NEWS

Serotonin’s link to autism, explained

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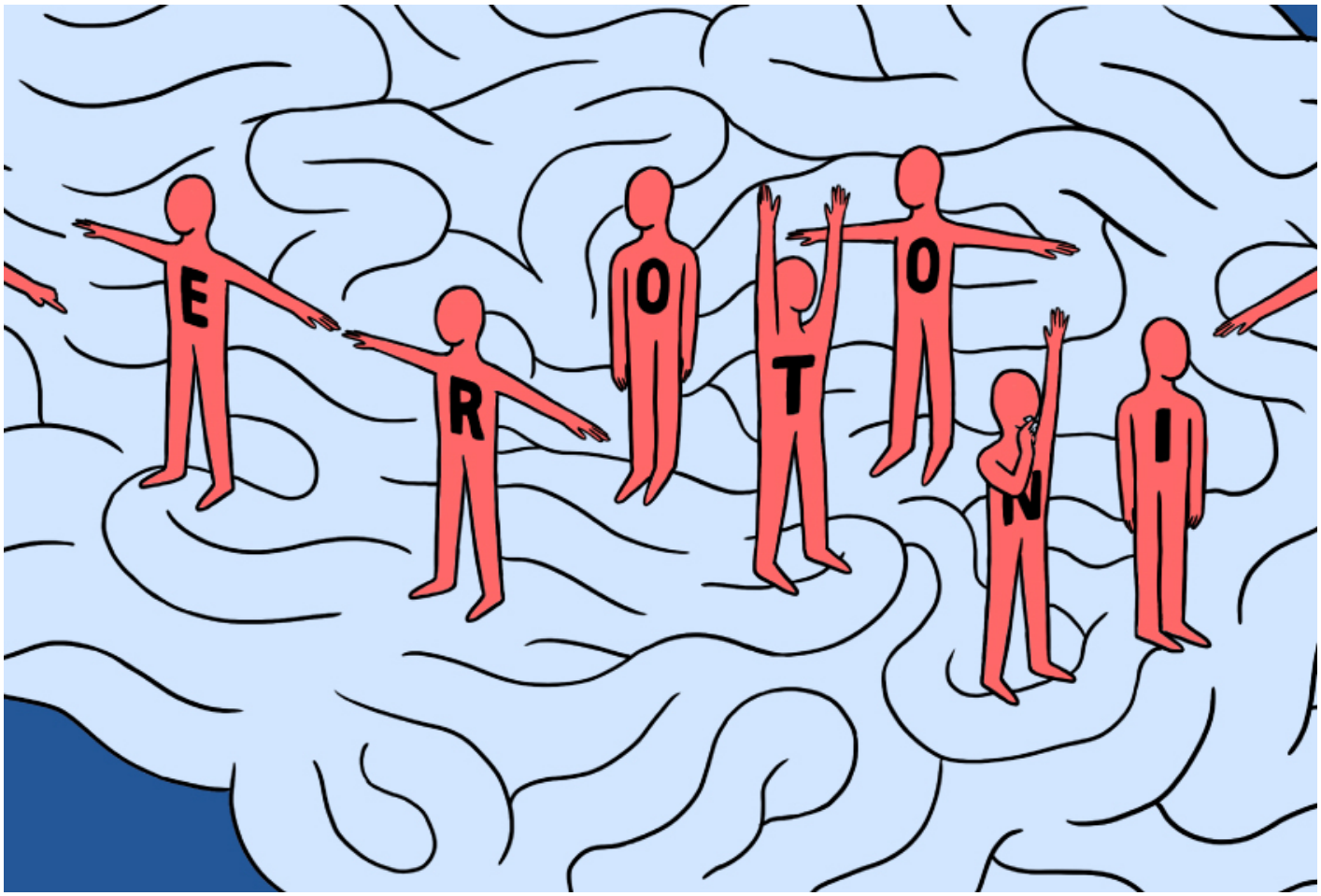

Serotonin, the brain chemical best known for its link to depression, may also be involved in autism.

Serotonin has many roles throughout the body, including in mood, sleep, appetite and sociability. In the intestines, it stimulates muscles involved in digestion; in the blood, it causes vessels to shrink or expand; and in the brain, it relays messages between neurons. Its levels in the brain are closely tied to depression. Many antidepressants work by increasing the levels of serotonin at neuronal

junctions.

Tenuous ties between serotonin and autism first surfaced decades ago. In 1961, a study of 23 autistic people reported that 6 of them had an unusually high level of serotonin in their blood. Since then, researchers have consistently found that about one in four people on the spectrum has **high blood serotonin**.

That result is “incredibly well replicated,” says **Jeremy Veenstra-VanderWeele**, professor of psychiatry at Columbia University.

Motivated in part by these results, several research teams have tested antidepressants as a treatment for autism over the past 20 years — with **mixed results**. Interest in serotonin’s role in autism has grown in the past five years, due in part to mouse studies that implicate the chemical in social behavior.

Here’s what we know so far about serotonin's role in autism.

What could explain the high serotonin levels in the blood of people with autism?

Blood serotonin levels are controlled in part by a protein called the serotonin transporter, which moves serotonin from the gut, where most serotonin is made, into certain blood cells.

These levels are highly heritable, suggesting that genetic factors control them.

Some people with autism may carry variants in the serotonin transporter that enhance its ability to move serotonin into blood cells[1]. Mice with these variants have unusually high blood levels of serotonin and behaviors reminiscent of autism[2].

What does serotonin do in the brain?

In the fetus, serotonin helps neurons form and travel to their correct locations; it also helps them link to other neurons at junctions called **synapses**[3]. Too much or too little serotonin can be harmful: Mice exposed to too much in utero show altered development in a brain region that responds to whisker movements[4]; those with too little have **repetitive behaviors** and social difficulties[5].

In the mature brain, serotonin is a **neurotransmitter**: It relays messages between neurons. Its level at the synapse is tightly controlled by the serotonin transporter, which pumps serotonin back into neurons and recycles it for later use. This transporter may be altered in people with autism[6].

What do blood levels of serotonin have to do with serotonin in the brain?

It is unclear, because serotonin in the blood cannot pass into the brain; the brain makes its own. Genetic variants that turbocharge the transport of serotonin into blood cells are predicted to have the same effect in neurons, effectively leaving less of it available to relay messages across synapses. Antidepressants might be able to help by restoring levels of serotonin at the synapse.

How does the brain's serotonin level relate to autism?

Some studies point to low serotonin levels in the brains of autistic people.

When autistic adults adopt a diet low in the amino acid tryptophan — the raw material for serotonin — their repetitive behaviors worsen and their irritability increases[7]. They also show altered patterns of brain activity in regions involved in face processing, suggesting that serotonin influences social behavior[8].

Brain-imaging studies also hint that some autistic children make too little serotonin in the brain, and in others, too little serotonin binds to its receptors[9,10].

Can treatments that increase serotonin levels ease autism traits?

Possibly. Antidepressants that allow serotonin to remain at the synapse for longer seem to **ease repetitive behaviors** in some autistic adults[11]. These drugs, called selective serotonin reuptake inhibitors (SSRIs), have not yet been shown to **benefit children with autism**. But clinical trials of these drugs are hampered by powerful **placebo effects** that might make it hard to tease out the benefit.

Preliminary evidence suggests that in adults with autism, the active ingredient in the **drug 'ecstasy,'** which raises serotonin levels in the brain, seems to ease **social anxiety**.

Some mouse models of autism have low brain serotonin levels. Treating one such strain of mice with an SSRI starting at birth prevents **autism-like social behaviors**. And artificially boosting serotonin in in another mouse model **makes the mice more social**.

Do serotonin levels in utero affect a child's autism risk?

Some studies have explored whether **exposure to antidepressants** in utero has any effect on autism risk. The answer is unclear. One problem is that researchers are often not able to separate the effect of the antidepressant from that of the mother's underlying depression. Simply having a **family history of depression**, for example, is associated with autism.

Where is research on serotonin and autism headed?

Some researchers are testing whether drugs that activate serotonin receptors make mouse models

of autism more sociable. Others are working on strategies that dampen the activity of the serotonin transporter without blocking it completely[12].

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