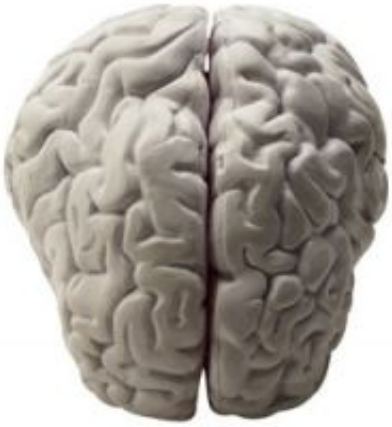
Trial and error: The brain learns from mistakes

February 8 2011



In the developing brain, countless nerve connections are made which turn out to be inappropriate and as a result must eventually be removed. The process of establishing a neuronal network does not always prove precise or error free. Dr. Peter Scheiffele's research group at the Biozentrum of the University of Basel have been able to document this phenomenon using advanced microscopy techniques in the developing cerebellum, a brain area required for fine movement control.

Dr. Scheiffele's group has discovered that a protein traditionally associated with bone development is responsible for correcting errors while neurons connect to their correct partners in the cerebellum. Their

results will be published next week in the online, open access journal PLoS Biology.

The brain is a highly complex set of neuronal networks, in which thousands of different neuron types establish neuronal connections, called synapses, with other neurons. To establish these synapses, neurons send out axons from their cell bodies, which are fiber like extensions that extend into the various regions of the brain. Each neuron must connect with particular partner neurons during brain development, and it is this precise specificity which allows different circuits and different brain regions to serve different functions.

The cerebellum, for example, has very precise connectivity that allows the brain to use sensory information (input) and convert it into an exact motor response (output). There are a number of cell types in the cerebellum, two of which are Purkinje cells and granule cells. Mossy fibers are a group of inputs in the cerebellum, which make synaptic connections only with granule cells.

In their study, however, Dr. Scheiffele's group have now been able to demonstrate that these mossy fiber inputs often connect with Purkinje neurons during early brain development, in addition to granule cells. These incorrect Purkinje connections are then subsequently eliminated within a week, establishing proper specificity in the cerebellum. They also find that Bone morphogenetic protein 4 (BMP4) helps correct these initial errors. Originally, BMP4 was linked with the specialization of cells during osteogenesis. That this protein is also responsible for the stability and removal of neuronal connections was not previously known.

"If inappropriate connections between neurons are not subsequently eliminated, this can lead to substantial disturbances in the brain. Autism could also be linked to this form of failure to correct errors," explains Scheiffele. The research group at the Biozentrum used a genetic mouse

model to make their observations. With the help of a fluorescent protein, the different nerve connections could be stained and made visible by an advanced imaging technique that combines light microscopy with electron microscopy. This allowed multiple types of changes in connectivity to be traced. "These processes can be applied to the development of the human brain and could play an important role in further brain research," added Scheiffele.

The brain undergoes drastic changes during its early life. While the neuronal connections in the brain of a newborn are still relatively unspecific, the selectivity of the synapses steadily increases. The question of what advantage these short-lived, inappropriate connections serve during brain development will become a major focus of Dr. Scheiffele's future research, in addition to their potential implications for neurological disorders such as autism, schizophrenia, and epilepsy.

More information: Kalinovsky A, Boukhtouche F, Blazeski R, Bornmann C, Suzuki N, et al. (2011) Development of Axon-Target Specificity of Ponto-Cerebellar Afferents. PLoS Biol 9(2): e1001013. doi:10.1371/journal.pbio.1001013

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