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Dispatches

Neuronal Wiring: Linking Dendrite Placement to Synapse Formation

Understanding the processes that drive the formation of synapses between specific neurons within a circuit is critical to understanding how neural networks develop. A new study of synapse formation between motor neurons and pre-synaptic partners highlights the importance of dendrite placement.

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Proper wiring of neurons within circuits early in development is essential for subsequent behavior. Neuronal circuits are remarkably dynamic, but the proper pattern of connectivity between pairs of genetically-identified cells is critical to ensure flexibility and reliability of the network function. Previous studies investigating sensory systems found highly stereotyped connections between pairs of neurons [1–3]. Unlike sensory systems, motor systems need to develop rapidly to ensure survival. Avoiding predation and ensuring food intake require functional neuronal circuits even at early stages of development. Synapse formation might therefore depend on simple mechanisms that allow for reliability of connectivity patterns in the motor network.

A new study by Couton *et al.* [4], reported in this issue of *Current Biology*, describes how initial contacts between axons of premotor interneurons and dendrites of motor neurons are formed based on spatial location of the dendritic processes. By genetically manipulating dendrite position of individually identified motor neurons in the *Drosophila* larvae, these authors show that neurons make connections with different axons when their dendritic arbors are geographically displaced (Figure 1). These results corroborate previous observations on the importance of overlap between the axonal projections and dendritic arbors for synapse formation in the motor network [5]. The new study also indicates how individually identified motor neurons may utilize diverse wiring strategies to connect with their presynaptic targets by controlling the placement of their dendritic arbor.

The importance of dendrite positioning for synapse formation has been suggested from observations made in diverse systems and species. In the *Xenopus* spinal cord, a pioneering study [5] with hundreds of paired recordings showed that contact probability could be predicted by the anatomical overlap of axons and dendrites. This suggests that synapse formation may not require axons to recognize specific dendrites. *In vivo* time lapse imaging of interneurons in zebrafish optic tectum showed that all synapses formed nascently on newly extended dendritic filopodia [6]. A fraction of these synapses were maintained, which in turn stabilized the filopodia to constitute a mature dendritic branch of the final arbor. Recently Kishore and Fetcho [7] observed in the spinal cord of zebrafish larva that dendrite dynamics have a topographic pattern within a pool of motor neurons that map onto their orderly patterns of recruitment during behavior. This indicates that dendrites have homeostatic properties that could adjust growth in part to increase or decrease the synaptic input to neurons to achieve a particular level of activity.

Elegant studies in *Drosophila* laid the groundwork for studying the

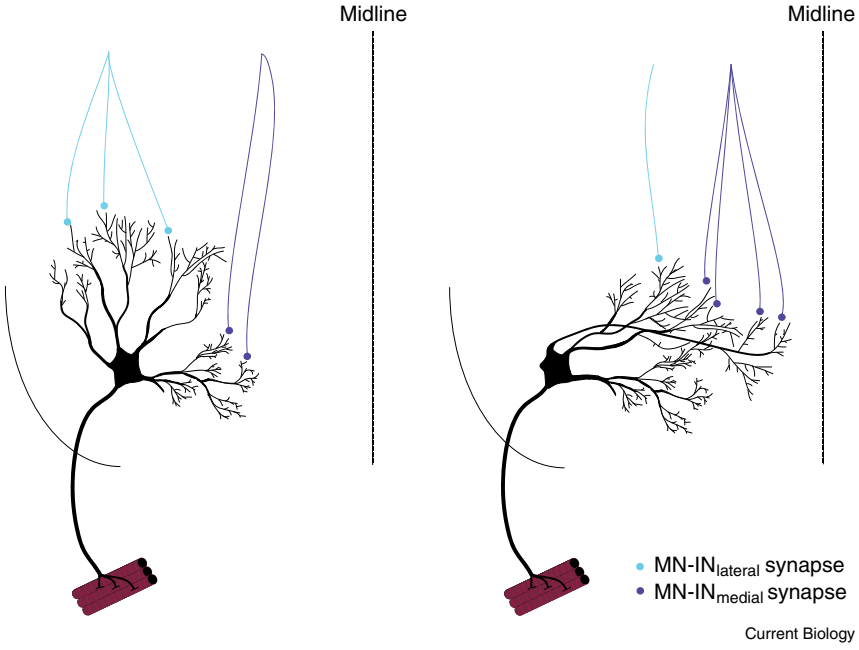

Figure 1. The number of synaptic connections received from premotor interneurons is conditioned by positioning of motor neuron dendrites.

(Left) In control conditions, a given motor neuron receives balanced synapses from both medial and lateral premotor interneurons. (Right) When dendrites are shifted medially due to an increased sensitivity to midline attractant Netrin, connections are preferentially formed with medial rather than lateral pre-synaptic inputs. This manipulation confirms previous observations from Li *et al.* [5] indicating that the degree of spatial overlap between the axonal projection and the dendritic arborization is critical to determine synaptic coupling between a pair of neurons in motor systems.

formation of motor units consisting of motor neurons and their muscle targets. The dendritic arborization patterns of larval motor neurons are largely stereotyped and thus provide a valuable model for the systematic analysis of how motor dendrites are established and patterned in the central nervous system [8]. Previous work of Landgraf *et al.* [9] showed that location of motor neuron dendritic arbors, and not soma position, indicated which muscle would be innervated. In the group's new study [4], the authors found that not only does dendritic arbor positioning correlate to which muscle will be targeted, but it also determines which pre-synaptic inputs will form synapses onto the motor neuron. The data together suggest that dendritic location could be a determining component in establishing a functional unit consisting of premotor interneurons, a motor neuron, and its muscle targets.

Couton *et al.* [4] utilized intersectional genetics to target expression of synaptic markers to specific types of premotor interneuron and well-characterized motor neurons in the motor circuits of *Drosophila* larvae. Many tools developed in recent years allow direct visualization of synaptic contacts and genetic targeting to identify individual cell types. This approach is amenable in *Drosophila*, in which the relatively simple nervous system enables the recognition of individually-identified neurons. The 'GFP reconstitution across synaptic partners' (GRASP) technique was developed in work on the nematode *Caenorhabditis elegans* and adapted to *Drosophila* to monitor membrane apposition reflecting connections [10–12]. By expressing in different cells complementary fragments of GFP, tethered to extracellular domains of transmembrane carrier proteins, GFP fluorescence appears only when complementary fragments are fused to ubiquitous transmembrane domains, thus restricting GFP expression uniformly along membrane contacts between two cells. To isolate synaptic connections from non-synaptic membrane apposition, immunohistochemistry for Brunchpilot, a presynaptic marker [13], was coupled with GRASP to identify putative synapses.

Taking advantage of the small size of the *Drosophila* larva, Couton *et al.* [4] were able to quantify the total number of synapses between defined premotor interneurons and motor neurons from 0 to 48 hours after hatching. The number of synapses varied dramatically between the same premotor interneuron–motor neuron pairs even within one individual. These results highlight the flexibility of wiring of premotor inputs onto motor neuron dendrites. In order to determine the role of the location of dendritic arbors in synapse formation, the authors over-expressed the guidance cue receptor Frazzled to shift dendritic branches medially in response to increased sensitivity to midline attractant, Netrin. As they were able to identify interneurons, comparisons of distributions of synapses could be made between individuals and at different stages of development. In these conditions, connections received from the lateral interneuron decreased whereas those from the medial interneuron increased (Figure 1). Placement of dendritic arbors thus dictates the number of synapses received by different pre-motor interneurons.

A major question that remains to be answered is whether there are functional consequences associated with the diversity in wiring between motor neurons and their pre-motor inputs. Though there are clearly changes in number of synapses when the dendritic arbor is geographically displaced, whether this corresponds to a change in synaptic drive is unknown. Homeostatic mechanisms could override alterations in synapse number by changing individual synaptic strength or proximal versus distal location of synapses along the dendritic arbor.

The new work of Couton *et al.* [4] is an important step in understanding the development of the motor system. By quantifying the number of synapses and manipulating the location of the dendritic arbor, this study established dendrite position as a critical factor for associating premotor interneurons, the motor neuron, and muscle targets into a functional unit. Further work will be necessary to understand the functional consequences of varied wiring on the recruitment of motor neurons during locomotion. Connecting these diverse wiring strategies to the physiology of motor neuron recruitment will be a key element in understanding how neural networks produce diverse locomotor outputs.

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