This is the podcast for the journal Neuropsychopharmacology, I'm Cynthia Graber.

Serotonin is a critical chemical when it comes to a number of psychiatric conditions, such as OCD, where it seems to play a particular role in cognitive flexibility. That is, serotonin levels are related to the fact that someone is perseverating on intrusive thoughts or compulsions and isn't able to be as flexible as otherwise would be necessary.

Trevor Robbins, professor of cognitive neuroscience at the University of Cambridge, is one of the authors of a recent study titled *Comparable roles for serotonin in rats and humans for computations underlying flexible decision-making*, and he says such cognitive flexibility also plays a role in depression and schizophrenia.

In this study, he and his colleagues united a series of studies: manipulations in rat models, human subjects that were presented with similar tests, and a framework that was employed to understand the subtleties of the results. Because one of the challenges to understanding serotonin's role in cognitive flexibility is the difficulty in teasing out the translation between rodent models and human studies.

Dr. Robbins, there's a lot going on in this paper. The rats' brains were manipulated by depleting serotonin with a neurotoxin, and also they were given doses of SSRI drugs. Humans serotonin levels were not manipulated with a neurotoxin but just with SSRI drugs. So can you talk through the tests they took part in to evaluate the role of serotonin in cognitive plasticity?

> TR: So what we did was to use the same basic task in rats and humans. You are given a choice between two options. One of them is rewarded 80% of the time. The other one is rewarded 20% of the time, which is to say also that they're punished 20% or 80%. And you have to work out what is your best strategy here.
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> Now, just to make it even more interesting and flexible, we change it around after you seem to have got the drift of this task. So the one that was originally 80% is changed to 20% and vice versa. Obviously you've got to watch out because on reversal you've got to really switch then carefully. So you've got to have a balance between repeating yourself and switching.
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> Now, you can measure behavior just with what we call traditional measures, how many you get right, how many rewards you get basically, and how quickly you reverse your behaviors.
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> Now, the previous studies we've had have all been based on basic behavioral results, but this new study, this new synthesis, has used this new reinforcement learning framework, which delves much more deeply into the data and produces a model about how reward learning and punishment learning are balanced, how sensitive you are to reward and punishment, and whether you have basic tendencies to repeat yourself or to switch.

Christelle Langley is a research associate in the department of psychiatry at the University of Cambridge, and she's another one of the study's authors. Dr. Langley, how does this model work?

> CL: Yes. So as Trevor's mentioned, he is nicely outlined the probabilistic reversal task, as well as some of the traditional behavioral measures that we've used, such as the number of trials taken or errors to reaching criterion.
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> But in more recent years, we've been able to use a more sophisticated hierarchical Bayesian modeling technique, which uses a reinforcement learning framework. And this better captures the complex relationships in decision-making specifically involved in this task. So essentially the model is given information about a subject's responding, which stimulus was chosen, what feedback they received. And the models use this trial-by-trial information to estimate a number of parameters.
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> So in our own research, and certainly in this cross-species paper, we showed that with this task, we've always found a model which encompasses four parameters as the best fit. So these include a learning rate from reward, a learning rate from punishment, a reinforcement sensitivity parameter, and a stickiness parameter.
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> And essentially these computational modeling techniques allow us to examine behavior on this task with greater specificity than traditional methods. Methods have offered and allows us to gain a unique insight into the mechanisms governing reinforcement learning cross species, and how they're affected by serotonin manipulations and including the drug therapeutic drug effects.

So using all this, what results did you see from serotonin manipulations?

> TR: First of all, I'm just going to mention in a sense the least agreeable between the species. We found that serotonin depletion in rats really impaired reward learning, whereas chronic treatment with serotonin reuptake blockers, which has in theory the opposite effect to boost serotonin, had the opposite effect to improve reward learning. We didn't see these effects in humans particularly, and we think this is because the humans really rapidly learn this task, where it takes the rats much longer.
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> Now, the other two major effects were first of all on reinforcement sensitivity. Now, this really did agree very interestingly. Reinforcement sensitivity, remember, is the parameter which basically says how well you implement this learning history. And we found that intriguingly, both chronic SSRIs in humans, which are therapeutic in patients, and also in the rat, chronic SSRI treatment both reduced reinforcement sensitivity.
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> Then the other result is a little more complicated in its interpretation, but the results are very clear here that we found similar effects on cognitive flexibility as measured by stickiness.

Now, actually, I have to confess one thing that stickiness in animals and humans was measured slightly differently. Because in the rat task they had to choose between left and right, whereas in the human task, they had to choose between two different stimuli on the computer screen, which danced around, but it's still stickiness in some general sense.

And some of the results may at first sight be a little contradictory to a plasticity hypothesis, because what we found is that the treatments which reduced serotonin actually also reduced stickiness. But that reduction of stickiness in this task isn't a very good result because what it means is that the animals and humans were probably randomly switching between the options rather than placing their bets on the one that paid off the best.

So bear that in mind because in a more deterministic reversal task where there isn't so much uncertainty, there's no doubt that serotonin loss makes you perseverate. That's been shown over and over again in all species studied. So there's some nuances here about plasticity and stickiness.

Dr. Langley, what are some of the clinical implications of these findings?

CL: So, yes, as Trevor mentioned, one of our very important findings was that the chronic SSRI treatment, both in rats and in humans, reduced this reinforcement sensitivity parameter. And there may be a number of mechanisms involved, but one potential interpretation is that it might be similar to the blunting effect reported by patients during SSRI treatments. So emotional blunting is when patients report feeling emotionally numb and they're not really reacting to either positive or negative events. And of we know that in patients with depression, they're obviously very often hypersensitive to negative feedback, and they have negative attentional biases. So this would be something as simple as when someone's walking down the street, they might see all the people smiling, but an individual with depression might focus on that singular person that looks upset or sad and therefore actually dampening down the negative emotions. And the distress felt by depressed patients might actually be part of the therapeutic process for these drugs.

However, unfortunately, they cannot selectively target the negative emotions, and it seems to take away some of the enjoyment as well. This doesn't necessarily mean that they're not effective nor does everyone who takes them experience this blunting, but it actually does give us a better understanding of how these drugs might work, and it also helps us to provide better treatment options.

What’s a major takeaway for you from a model perspective?

If we look at these manipulations in terms of traditional sort of error measures, we don't get quite such a nuanced understanding of that relationship of behavior. All you're basically seeing is a change in errors. You can't tell the underlying mechanisms that

actually contribute to those errors. And that's where that strength really comes in from the reinforcement learning framework, because now we are not just simply looking at — are they correctly responding? We can actually see whether reinforcement plays a role, does stickiness play a role. So they really do help to sort of understand this complex decision making in much greater detail.

This is the podcast for the journal Neuropsychopharmacology. To read the paper discussed in the podcast, go to www.nature.com/npp. I'm Cynthia Graber.