VIEWPOINT

New tool may speed up drugs to ease need for sameness in autism

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Sheldon Cooper, a character in the long-running television show “The Big Bang Theory,” becomes flustered at the smallest change in his routine — if someone sits in what he considers to be his spot on the couch, for example, or if something disrupts his morning routine of eating cereal while watching “Dr. Who.”

Some fans of the show have suggested that Cooper has autism, in part because of his intense need for sameness. On TV, this may seem like a harmless quirk, but the need for sameness can cause profound distress for many people on the spectrum.

Everyone can relate to the discomfort that comes from facing the unexpected. But for some people with autism, even an apparently trivial change can trigger extreme emotions. Years ago, when one of us was working as a behavioral therapist at a school in New Jersey, a student became increasingly anxious.

Lacking the words to express himself, he ended up screaming, crying and banging his head on the floor. We had no idea what was upsetting him. Finally, a teacher who knew the child well entered the room. She calmed him, then asked him to show her the problem. He led her to a shelf and was able to communicate that some of the toys had not been put away in their usual places. When she let him move them to their regular positions, he relaxed, as if a weight had been lifted off his shoulders.

Another child we know of removed his seatbelt and tried to bolt from a moving car when road construction required his parent to take an unfamiliar route to school. Still another suffered melt-downs for weeks after his parents gave away the family piano; years later, he still frequently refers to the incident.

At mainstream schools, children with autism may resist the daily transitions from one activity to the

next — mathematics, reading, gym — disrupting everyone's learning. The need for sameness can also put a chokehold on family life[1]. Parents try to anticipate every shift, such as a switch to warmer clothes in the autumn, and prepare their children in advance. They may sacrifice their own needs to minimize change — for example, by opting not to replace worn-out furniture.

To address the problem, we and our colleagues have been investigating the brain systems that underlie the need for sameness. We have developed tasks aimed at measuring cognitive issues that may underlie this need. Importantly, for one of these tasks, we have developed parallel versions for people and for mice. We are using these tasks to better understand the need for sameness so that we can find ways of moderating this trait.

Of mice and men:

We have been investigating the brain mechanisms that underlie the need for sameness over the past 10 years. Work from our lab and others' indicates that it is linked to problems with both response inhibition — the ability to suppress an inappropriate reaction — and behavioral flexibility, or the ability to stop doing an enjoyable or rewarding activity when asked or expected to do so[2,3,4].

One of us works with mice and the other with people, and among our most exciting accomplishments has been to develop matching tests of behavioral flexibility for people and rodents. We developed a strong theoretical model of the brain issues that may underlie the need for sameness. Then we tested our hypotheses in experiments that could be applied in parallel to mice and people. (We did this work in collaboration with **John Sweeney**, professor of psychiatry and behavioral neuroscience at the University of Cincinnati in Ohio.)

In these experiments, we found that people and mice act in strikingly similar ways. So our tasks represented key tools for investigating the physiological underpinnings of the need for sameness.

In the human version, we presented people with two identical animal photos on a touch screen. Some of the participants have autism, and others are neurotypical but of comparable age, gender and intelligence. We asked the participants to randomly choose one of the photos, then repeated the trial up to 50 times.

Unbeknownst to the participants, we had designated one side of the screen the 'correct' side. When a participant picked the photo on that side, a coin appeared on the screen 80 percent of the time, moved into a money bag and increased their total winnings by 10 points. Once the participants had become accustomed to getting their reward and consistently chose the rewarding photo, we switched the 'correct' choice to the other side of the screen[5].

The people with autism noticed the change and made the switch as fast as the controls did. However, they kept straying back to the side of the screen that had initially offered the coin. Their tendency to revert to their original response is strongly related to their need for sameness.

This result confirmed our hypothesis that people with autism struggle to shift their behavior away from an activity that was previously rewarded.

In the rodent task, we used both common lab mice and mice that display compulsive behaviors and resistance to change. We gave the animals a choice between two paths. One was bare; on the other we placed a piece of Fruity Pebbles breakfast cereal 80 percent of the time. All the mice quickly learned which direction to go to get the reward.

We then switched the food to the other path. Whereas the regular mice quickly prioritized the new food spot, the compulsive mice frequently strayed back to the original path[6].

The mice's behavior was virtually identical to that of the people with autism in the touch-screen experiment. It's rare that mouse data match up so well against human trials. We knew we had created a valuable tool.

Parallel processing:

We've begun using this tool to test potential treatments for the need for sameness.

A drug called **risperidone**, which is approved for treating irritability in autism, seems to have potential to alleviate behavioral inflexibility. But risperidone is what's known as a 'dirty' drug, in that it affects multiple **neurotransmitter** systems and so can have unintended effects.

One of the neural systems risperidone affects is a serotonin receptor known as 5-HT2A. If we could target only that receptor, we wondered, might we get the desired response without side effects?

In 2011, we gave rats a chemical that targets 5-HT2A and found that it increases the animals' behavioral flexibility: They improved in their ability to stop a behavioral pattern they had learned and instead make a new choice[7].

We then tested that drug and risperidone in both common mice and BTBR mice, which have autism-like traits. We used the study design described above, in which we switch a sweet reward between two locations.

When they received low doses of risperidone, the autism-like mice were less inclined to stray back to the original reward location. In other words, they were more flexible to change. (At high doses, the mice and people both become woozy.)

The 5-HT2A drug also made the mice adapt to the change in the treat's location, but did not have side effects at high doses or any of the doses we tried[8].

We hope to test this risperidone alternative in people with autism using the touch-screen test that

corresponds to the rodent task. By investigating new treatments first on mice, then applying the results to equivalent behaviors in people with autism, we hope to discern the biochemical triggers for the need for sameness, and discover therapies.

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