proteins (Figure 1A). Furthermore, in many species the subsequent diversification of MNs into muscle-specific subtypes is mediated by the large family of Hox transcription factors [1].

Rhythm and Pattern Generation in Locomotor Circuits

While there is evidence for deep conservation of MN specification programs,

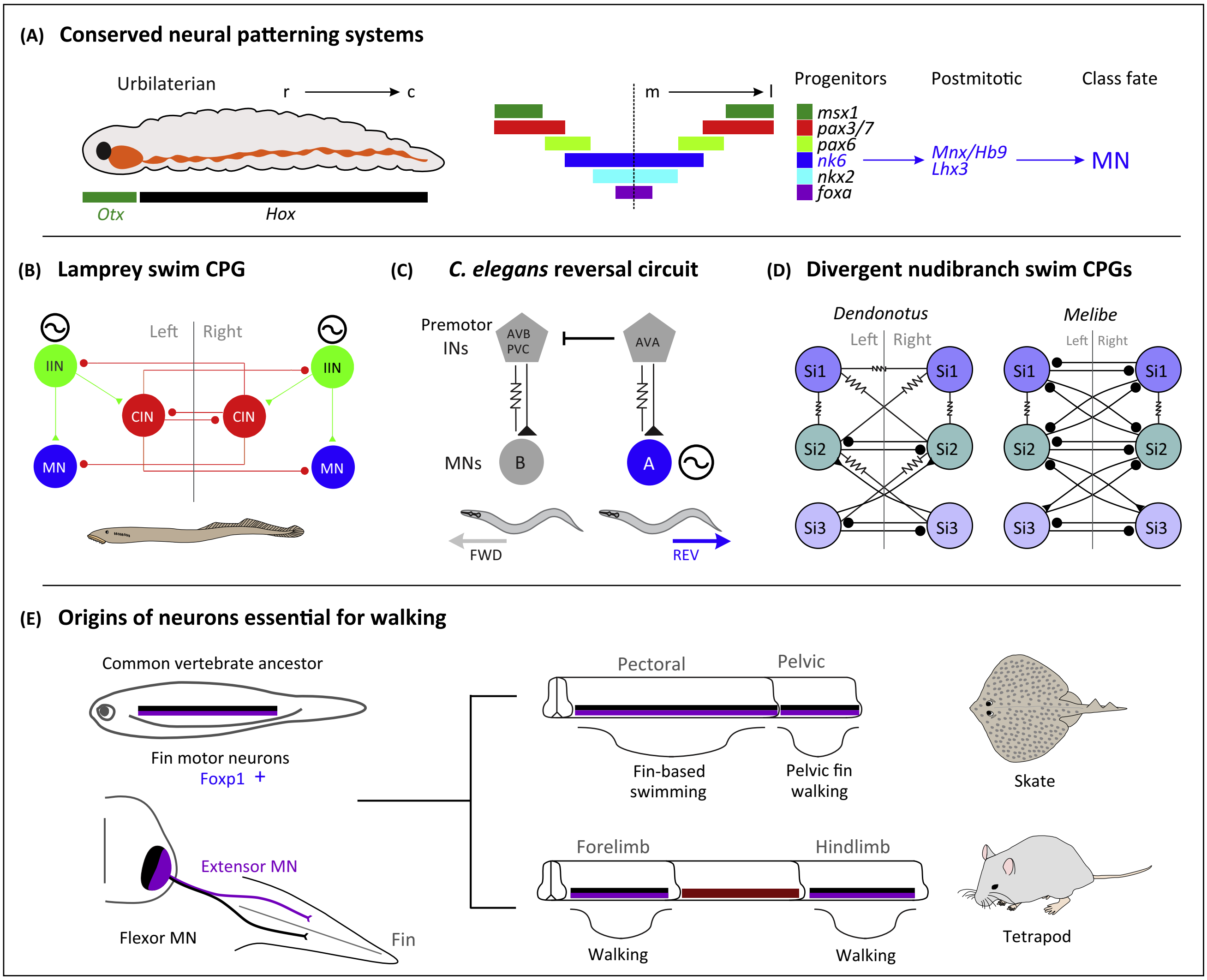

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Figure 1. Evolution and Development of Locomotor Circuits. (A) Conserved expression domains of transcription factors suggest a complex nervous system in the common ancestor to all bilaterians (urbilaterian). Left and middle panels: Simplified schematic of rostral (r) – caudal (c) and medial (m) – lateral (l) patterning, respectively. Mediolateral expression domains in invertebrates correspond to ventrodorsal domains in vertebrates. Right panel: The progenitor domain defined by Nk6 expression gives rise to motor neurons (MNs), which express Mnx/Hb9 and Lhx3. Schematic adapted from [3] with permission. (B) Locomotor central pattern generator (CPG) in lamprey. Each of the ~100 segments in lamprey contains rhythmically active excitatory ipsilateral interneurons (IINs) that activate MNs and inhibitory commissural interneurons (CINs). Triangles at the end of axons indicate excitatory synapses, circles indicate inhibitory ones. (C) In *Caenorhabditis elegans*, A-type MNs are intrinsically oscillatory and are sufficient to drive reverse (REV) locomotion in the absence of premotor input. B-type MNs, required for forward (FWD) locomotion, and premotor interneurons (AVB, PVC, AVA) are also shown. Circuit diagram based on data in [7]. (D) In nudibranchs, homologous swimming behaviors are controlled by similar neurons that have distinct connections within the CPG. Circuit diagram adapted from [8] with permission. (E) Evolution of neural substrates for walking. The common ancestor to skates and tetrapods likely contained MN subtypes essential for selective innervation of fin/limb muscle. These conserved features include expression of the limb MN determinant Foxp1, and the segregation of MN populations in limb flexor and extensor subtypes. These pathways are conserved in skate and tetrapods, although the circuit mechanisms differentiating fin-based swimming and walking are unknown.

whether this extends to other neuronal classes within motor circuits is largely unknown. The activities of MNs during locomotion are shaped by the types and distribution of inputs they receive from local and descending premotor neuronal populations. A well-studied premotor network required for locomotion is the central pattern generator (CPG), which directly controls MN firing patterns. CPGs consist of a rhythm-generating component, responsible for network oscillations, and have a specific output pattern that varies according to type of locomotion [4]. In swimming vertebrates, spinal locomotor CPGs govern the pattern of axial MN activation, while in walking animals, CPGs are predominantly directed to control of limb-innervating MNs.

Undulatory locomotion, driven by axial muscle, is pervasive amongst bilaterians. This locomotor strategy depends on alternating contractions of muscle across the left–right sides or along the dorsoventral axis of the animal, which travels as a sinusoidal wave along the body. In lamprey, the CPG coordinating left–right alternation during swimming involves two half-center oscillators containing rhythmically firing, ipsilaterally projecting, excitatory interneurons (Figure 1B). In addition to controlling MNs, rhythmic excitatory neurons activate inhibitory interneurons projecting across the midline and inhibit the contralateral half-center. Tetrapods also rely on similar mutual cross-inhibition for left–right limb alternation, but additionally require ipsilaterally projecting inhibitory interneurons to coordinate reciprocal activation of limb-flexor and extensor muscles [4].

In vertebrates, a major source of excitatory inputs onto MNs derives from glutamatergic spinal interneurons, characterized by expression of the transcription factor Chx10. In adult zebrafish, $Chx10^+$ interneurons (V2a) are essential for rhythm generation and also play important roles in controlling the timing of MN activation at different locomotor speeds. However, in mice in which V2a interneurons haven been genetically ablated, rhythm generation is largely preserved. By contrast, suppressing all excitatory glutamatergic transmission in the rodent spinal cord blocks rhythmicity in *ex vivo* spinal preparations [5]. It is therefore likely that several excitatory interneuron classes contribute to rhythm generation in mammals and that CPGs controlling limb-based locomotion comprise multiple oscillatory microcircuits.

What accounts for the rhythmic activity of excitatory interneurons? One possibility is that the rhythmic bursting of excitatory neurons emerges as a consequence of their connections with other neurons in the CPG. Alternatively, rhythm generation may be dependent on a few neuronal types, with intrinsic pacemaker-like properties [4,6]. While the neuronal source of CPG rhythmicity in vertebrates is unclear, recent studies in *Caenorhabditis elegans* show that MNs exhibit intrinsic oscillatory activities, which are independent from premotor interneurons [7]. Interestingly, the intrinsic rhythmic properties of MNs are sufficient to drive reverse locomotion in the absence of premotor inputs. Collectively, studies from multiple species suggest there is no single evolutionarily conserved neuronal population driving CPG oscillations.

Given that neuronal patterning and locomotor behaviors are often similar across species, it is plausible that CPGs governing similar locomotor output patterns have conserved compositions and architectures. While this appears to be the case among vertebrate species displaying similar locomotor behaviors, recent studies in invertebrates suggest that divergent neural mechanisms can encode the same locomotor behavior. For example, two related species of nudibranchs (sea-slugs) use left–right body undulation to produce similar swimming patterns. Although the neural composition of the locomotor CPG is comparable between these species, they have distinct patterns of connectivity (Figure 1D) [8]. Similarly, in the crab stomatogastric system, divergent circuit mechanisms can operate within the same species to generate similar motor rhythms [6]. These studies highlight the capacity of neural circuits to encode similar locomotor behaviors despite using distinct wiring strategies.

Ancestral Origins of Limb-Based Locomotion

While rhythmic contraction of axial muscles is a prevalent locomotor strategy used by animals, locomotion is driven by limb muscle in most terrestrial vertebrates. A common view is that during the transition from sea to land, there was a gradual shift from axial muscle-based locomotion to the limb-driven system employed by most tetrapods [1]. However, in certain fish species, such as skates and rays, swimming is driven by contraction of the pectoral fins, a pattern of motor output resembling wing movement in flying tetrapods. Skates also use their pelvic fins to generate walking-like locomotor gaits on the seafloor. Since skates and tetrapods shared a common ancestor over 400 million years ago, it is possible that the spinal circuits encoding fin/limb-based locomotion originated in early marine vertebrates.

A recent analysis indicates that many of the developmental programs essential for limb-based locomotion are deployed within the skate spinal cord [9]. These conserved neural fate specification programs include the generation of specialized MN subtypes controlling fin/limb muscle, as well as spinal interneuron classes known to be essential components of tetrapod CPGs (Figure 1D). While the organization and functional properties of locomotor CPGs circuits in skates are yet to be determined, skates appear to contain the necessary cellular components to generate tetrapod-like locomotor gaits.

If the neuronal classes essential for both axial and limb-based locomotion are present in most vertebrates, what determines the specific strategy that an animal employs? Given that differences in *Hox* gene expression account for much of the segmental specialization of spinal MNs [1], it is possible that premotor CPG interneurons are governed by similar level-restricted specification programs.

Alternatively, MNs themselves may play an instructive role in determining the pattern of locomotor output. Consistent with this idea, mutation in the limb MN determinant *Foxp1* in mice leads to a loss of limb-specific output patterns, including the ability to reciprocally control extensor and flexor muscles [10]. Moreover, MNs of both vertebrates and invertebrates have been shown to retrogradely influence locomotor CPG output patterns [10,11].

MN subtype identity also appears to play an instructive role in shaping connections within spinal premotor networks. Conversion of hypaxial MNs to a limb MN fate in mice, through mutation in the *Hoxc9* gene, causes dramatic changes in the specificity of connections between MNs, spinal interneurons, and proprioceptive sensory neurons [12]. These changes in premotor input pattern appear to be a consequence in the altered position and dendritic architecture of the transformed MN populations. Although it is currently unknown whether these premotor connectivity alterations affect CPG function, their presence demonstrates that MNs play a critical role in shaping the connectivity and output patterns of locomotor circuits.

Comparative studies have revealed both highly conserved and divergent mechanisms contributing to the development and functional properties of locomotor rhythms. Whether early nervous systems contained circuit elements that are still used in modern species for locomotor control remains to be determined. Recent methods for sequencing large numbers of neuronal types, in conjunction with comparisons across multiple species, should allow us to infer what common circuit elements contribute to the establishment of locomotor behaviors. The prevalence of locomotor CPGs in animals, as well as shared early patterning and MN specification programs among bilaterians, suggest that additional conserved features of motor networks await to be discovered.

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Special Issue: Time in the Brain

Forum

Language and the Construction of Time through Space

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Speakers of different languages think about time differently in accordance with the spatial metaphors common in their languages. Furthermore, learning new spatial metaphors in language instills new non-linguistic representations of time, suggesting that language can play a causal role in constructing mental timelines.

What is the role of language in constructing our representations of time? Time is a central topic of conversation in many languages. In English, the word ‘time’ is the most frequent noun, with other temporal words such as ‘day’ and ‘year’ also ranking in the top ten [1]. Do the ways we talk about time help construct the ways we think about it?

In English, talk about time strongly overlaps with talk about space, with many of the same words and constructions used to talk about both domains [2]. Just as we might say that a saucer flew by, we can say that a day flew by. We can push forward a wheelbarrow or a meeting, believe that a wall or a semester is behind us, or worry that a moose or a birthday is approaching. Prior work has demonstrated that people do not just talk about time using spatial words; they also appear to use specific spatial representations when thinking about time.

For example, English metaphors commonly place events on a horizontal mental timeline with the future in front (e.g., ‘looking forward to the year ahead of us’) and the past behind (e.g., ‘the worst is behind us’). Correspondingly, English speakers show evidence of horizontal front-back mental timelines. For example, they are faster to move their arm forward to indicate that an event is in the future and pull their arm back to indicate the past than for the reverse mapping [3]. They are also