Scientists find zebrafish brains hardwired for automatic action based on visual cues

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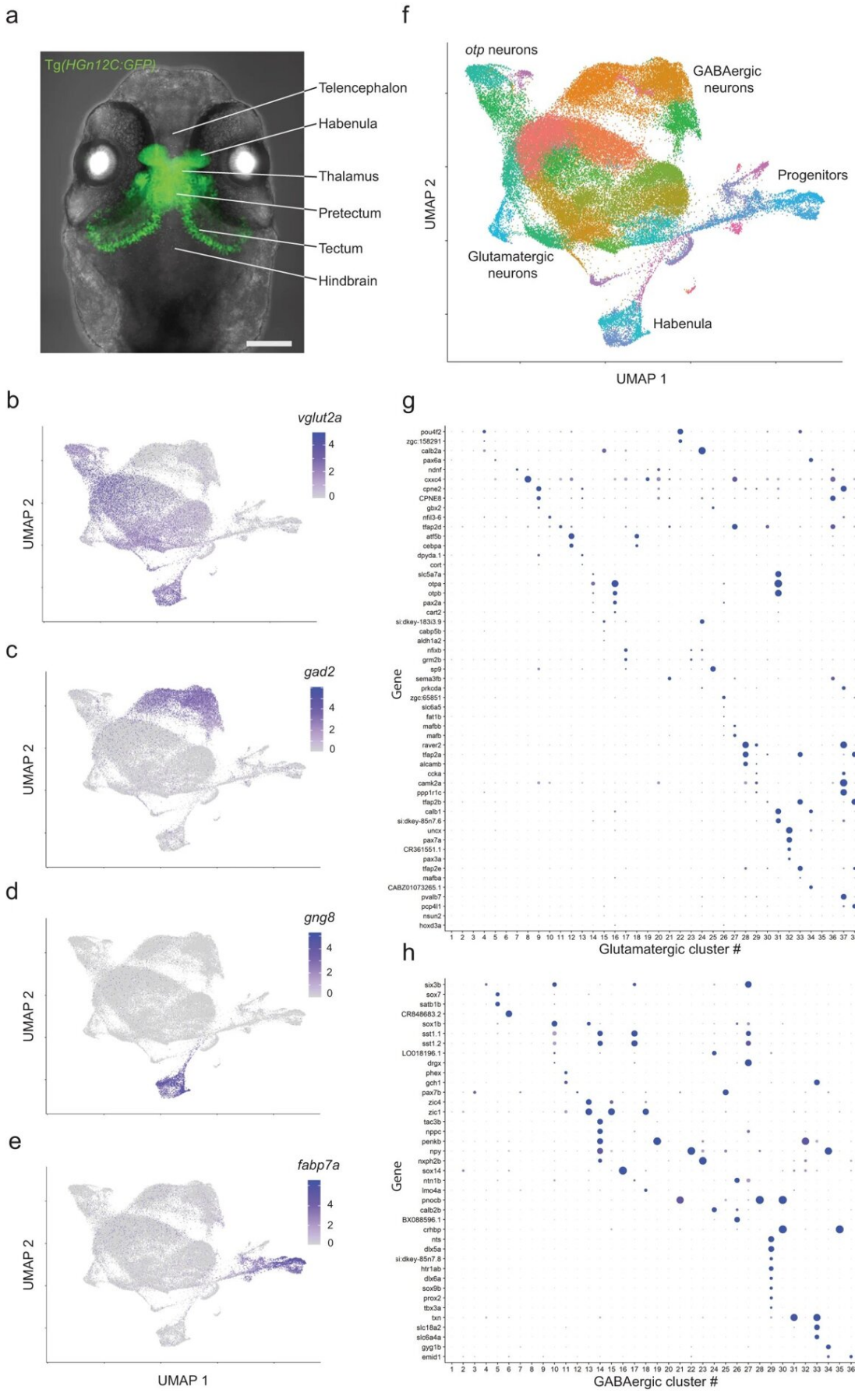
a
Tg(HGn12C:GFP)
Telencephalon
Habenula
Thalamus
Pretectum
Tectum
Hindbrain
f
otp neurons
GABAergic neurons
Progenitors
Glutamatergic neurons
Habenula
UMAP 2
UMAP 1
b
vglut2a
c
gad2
d
gng8
e
fabp7a
g
Gene
Glutamatergic cluster #
Average expression
Percent expressing
h
Gene
GABAergic cluster #
Average expression
Percent expressing

Transcriptional profiling reveals cell types across central visual areas. **a** Maximum z-projection of the *HGn12C:GFP* expression pattern in green. Transmitted light is in gray. Lines and labels annotate major anatomical brain areas of the larval brain (scale bar = 100 µm). **b–e** Gene expression plots of cells embedded in UMAP space (*vglut2a*, glutamatergic neurons; *gad2*, GABAergic neurons; *gng8*, habenula neurons; *fabp7a*, progenitors). (f) UMAP embedding of all sequenced cells. Color-coding represents different clusters. Text labels adjacent cell classes. UMAP space is the same as in (**b–e**). **g**, **h** Markers for glutamatergic (top) and GABAergic (bottom) clusters. Color shade represents the average level of marker expression in a cluster (average expression). Dot size represents the percentage of cells expressing the marker in a cluster (percent expressing). Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40749-1

Animals possess specialized networks of neurons in the brain that receive signals about the outside world from the retina and respond by initiating appropriate behavior. Researchers at the Max Planck Institute for Biological Intelligence studied a genetic mutation in zebrafish that eliminates all connections between retina and brain throughout development.

The team found that in these "deep-blind" fish the brain circuits are fully functional, as direct brain stimulation with optogenetics can drive normal visual behavior. This shows that the assembly of the brain in zebrafish requires little, if any, visual experience.

Zebrafish, just like humans, rely heavily on vision: large parts of the brain are dedicated to processing visual information, and vision is crucial for the animal to find food and navigate its environment. Just like human

babies, young zebrafish also learn from experience: They prefer familiar food and memorize where they found it. Underlying this process is the formation of new connections between brain cells and the refinement of old ones.

"When we study brain development, we broadly distinguish between innate and experience-dependent processes," explains Herwig Baier, director at the Max Planck Institute for Biological Intelligence. "The assembly of neuronal circuits, for example in visual brain areas, is classically considered an experience-dependent process: the neuronal networks are thought to be shaped by visual inputs and neuronal activity." But what happens if the visual information is never there in the first place?

To address this question, researchers have investigated how animals like fish or mice develop when they grow up in the dark. In this case, the brain is deprived of visual experience—but the eyes still send many signals to the brain. The retina normally converts patterns of photons that hit the back of the eye to patterns of electrical impulses, which are then transmitted to the brain by specialized cells with long axons called retinal ganglion cells.

Retinal ganglion cells are the gatekeepers for the visual input that reaches the brain. Their activity pattern contains all the information that animals have about the visual surroundings. But this is not the only way in which the eye can talk to the brain.

During development, the retinal ganglion cells also generate their own neuronal activity. Sometimes, waves of electrical activity sweep across the retina's entire surface, reach the central brain areas and fine-tune the synaptic connections. In addition, the axons of retinal ganglion cells secrete molecular factors that are received by cells in the central brain and induce developmental changes.

All these signals could potentially shape the circuitry of the brain. However, previous studies only looked at the effects of these factors in isolation and analyzed, for instance, how blindness affects brain development.

"To really understand how brain development depends on stimulation from the eyes, one needs to look at what happens when retinal ganglion cells are taken out of the equation," says Shachar Sherman, lead author of a new study that investigated just this. To do so, the former graduate student in Herwig Baier's department and his colleagues studied a zebrafish mutant known as lakritz.

These mutants have a genetic defect that prevents retinal ganglion cells from forming. Importantly, the defects are restricted to the eye. If it weren't for their dark color—"Lakritz" is the German word for licorice—one wouldn't be able to tell the difference between mutants and their wildtype siblings.

Herwig Baier explains, "The lakritz mutant is not just blind; it is deep-blind. Its brain is entirely disconnected from the visual world and any retina-derived signals. This unique situation opened up the possibility to study the influence of retinal ganglion cells on brain development and behavior in a systematic and comprehensive fashion."

The researchers raised young lakritz zebrafish and compared their brain development to zebrafish without the genetic defect. A virtual cell atlas of the zebrafish brain, developed in the department, helped to identify individual cells and to track their development. "To our surprise, we didn't see much of a difference," says Shachar Sherman. "In lakritz, all types of neuronal cells formed at the right place and numbers, only the speed of differentiation was slightly off."

Given that the brains of lakritz zebrafish developed relatively normally,

the researchers wanted to know if the fish are still able to perform behaviors usually triggered by vision. They looked at two such behaviors: orientation towards prey and so-called optokinetic eye movements, which are normally used to stabilize an image of the outside world.

"Since lakritz cannot see, they normally will never perform these behaviors, but the brain circuits might still be there waiting to act," says Shachar Sherman.

To test this, the team used optogenetics to directly activate the brain neurons that would normally become active when needed. Optogenetics is a technique that allows neuroscientists to introduce 'light switches' into the neurons of living brains. This way they can remotely control neuronal activity, provided they find ways to stimulate the neurons from the outside with light, a task made easy in zebrafish due to their small size and transparency.

"Strikingly, lakritz reacted to the artificial stimuli as if they had actually seen a prey object," recalls Shachar Sherman. "This shows us that the brain circuits required for these actions develop and function properly even when there is no input from the eyes at all."

Taken together, the latest research from the Baier department shows that brain development is hardwired to a greater extent than previously thought. "Shachar's work shows that a complex part of the vertebrate brain, with many dozens of cell types, can develop just fine without sensory inputs," says Herwig Baier. "This highlights the power of genetically programmed algorithms in building the brain. If this works in zebrafish, why not also in larger animals?"

Future studies will tell how strongly the development of sensory systems across the animal kingdom depends on input from the outside; the eyes and visual brain areas are just one example. The more we know about

these processes, the closer we will get to answering the philosophical question of "what's nature and what's nurture?"—or, in other words, how much of our brain wiring is innate and how much of it depends on our biography. For now, at least in the zebrafish visual system, nature appears to be the winner.

The findings are published in the journal *Nature Communications*.

More information: Shachar Sherman et al, Retina-derived signals control pace of neurogenesis in visual brain areas but not circuit assembly, *Nature Communications* (2023). DOI: 10.1038/s41467-023-40749-1

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