Gene therapy cures blindness by healing eyes and brain together

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Visual pathways in the brain are made up of millions of interconnected neurons. When sensory signals are sent along them, the connections between neurons become strong. If underused – for example, as people lose their sight – the connections become weak and disorganised.

Over the past few years, a type of gene therapy – injecting healthy genes into the eye to repair mutations – has emerged as a promising way to treat congenital and degenerative blindness.

One of the first successful trials began in 2007. It involved 10 blind volunteers with a hereditary disease called Leber's congenital amaurosis. The condition causes the retina to degenerate and leaves people completely blind early in life.

Mutations in at least 19 genes can cause the disease, but all of the people in the trial had mutations in a gene called *RPE65*.

The participants got an injection of a harmless virus in one of their eyes. The virus inserted healthy copies of *RPE65* into their retina.

Let there be sight

Some of the volunteers went from straining to see a hand waving half a metre from their face to being able to read six lines on a sight chart. Others were able to navigate around an obstacle course in dim light – something that would have been impossible before the therapy.

Manzar Ashtari at the University of Pennsylvania, Philadelphia, and her colleagues wondered how well the participants' visual pathways had recovered after the therapy. So, two years after the treatment, she got them back to the lab to scan their brains. Now the results are in.

Pathways associated with the treated eye looked very similar to pathways in people who had no problems with their vision. They were also much stronger than pathways associated with the untreated eye, which had degraded further.

Although the team expected to see brain changes, the extent was surprising, says Ashtari – particularly given the age of the participants. "Most of our patients were in their 20s, and one was 45," she says.

Eyes are the prize

There is a general consensus that there is a critical window early on in life when neurons can be shaped, pruned and reshaped. This plasticity is thought to diminish with age. "There may be a critical window of accelerated brain plasticity, but we have shown that doesn't mean you lose the capability of restructuring pathways as an adult," says Ashtari.

The team is now seeking approval from the US Food and Drug Administration for the gene therapy to be used as a prescribed drug for Leber's congenital amaurosis.

Eric Pierce, an ophthalmologist at Harvard Medical School, agrees that the trial shows the potential plasticity of the adult visual system. Previously, he says, it has been assumed that disrupted neuronal development in the brain can't be reversed in adults. He gives the example of amblyopia, "or lazy eye", which is much more difficult to treat in adults than young children.

One of the questions that people have asked about this gene therapy, says Pierce, is whether it might repair the retinal cells but not affect the brain pathways. That would leave people unable to perceive the visual signals that the therapy had enabled to get through.

Alternatively, if people's degraded pathways still had some left-over functionality, the therapy might give them limited vision. This paper is important because it shows that neuronal plasticity is at least in part responsible for the improvement in vision seen in the trial participants, says Pierce.