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RESEARCH HIGHLIGHT

Fluoxetine incentivizes ventral striatum encoding of reward and punishment

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Selective serotonin reuptake inhibitors (SSRIs) are used as a first-line treatment for mood disorders. Since their discovery, much has been learned about the neuropsychopharmacology of this class of drugs, which increase the availability of serotonin by blocking its reuptake through the serotonin transporter. But it is not well understood how SSRIs affect the activity of neuronal populations organized into neural circuits that control motivated behavior [1, 2]. This has been an obstacle in refining their use in psychiatry. In this issue of *Neuropsychopharmacology*, Pasquereau et al. [3] demonstrate how fluoxetine treatment alters neuronal encoding of rewards and punishments by putative medium spiny neurons in the primate ventral striatum, a key node in the neural circuitry underlying motivated behavior [1, 2, 4]. Fluoxetine caused changes in neuronal encoding of reinforcer valence that coincided with changes in the monkeys' motivation to approach or avoid stimuli predictive of reward or punishment. These results are a clear indication that serotonin plays an important role in balancing ventral striatal encoding of hedonic valence.

The monkeys performed an approach-avoidance task, in which they viewed a visual stimulus that appeared at one of two locations at the start of each trial. The monkeys had learned from previous experience that each stimulus was associated with either an appetitive outcome, a drop of juice, or an aversive outcome, an air puff directed at the face. The monkeys could choose to either approach the location where the stimulus had appeared or avoid it by choosing the alternate location. If the monkeys approached a stimulus, they received the reinforcer associated with that image, but if they avoided it there was no outcome. Because the therapeutic effects of SSRIs can take several weeks to develop, the authors examined behavior and the responses of ventral striatum neurons after several weeks of daily treatment. They also verified where in the brain serotonin levels were affected following treatment using positron emission tomography (PET). Before treatment there was substantial binding of a competitive PET ligand in the ventral striatum and amygdala. After treatment, this binding was reduced.

Pasquereau and colleagues compared the monkeys' approach or avoidance behavior related to the presentation of the conditioned stimuli between baseline and treatment. They found that after treatment the monkeys more frequently and more rapidly approached rewarding stimuli and avoided punishing stimuli. After treatment, the animals also worked harder at the task by completing substantially more trials per day. When they examined the responses of individual neurons in the ventral striatum, they found that treatment altered neural encoding of the different valence outcomes. Compared to baseline, neural responses to reward and punishment were more readily discriminated after fluoxetine treatment. Neural responses that encoded the cue, however, were only slightly increased with treatment. The combined effects of fluoxetine on the monkeys' behavior and neuronal encoding of reward and punishment in the ventral striatum are remarkable because it suggests fluoxetine might treat depression and anxiety by facilitating incentive learning and strengthening tendencies to approach or avoid based on reinforcement.

Incentive learning is one of the multiple learning processes that underlie instrumental and Pavlovian conditioning [5]. Unlike reinforcement learning which describes how the contingencies between actions and outcomes are acquired, incentive learning describes how changes in affect linked to the sensory properties of unconditioned stimuli modulate conditioned responses. For example, hunger or satiety manipulations will lead to increases or decreases in execution of specific responses associated with a particular food item. If the valence of unconditioned reinforcers is more strongly represented in the ventral striatum following fluoxetine treatment, incentive learning [5] would predict the observed changes in the monkeys' approach and avoidance behavior following fluoxetine treatment. Also, because incentive learning should not alter encoding of the approach-avoidance contingencies, incentive learning also potentially explains why fluoxetine treatment did not alter encoding of visual cues that reliably predicted receipt of either a juice reward or an air puff. A considerable amount is already known about the neural mechanisms underlying incentive learning, but its application has mainly been used to understand addiction and not depression [5]. Anhedonia is a core symptom of depression and it will be of interest to determine if fluoxetine is effective in reducing anhedonia because it rebalances the activity of neural circuits engaged during incentive learning procedures.

Pasquereau and colleagues also found that despite being interspersed within the ventral striatum, subsets of striatal projection neurons preferentially encoded either appetitive or aversive outcomes and that a greater proportion of neurons specifically encoded aversive outcomes. This fits with evidence that the ventral striatum contains interdigitated valence modules. Although these are more readily seen in the nucleus accumbens shell [6] and in primates it is difficult to distinguish whether neurons are recorded from the nucleus accumbens shell or core. After fluoxetine treatment, there was an overall increase in the proportion of ventral striatum neurons that specifically encoded

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appetitive outcomes. So, fluoxetine treatment not only led to the activity of individual neurons more robustly encoding the valence of outcomes, but at the population level encoding of appetitive outcomes in the ventral striatum was strengthened relative to baseline. An equalized or slightly biased encoding of appetitive outcomes is consistent with prior evidence in non-human primates that ventral striatum neurons encode the overall appetitive value of choices [4, 7] and in humans that ventral striatal activation is greater in response to appetitive versus aversive events [8]. This might reflect a stronger association following treatment between the affective value of reinforcers and their sensory properties. At the very least, it argues that serotonin in the striatum plays a role in regulating affect and by extension incentive learning. Consistent with this idea, ventral striatum hypoactivation to positive and negative emotional stimuli in depressed patients is rescued with SSRI treatment [9].

There is an important caveat to this compelling demonstration that fluoxetine may improve symptoms in depression by modulating valence processing in ventral striatum. Using PET, a therapeutic dose of fluoxetine reduced binding not only in the ventral striatum, but also in the amygdala. Basolateral amygdala inputs to the striatum and orbitofrontal cortex are known to be important in incentive as well reinforcement learning [1, 2, 5]. But prior studies have mostly examined how amygdala inputs to the striatum are dependent on dopamine [1, 5] and have not equally considered how serotonin might modulate amygdala-dependent changes in striatal function. This is a rich area of investigation considering that SSRIs can enhance dopaminergic modulation of behavior and neurophysiology [10]. Furthermore, the ventral striatum is embedded within a broader network of brain regions, that includes the ventral pallidum, lateral hypothalamus and the paraventricular nucleus of the thalamus. Much of this circuitry receives input from and projects back to the dorsal raphe [2]. There are clearly numerous and exciting opportunities to establish the specific effects of fluoxetine and related drugs on valence processing in the ventral striatum and its broader circuitry.

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AUTHOR CONTRIBUTIONS

VDC and BBA both wrote the manuscript.

ADDITIONAL INFORMATION

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