Biological Psychiatry: Celebrating 50 Years

Commentary

A Model of Restraint: Nucleus Accumbens Fast-Spiking Interneurons Inhibit Unwanted Actions

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Striatal fast-spiking interneurons (FSIs) are perfectly positioned to have an outsized influence over spiny projection neurons (SPNs, also known as medium spiny neurons), the output cells of the striatum (1). A given FSI exhibits strong, fast, inhibitory synapses onto the soma of many SPNs and receives substantial input from cortex (1), suggesting that they are poised to exert potent feedforward inhibition. However, until recently, the precise in vivo function of striatal FSIs has been elusive, in large part because they are so sparse, making up just 1% of the striatum (2). Tools to target, monitor, and manipulate FSI function in vivo have now begun to shed light on both the microcircuit and behavioral functions of these cells. In this issue of *Biological Psychiatry*, Pisansky *et al.* (3) take advantage of several of these approaches, including fiber photometry, chemogenetics, and optogenetics, to investigate the role of FSIs in the nucleus accumbens (NAc) in impulsive action.

Although previous work has implicated the NAc in reinforcement learning and the regulation of impulsivity (4) and other studies have independently linked FSIs in the NAc to behavioral effects of drugs of abuse, no previous studies have directly explored the role of NAc FSIs in impulsive action. To tackle this challenge, Pisansky *et al.* (3) used the 5-choice serial reaction time task. In addition to measuring impulsivity, this powerful paradigm dissociates other key variables that are important for decision-making and action selection, including attention and motivation (5). In this task, an intertrial interval (ITI) is followed by a brief cue light in 1 of 5 nose ports; the animal must then make a nose poke into the port that was briefly illuminated to obtain a reward (Figure 1A). By parametrically varying the ITI, it is possible to determine the threshold at which animals make premature responses before cue presentation, which serves as a measure of impulsive action. Importantly, within the same animals, levels of attention and motivation can be determined by varying the length of time the cue light is presented and by monitoring the number of omitted responses, respectively. Thus, within a single task, potential contributions from confounding factors can be teased apart so that the likelihood of premature responding can be assessed in relative isolation.

To examine neural activity during the 5-choice serial reaction time task from the sparse population of NAc FSIs, Pisansky *et al.* (3) expressed the calcium indicator jGCaMP7s in FSIs and monitored bulk calcium signals through fiberoptic probes in the NAc (fiber photometry). Interestingly, in well-trained animals, FSI activity was abnormally low during trials in which the mice exhibited premature responses relative to trials with correct, properly timed responses. This suggests that a lack of appropriate FSI activity leads to maladaptive impulsive behavioral responses. To test causality of this association, they used a combination of chemogenetic and optogenetic strategies to inhibit FSIs during different task epochs. First, they found that chemogenetic inhibition of NAc FSIs for the entire duration of the task caused an increase in premature responses. Interestingly, this phenomenon was only observed for longer ITIs (≥10 seconds), suggesting that FSI activity is particularly important for restraining prepared actions during long periods of waiting. Importantly, there was no negative impact of this intervention on other task elements, such as attention or response omissions, and no nonspecific effects of NAc FSI inhibition on locomotion or reward retrieval. Finally, to resolve the timing of the impact of this inhibition on prepared responses, they used optogenetics (enhanced *Natronomonas* halorhodopsin 3.0) to specifically inhibit FSIs during either the ITI or the cue, during interleaved trials. This experiment found a specific requirement for FSIs during the ITI, confirming that NAc FSIs are particularly important for preventing unwanted actions during the period that animals need to withhold a prepared response.

Taken together, these data suggest that the natural reduction in FSI activity observed during premature response trials via fiber photometry should result in greater SPN firing and corresponding downstream behavioral responses. This likelihood is further supported by the authors' direct demonstration of decreased or increased SPN population calcium activity after optogenetic excitation or inhibition of FSIs, respectively—not a trivial finding, given that single-cell resolution studies have found that stimulating FSIs can lead to both decreased and increased SPN firing (6,7). The authors also showed that FSI activity is transiently reduced at the onset of a behavioral response, whether it be premature or correctly timed, supporting the idea that activity in FSIs must be decreased to allow SPNs to initiate actions. FSI-mediated inhibition of SPNs may therefore be necessary for maintaining a current behavioral state (i.e., waiting to make a response) or restraining prepared actions. These data suggest that dynamics in NAc FSI activity play an important role in deciding when to initiate instrumental responses.

The present work is consistent with previous findings in the dorsolateral striatum suggesting that FSIs function to refine SPN ensemble configuration and activity during the learning of stimulus–response associations (6,8). For example, dorsolateral striatum FSIs have been shown to be important for normal striatal-based egocentric learning using a caspase 3–mediated ablation technique (8), and FSIs are involved in shaping SPN lick-related activity early in the learning of a conditioned lick task (6). However, this study is the first to suggest that FSIs

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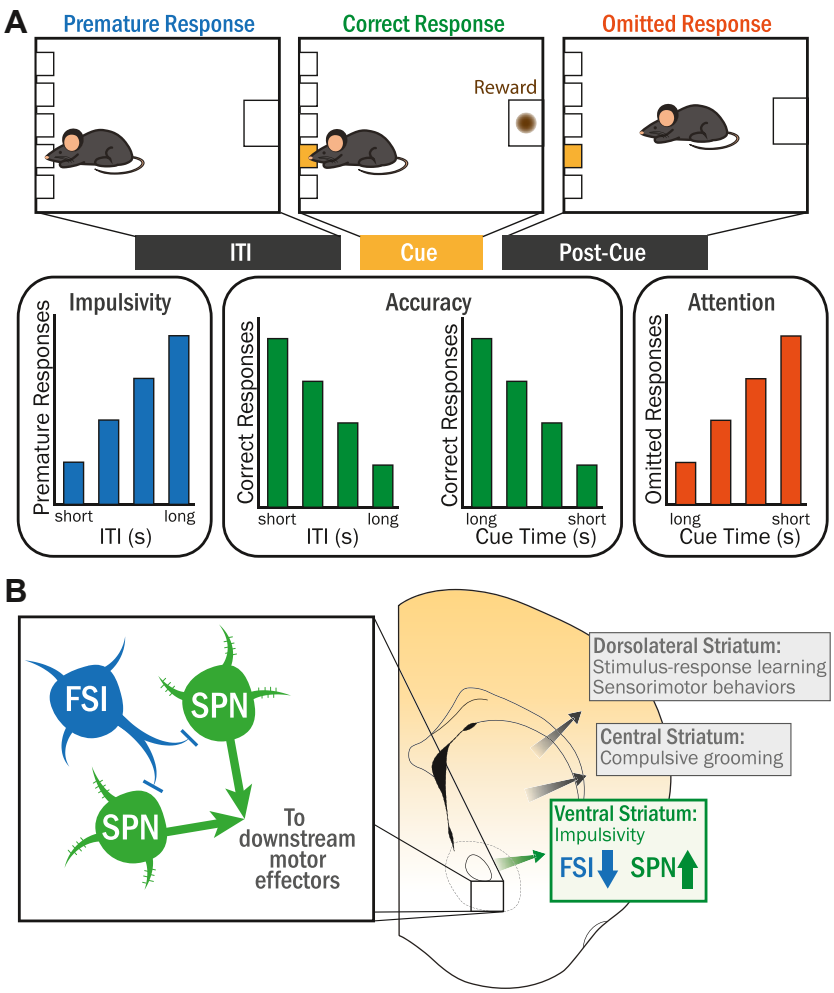

Figure 1. The 5-choice serial reaction time task allows for the investigation of the role of nucleus accumbens fast-spiking interneurons (FSIs) in impulsive action. **(A)** A schematic of the 5-choice serial reaction time task. Following an intertrial interval (ITI), mice obtain a reward by performing a nose poke in the port that was briefly illuminated. Measures of impulsivity, accuracy, and attention are obtained by tracking premature, correct, and omitted responses, respectively. Parametric variation of ITI and cue length can be used to assess thresholds for impulsive action and attention. **(B)** Model of striatal FSI function. FSI-mediated inhibition of spiny projection neurons (SPNs) prevents downstream motor responses. Conversely, directly inhibiting FSIs leads to premature motor responses, as seen in Pisansky *et al.* (3). The type of behavioral response controlled by FSIs may be determined by the particular striatal subregion.

refine SPN ensembles by shaping their activity levels and patterns during the execution of an already learned task. This is particularly exciting because it suggests that FSI activity is important not only for delineating SPN behavioral ensembles during training but also for modulating that ensemble activity in a given behavioral context. The idea of a broad role for both dorsal and ventral striatal FSIs in preventing unwanted movements is also supported by previous work examining untrained behaviors. Transient inhibition of dorsal striatal FSIs with IEM-1460 produces dyskinesias (9), and a reduction in central striatal FSI activity has been implicated in compulsive grooming behavior (10). While impulsivity, compulsivity, and dyskinesias are thought to have different neural circuit substrates, the accumulated findings from these studies support a model in which 1) impaired FSI-mediated inhibition of striatal SPNs results in an inability to restrain or prevent excessive or unwanted behaviors and 2) the behavioral constructs that are affected depend on the location of the SPN ensemble within the striatum (Figure 1B). It could be argued that this places the striatum, and FSIs specifically, at a more direct go/no-go point in the decision-making pathway, whereas the more cognitive aspects of these phenomena—i.e., the urge or craving to conduct these behaviors—may be localized to upstream cortical regions.

Together, these findings by Pisansky *et al.* (3) support a model in which FSIs serve as a brake on SPN activity, constraining SPN ensembles and preventing the transmission of striatal output downstream to evoke a behavioral response. With rigorously validated methods, they used convergent strategies to test the hypothesis that FSIs in the NAc prevent impulsive actions. Integrating their work with previous findings, these data suggest that FSIs may generally function to refine and dampen SPN ensemble activity, thus shaping downstream actions. Though the behavioral manifestation of this ensemble modulation may differ slightly depending on the specific striatal subregion, the widespread connectivity and inhibitory action of FSIs allows them to generally serve as a brake on striatal output. While this regulatory role has been loosely hypothesized since the first investigations of these cells (1), recent studies using new techniques for direct observation and manipulation have led to major advances in delineating their function in vivo. To further investigate how NAc FSIs may inhibit and refine SPN behavioral responses, future work could test whether activation of NAc FSIs can prevent impulsive actions or whether reduced

FSI activity is present in disease models that include impulsive or compulsive behaviors. A greater understanding of how NAc FSIs play a role in regulating striatal output to downstream structures will potentially provide a target for modulation of these circuits to treat impulsive behavior in disorders such as addiction and attention-deficit/hyperactivity disorder.

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Article Information

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