Journal Club

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Behavioral Inflexibility from a Neuronal Population Perspective

Jinkang Xiang,^{1,2,4,5,6} Yilin Chen,⁷ and Megan Roussy^{2,3,5,6}

¹Department of Psychology, Western University, London, Ontario N6A 5C2, Canada, ²Department of Physiology and Pharmacology, Western University, London, Ontario N6A 5C1, Canada, ³Department of Psychiatry, Western University, London, Ontario N6C 0A7, Canada, ⁴Department of Applied Mathematics, Western University, London, Ontario N6A 5B7, Canada, ⁵Brain and Mind Institute, Western University, London, Ontario N6A 3K7, Canada, ⁶Robarts Research Institute, Western University, London, Ontario N6A 3K7, Canada, and ⁷Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, People's Republic of China

Review of Mueller et al.

Behavioral flexibility, the ability to adapt behaviors in response to changes in the environment, is of great importance for everyday functioning (Klanker et al., 2013). Behavioral flexibility is typically assessed using reversal learning tasks, in which subjects learn to perform a specific action to receive a reward, then must alter their behavior when a different action is rewarded instead (Izquierdo et al., 2017). Impairments in such flexibility are observed in substance use disorder, characterized by persistent drug use despite negative outcomes (Mueller et al., 2021). Individuals with substance use disorders may choose to use drugs even when more rewarding alternatives are available especially in contexts that were previously associated with drug use. Similar features of behavioral inflexibility appear in animal models exposed to cocaine and may manifest through subjects selecting a previously rewarded object when more highly rewarded objects are subsequently presented.

Previous studies have revealed that the prefrontal cortex (PFC) and striatum are key components of the neural circuitry underlying behavioral flexibility (de Bruin et al., 1994; Castañé et al., 2010). In humans, neuroimaging studies have demonstrated that the dorsal (Rogers et al., 2000; Izquierdo et al., 2017) and ventral (Cools et al., 2002; Izquierdo et al., 2017) regions of the striatum are involved in reversal learning. In rodents, anterograde tracing shows how these areas are connected: the orbitofrontal cortex projects to the dorsomedial striatum and receives reciprocal input from the striatum through the mediodorsal nucleus of the thalamus (Schilman et al., 2008; Izquierdo et al., 2017). Furthermore, lesions of the dorsomedial striatum result in impairments in behavioral flexibility in rodents (Castañé et al., 2010). Notably, the behavioral impairments observed after striatal lesions are similar to those observed after cocaine use. While many studies have shown that cocaine use changes striatal processing, it is unclear how these changes relate to behavioral deficits observed after cocaine use.

To address this question, Mueller et al. (2021) examined how prior cocaine use affected performance and dorsomedial striatum neuronal activity during a reversal learning task in rats. Rats with prior cocaine or sucrose self-administration

experience were trained to perform an odor-guided choice task in which two of three instructional odors were associated with a big and a small reward, on the left and right fluid well, respectively. When one of these two odors was presented, rats received the corresponding reward only if they went to the appropriate fluid well. The third odor indicated that rats could choose which fluid well to go to: likely the one that was expected to yield the greater reward. After a block of trials, the odor previously associated with a large reward would then be associated with a small reward, and vice versa, requiring rats to alter their pattern of response to maximize the reward they received in the free choice trials. Rats with greater behavioral flexibility were expected to learn which fluid well yielded greater reward in fewer trials after a block switch. Single-unit activity was recorded from the dorsomedial striatum while the rats were performing the reversal learning task. Units were classified into fast-spiking interneurons (FSIs), medium spiny neurons (MSNs), or unidentified units based on their waveforms.

To assess striatal neural population activity, pseudo-ensembles were constructed by randomly pulling 100 neurons from populations of recorded units across all measurement sessions and all subjects within control and cocaine groups (784

Received Mar. 16, 2021; revised Apr. 25, 2021; accepted May 1, 2021.

We thank Dr. Marieke Mur, Dr. Geoffrey Schoenbaum, and Lauren Mueller for comments and feedback in the preparation of this manuscript.

Correspondence should be addressed to Jinkang Xiang at jxiang27@uwo.ca.

<https://doi.org/10.1523/JNEUROSCI.0559-21.2021>

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and 1253 single units from 22 recording sessions performed by four control and five cocaine-experienced rats, respectively). To examine the information represented by the neural populations during the behavioral task, patterns of the pseudo-ensembles were then fed into support vector machines to decode trial-type information, which specifies both the fluid well and the reward size associated with an instructional odor. In other words, trial-type information reflects the odor–reward contingencies in a task block. Statistical inference revealed that the decoding accuracies for MSN and FSI pseudo-ensembles from the cocaine group were significantly higher than those from the sucrose group in some trial phases, suggesting that prior cocaine use increases the amount of reward-related information being encoded by the pseudo-ensembles (Mueller et al., 2021).

The behavioral results showed that prior cocaine use impaired the task performance of rats. Specifically, the rats that had self-administered cocaine required more trials after the block switch to learn the new odor–reward contingency. This suggests that stronger encoding of an odor–reward contingency impairs the ability to switch once the contingency changes. In addition to slower switching, the reaction times of rats that had self-administered cocaine were significantly longer than those of control rats that had self-administered sucrose.

To investigate the relationship between the neural and behavioral findings, Mueller et al. (2021) further analyzed decoding misclassifications using confusion matrices and found that information represented by pseudo-ensembles from the sucrose group changed over time, from reward contingency to response information, resulting in faster reaction times. However, cocaine prevented this information change from occurring, ultimately blocking the optimization of decision-making in rats (Mueller et al., 2021).

The results suggest that impairments in behavioral flexibility after cocaine use may be partly related to paradoxical overrepresentation of reward contingencies by the dorsomedial striatum, which comes at the cost of task switching and response speed. These findings are exciting because they help bridge the gap between neurochemical changes induced by cocaine use and behavioral flexibility. One important piece of the puzzle unsolved by the study, however, is whether cocaine induces this information-processing change via local effects, and if so, how? Previous

results suggest that dopamine signaling plays a role.

Dopamine is a key neuromodulator in regulating frontostriatal circuits. Burst firing of midbrain dopaminergic neurons has been proposed to provide a prediction error signal that guides learned behavior through phasic dopamine release in the striatum (Klanker et al., 2013; Keiflin and Janak, 2015). The most prevalent cells in the striatum are MSNs, many of which have D₂ dopamine receptors (Yager et al., 2015) that are sensitive to phasic dopamine release. Previous studies have shown that the reduced availability of D₂ receptors in the dorsal striatum impairs the use of negative feedback and the maintenance of a new response during reversal learning (Groman et al., 2011; Klanker et al., 2013). At the same time, there might be an increase in the availability of D₃ receptors, likely serving as a functional compensation for deficient D₂ receptor-related processes (Worhunsky et al., 2021). Brain-imaging studies suggest that decreases in D₂ receptors and decreases in dopamine release in the striatum are observed in subjects with long-term cocaine experience (Volkow et al., 2007). Such changes to D₂ (and D₃) receptors may alter the balance of error signaling, impacting the activity of dorsomedial striatum ensembles, resulting in more specific learning or less effective generalization. This might explain the reported overrepresentation of reward contingencies in the dorsomedial striatum after chronic cocaine use.

The results in the study by Mueller et al. (2021) offer a new perspective for understanding how cocaine affects behavioral flexibility, and results are reflective of what may occur in substance use disorder. Overencoding of reward contingencies in neuronal populations may be related to the inability to optimize behavior when contingencies shift. Similarly, initial reward signals triggered by cocaine use may result in overencoding for this behavior. Even when drug use results in negative outcomes, this behavior may not change and new information that should result in more adaptive behaviors may not be incorporated during decision-making. Such maladaptive behavior likely results from changes in brain regions involved in behavioral flexibility, including the striatum and PFC.

Future research might conduct reversal learning tasks while recording neural responses in individuals with substance use disorder. Although conventional methods of measuring brain activity in humans cannot detect single-neuron

activity, methods using functional magnetic resonance imaging and electroencephalography may be able to detect patterns of activity reflective of state-dependent and reversal learning. Moreover, task-related changes in dopamine release in the striatum may be determined using positron emission tomography or single-photon emission computed tomography imaging. This would be valuable for determining the impact of long-term cocaine use on dopamine release during reversal learning and decision-making. Future multimodal studies in humans may also further examine the role of prefrontal cortex in these processes. In animal models, cocaine use has been associated with hypoactivity in the prefrontal cortex (Chen et al., 2013; Lucantonio et al., 2014). Furthermore, restoring prefrontal activation normalizes behavioral deficits observed after cocaine use (Chen et al., 2013; Lucantonio et al., 2014). Perhaps altered representations in the striatum are secondary to changes in prefrontal cortex. Determining irregularities in behavioral flexibility and underlying neural changes in people with substance use disorder may eventually facilitate diagnosis and treatment in the future.

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