The mechanical control of CNS cell development and function

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During the development of the nervous system, neurons migrate and grow over great distances. Similarly, during many pathological processes, neurons and glial cells need to migrate and regenerate. During these processes, CNS cells are exposed to a multitude of signals determining how they grow. Currently, our understanding of biological systems is, in large part, based on studies of biochemical signaling. Despite the fact that forces are involved in any kind of cell motion, mechanical aspects have so far rarely been considered. Here we used compliant cell culture substrates and traction force microscopy in combination with cell biological approaches to investigate how glial cells and neurons respond to their mechanical environment. Axonal growth velocities, directionality, fasciculation, i.e., their tendency to grow in bundles, and maturation, as well as glial cell morphology and activation all significantly depended on substrate stiffness. Moreover, when grown on substrates incorporating linear stiffness gradients, glial cells migrated towards stiff substrates, while axon bundles were repelled by them. In vivo atomic force microscopy measurements revealed stiffness gradients in developing brain tissue, which axons followed as well towards soft. Interfering with brain stiffness and mechanosensitive ion channels in vivo both led to similar aberrant neuronal growth patterns with reduced fasciculation and pathfinding errors, strongly suggesting that neuronal growth is not only controlled by chemical signals – as it is currently assumed – but also by the tissue’s local mechanical properties.