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Interneuron migration impairement could lead to macrocephaly

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A team from the University of Liège (Belgium) has discovered crosstalk between the migrating inhibitory interneurons and the stem cells that generate the excitatory neurons. The researchers discovered that this cellular dialogue controls the growth of the cerebral cortex and that its impairment leads a cortical malformation previously associated with autism in mice. Their results are published in the prestigious scientific journal *Cell*.

The cerebral cortex contains excitatory and inhibitory interneurons. The former are produced locally and move by radial sliding to reach their final position within the cortex. Interneurons are born in distant regions from the cerebral cortex and migrate along tangential corridors by saltatory displacement or "jumps." Researchers led by Dr. Laurent NGUYEN have identified the physiological role of the saltatory migration of interneurons. By modulating the cytoskleton of interneurons, the researchers were able to enhance their rate of cortical invasion, which in turn increased the rate of production of projection neurons by their progenitors. They also suggest that such modification could lead to macrocephaly and to the development of symptomes characteristic of psychiatric disorders such as autism.

"More precisely, the conversion of the interneuron migration mode is made possible by eliminating the activity of an enzyme called carboxypeptidase 1 (CCP1). The genetic invalidation of CCP1 reduced the saltatory displacement of neurons, convering their movement into a gliding mode of migration without altering their average migration

speed," says Carla SILVA, a researcher in Dr. Laurent NGUYEN's team.

This work demonstrates the physiological function of the saltatory migration: This mode of migration is characterized by unsynchronized pausing periods within the population of migrating interneurons. This heterogeneity of movement regulates the flow of interneurons reaching the developing cerebral cortex, limiting the number of cells that enter into dialogue with the stem cells that generate the excitatory neurons. This control regulates the production of excitatory neurons. When pauses are eliminated, more interneurons migrate at the same time and the cortex is temporarily colonized by supernumerary interneurons. This results in a massive influx of information that stimulates stem cells to generate excessive numbers of excitatory neurons.

"This discovery was made possible by combining biological analysis with bioinformatics modelling of cellular movements at the population scale. To use a daily life analogy, one can make a parallelism with the zipper principle to control traffic flow. In fact, the road zipper makes road traffic more fluid by avoiding car breaks," explains Laurent NGUYEN.

Provided by University de Liege