

# 'Timing is everything' in ensuring healthy brain development

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Work published today shows that brain cells need to create links early on in their existence, when they are physically close together, to ensure successful connections across the brain throughout life.

In people, these long-distance connections enable the left and right side of the [brain](#) to communicate and integrate different kinds of information such as sound and vision. A change in the number of these connections has been found in many developmental brain disorders including autism, epilepsy and [schizophrenia](#).

The Newcastle University researchers Dr Marcus Kaiser and Mrs Sreedevi Varier carried out a sophisticated computer analysis relating birth-time associated data to connectivity patterns of [nerve cells](#) in the roundworm, [Caenorhabditis elegans](#). They demonstrated that when two nerve cells develop close together, they form a connection which then stretches out when the two nerve cells move apart as the organism grows. This creates a link across the brain known as a long-distance connection.

Publishing today in *PLoS Computational Biology*, the researchers have demonstrated for the first time that this is the most frequent successful mechanism by which long distance connections are made.

Dr Marcus Kaiser, at Newcastle University, says: "You can draw parallels with childhood friendships carrying on into adulthood. For example, two children living close to each other could become friends through common activities like school or playing at the park. The

friendship can last even if one of them moves further away, while, beginning a lasting friendship with someone already far away, is much more difficult."

Mrs Sreedevi Varier adds: "Although it's too early for this research to have direct clinical applications, it adds to our understanding of the structural changes in the brain and raises some interesting questions as to how these connections can become faulty. In further studying this mechanism, we may eventually contribute towards insights into the diagnosis and possibly the treatment of patients with epilepsy and autism."

It has long been understood that the first connections in the brain created in the early days of development can be formed over long distances using guidance signals to direct nerve fibres to their correct positions – known as axonal guidance. Subsequently, other connections can follow those pioneer fibres to a target location creating connections between distant parts of the brain. Through these long-distance connections different kinds of information, such as sound and vision, can be integrated.

This EPSRC-funded research showed that most neurons are able to create a connection early on in their development when they were physically close together, potentially giving them more time to host and establish connections. These developed into a long-distance connection, the two cells pulling apart as the organism grows larger.

Studying the connections in the neuronal network of the roundworm *Caenorhabditis elegans* the Newcastle scientists - who are also affiliated with Seoul National University, Korea - found that most neurons with a long-distance connection had developed in this way.

This new mechanism differs from the previous model for long-distance

connectivity. An axon is a fibre that is extended from one nerve cell and, after travelling through the tissue, can contact several other nerve cells. Normally, axons would grow in a straight line. For several targets, however, the axon has to travel around obstacles, as a straight connection is not possible. In such cases, cells along the way can release guidance cues that either attract or repulse the travelling axon. One example of bended fibres is the visual pathway that at several points takes a sharp 90-degree turn to arrive at the correct target position.

Instead, establishing potential links early on when neurons are spatially nearby might reduce the need for such guidance cues. This reduces costs in producing guidance cues but potentially also for genetically encoding a wider range of cues. An early mechanism opens up the possibility that changes in long-distance brain connectivity, that are observed in children and young adults with brain disorders, arise earlier during [brain development](#) than previously thought. These are questions that the team continue to work on through data analysis and computer simulations of brain development.

**More information:** Neural development features: Spatio-temporal development of the *Caenorhabditis elegans* neuronal network, Sreedevi Varier and Marcus Kaiser Published in: *PLoS Computational Biology*

Provided by Newcastle University

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