The most important hair on your head is on the inside

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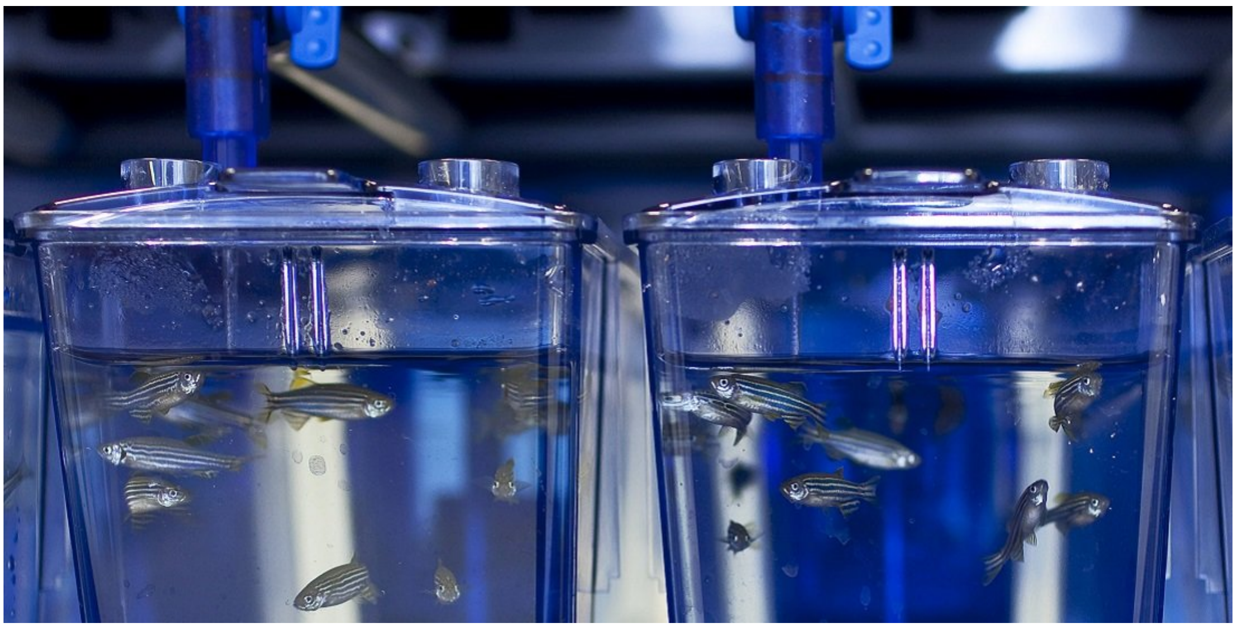

Researchers in the Yaksi group at the Norwegian University of Science and Technology's Kavli Institute for Systems Neuroscience are able to peer directly into zebrafish brains to study brain anatomy and function. Credit: Kavli Institute for Systems Neuroscience, Yaksi Group

Cells along the brain's cavities are equipped with tiny hair-like protrusions called cilia. Cilia are still poorly understood, but we know a few things about what can happen if they are not doing their job.

People with ciliary defects can develop neurological conditions like hydrocephalus and scoliosis. New research from the Yaksi group at Kavli Institute for Systems Neuroscience at the Norwegian University of Science and Technology (NTNU) shows that cilia are essential for the brain to develop normally.

An article now published in *Current Biology* reports insight into how cilia work and why they are so important for brain development. The human brain has four fluid-filled cavities called ventricles, all of which are interconnected. The ventricles are filled with cerebrospinal fluid, which is also produced here. The cerebrospinal fluid is in constant motion, but the movement varies depending on activity.

"Several theories exist, but for many years this circulation of fluid has been recognized as supplying nutrients to the brain, while also removing waste products," says senior researcher Nathalie Jurisch-Yaksi at NTNU's Kavli Institute.

"The cerebrospinal fluid flow also contributes to transmitting molecular signals across the brain," says Emre Yaksi, a professor at the Kavli Institute.

It would not be possible to conduct this kind of research on humans for ethical and practical reasons. Hence, the research group has chosen to do their research on zebrafish larvae, which are ideal for this type of research. They are vertebrates just like humans, and exhibit often analogous processes to human brain development and function.

On a practical note, zebrafish are transparent during their larval stage. This means that it is possible to investigate brain development and function in astonishing detail without any intervention, and without causing them any pain. "We could even investigate each individual cell and cilia," says Ph.D. candidate and co-author Christa Ringers.

The Yaksi group researchers found that groups of cells with cilia are organized in different zones of the ventricles, which together create a stable, directional flow of the fluid. Heartbeat pulsations and body movements also affect the circulation of cerebrospinal fluid, but the movements of the cilia appear to provide a stable fluid flow within individual ventricles.

This flow is local, so it is largely limited to each of the ventricles. But at the same time, it seems that the compartmentalized flow is necessary to keep the ducts between the cavities open. "If we stop the cilia's motion, the ducts close," says Jurisch-Yaksi.

The fluid flow in each ventricle and the exchange of fluid between the different ventricles depend on whether the subject is at rest or moving. "We found surprisingly little exchange of fluid between the ventricles as long as the fish were at rest, even though the heartbeat pulsations caused some flow between them," says Ph.D. candidate Emilie Willoch Olstad, the first author of the article in *Current Biology*. But all this changes during movement. Locomotion leads to a great degree of fluid exchange between the ventricles.

Cilia fall into one of two main groups, motile or non-motile, also called primary cilia. The Yaksi groups examined motile cilia. Unlike most other cilia in the human body that contribute to the transfer of fluids, such as the brush-like respiratory cilia that protect the lungs, the Kavli researchers found that the cilia along the brain ventricles of the developing zebrafish brain have a propeller-like motion, much like the tail of sperm.

The cilia may also indirectly contribute to keeping the brain young and healthy. New nerve cells are born near the wall of the fluid-filled brain ventricles. From here, they migrate throughout the brain. The differentiation of these newborn cells is believed to be influenced by nutrients and molecular signals that are distributed by the flow of the cerebrospinal fluid near the ventricular walls.

In zebrafish, the birth of new neurons, also called neurogenesis, happens not only in the developing brain, but also in adult fish. Recent studies have revealed that this kind of adult neurogenesis also happens in humans.

Studying the dynamic movements of fluids is extremely complicated and requires a multidisciplinary approach. Mathematicians, engineers and physicists are among those who can help understand how cilia movement occurs and generates flow. The Yaksi group at the Kavli Institute is eager to collaborate with engineers who could develop better analytical tools and computer models to study fluid circulation in the brain. They are actively looking for people and collaborators with the right skills.

The research is far from over. The next step is to see if it is possible to influence the brain function of the zebrafish by manipulating the cilia and vice versa. For example, how would the neural activity, or even circadian rhythms, change when cilia mediated flow is perturbed? The zebrafish are usually far more active during the day than at night. Would altering the cerebrospinal fluid flow change the way fish perceive and respond to their environment during different times of the day? These are the next questions the researchers plan to address.

More information: Emilie W. Olstad et al. Ciliary Beating Compartmentalizes Cerebrospinal Fluid Flow in the Brain and Regulates Ventricular Development, *Current Biology* (2019). DOI: 10.1016/j.cub.2018.11.059

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