Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

The Ventromedial Ventral Pallidum Subregion Is Necessary for Outcome-Specific Pavlovian-Instrumental Transfer

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Review of Leung et al.

Learned environmental stimuli influence everyday reward and safety-seeking behaviors. During pathological conditions, such as drug addiction and obesity, learned cues influence maladaptive reward-seeking behaviors. One model of investigating the influence of learned cues upon reward-seeking behavior is outcome-specific Pavlovian-instrumental transfer (PIT). In this model, Pavlovian cues (e.g., lights or tones) are associated with distinct rewards, such as palatable foods or solutions. In separate training sessions, these same rewards are earned by responding on independent levers. During the outcome-specific PIT test, presentation of the Pavlovian cue predicting one reward increases response rates selectively on the lever that delivered the same reward. This type of PIT depends upon the integrity of the nucleus accumbens medial shell, but not nucleus accumbens core (Corbit et al., 2001; Shiflett and Balleine, 2010). Lesions of the core reduce responding levels in general, especially after reducing the value of one of the rewards through satiation (Corbit et al., 2001). These data from the Bal-

leine lab suggested the shell may mobilize reward-directed actions in response to Pavlovian cues, whereas the core may invigorate responding through a different mechanism.

The primary targets of nucleus accumbens shell and core neurons are the neurochemically distinct ventromedial (vm) and dorsolateral (dl) subregions of the ventral pallidum (VP), respectively (Zahm et al., 1996). Given the differential functions of the accumbens shell and core, it is likely that VPvm and VPdl subregions differentially participate in motivated behaviors as well. Consistent with this, VPdl neurons exhibit greater changes in firing rate than VPvm neurons specifically when rats approach and respond to self-administer cocaine (Root et al., 2013). In contrast, neurons exhibiting firing patterns after cocaine acquisition alone (retreat behavior) or during both drug-taking and following cocaine acquisition (response–retreat behaviors) were observed more often in the VPvm (Root et al., 2013). Therefore, the shell–VPvm pathway is a strong candidate for mediating goal-directed processing, a necessary component of outcome-specific PIT.

In a recently published paper, Leung and Balleine (2013) examined the influence of the shell–VPvm pathway during outcome-specific PIT, extending the known functions of the VP subregions. Three groups of rats were trained similarly, but were subsequently given

different tests. Animals were first trained to associate a conditioned stimulus (CS1) with one reward and to associate a second CS (CS2) with a second reward. After this Pavlovian training, animals were trained in separate instrumental conditioning sessions to obtain the first reward by pressing one of two levers and to obtain the second reward by pressing the second lever. Following training, animals were returned to testing chambers but no rewards could be earned. After a period to reduce baseline response levels, PIT group animals received individual presentations of CS1 and CS2 cues and magazine entries and lever presses were recorded. For the lever press (LP) control group, the levers were presented to animals, but CS cues were not. Conversely, in the CS control group, the levers were not presented to animals, but the same order of CS1 and CS2 cues from the PIT group were presented. As expected, CS presentations in the PIT group elevated response rates on the levers associated with the same reward as the CS, compared with response rates before CS presentation and response rates after presentation of the CS associated with the different reward. Both PIT and CS control groups exhibited increased magazine entries after CS presentation compared with before CS presentation. LP control group animals exhibited high rates of responding in the absence of cues.

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The authors next used a measure of neural activity, c-fos immunoreactivity, and intra-VP muscimol injections to examine the role of VP in outcome-specific PIT. For these experiments, instead of examining the VPvm and VPdl subregions, VP was divided into anterior “rostromedial” and posterior “caudolateral” areas. Rostromedial VP exhibited greater c-fos immunoreactivity in the PIT group than in LP and CS control groups, whereas caudolateral VP did not. The number of c-fos immunoreactive neurons was positively correlated with PIT performance in rostromedial VP but not caudolateral VP. Furthermore, muscimol injection into rostromedial VP blocked PIT, but the effect of muscimol injection into caudolateral VP was not examined.

At first glance, these data might provide support for functional differences between anterior and posterior VP, which has been previously suggested (Smith and Berridge, 2005; Root et al., 2012; Kupchik and Kalivas, 2013). The rostromedial and caudolateral VP divisions used by Leung and Balleine (2013) contained both VPvm and VPdl subregions, somewhat limiting comparisons to previously demonstrated VP subregional differences. For example, the rostromedial panels in Leung and Balleine's (2013) Figure 2A include the VPdl, and the caudolateral panels in their Figure 2B include the VPvm (compare to Zahm et al., 1996, their Fig. 1).

Two additional methods used by Leung and Balleine (2013) suggest involvement of the VPvm subregion in outcome-specific PIT, however. In the first method, the retrograde tracer FluoroGold was injected into VP and c-fos immunoreactivity was examined in accumbens shell neurons coexpressing FluoroGold in the three behavioral groups. Significantly more c-fos immunoreactive shell neurons coexpressed FluoroGold in the PIT group compared with the LP and CS control groups. Given that the shell projects to the VPvm (Zahm et al., 1996; Tripathi et al., 2010), this analysis suggests a role for VPvm-projecting shell neurons in PIT. Because FluoroGold injections included both VPvm and VPdl subregions (Leung and Balleine, 2013, their Fig. 4), it would have been useful to know how core neurons, retrogradely labeled from VPdl, exhibited coexpression of c-fos immunoreactivity and FluoroGold. In the second method, the authors used a contralateral disconnection procedure in-

volving unilateral shell muscimol injection together with contralateral VP muscimol injection during PIT. Disconnection of shell and VP blocked PIT, whereas unilateral muscimol injections had no effect, suggesting the shell–VPvm pathway is critically involved in PIT. The earlier investigations by Leung and Balleine (2013) suggesting the involvement of anterior VP might indicate that a subpopulation of neurons in the shell–VPvm pathway is primarily involved in PIT. In fact, a distinct type of slow phasic firing pattern confined to the anterior portions of VP was observed in the minutes between cocaine self-infusions (Root et al., 2012), and this pattern has also been observed predominantly within medial shell (Fabbriatore et al., 2010), perhaps reflecting a potential difference between shell–anterior VPvm and shell–posterior VPvm pathways.

Knowledge that the shell–VPvm pathway participates in PIT provides unique insights into the neuronal circuits involved in goal-directed behavior. VPvm receives projections primarily from accumbens shell and projects to the ventral tegmental area and mediodorsal thalamus (Zahm et al., 1996; Tripathi et al., 2010, 2013), both of which are important for PIT (Corbit et al., 2007; Ostlund and Balleine, 2008). As mentioned by Leung and Balleine (2013), determination of the specific contributions of ventral tegmental area and mediodorsal thalamus-projecting VPvm neurons is of high interest. In the study of cocaine self-administration by Root et al. (2013), VPvm neurons were not only heterogeneous with respect to behavioral firing patterns, but also in firing direction (increases vs decreases from baseline). The heterogeneity of VPvm firing patterns suggests its involvement in a wide array of situations involving reward or safety-seeking behaviors. Given that intra-VP muscimol reduced PIT, one could speculate that VPvm neurons that exhibit increased firing rates during reward-seeking behaviors were involved in PIT; further testing will be necessary to examine this, however.

Another subregion of the VP, VPdl, also plays a significant role in motivated behaviors and participates in different neuronal circuits. VPdl receives projections from accumbens core and projects to subthalamic nucleus and substantia nigra pars reticulata (Zahm et al., 1996; Tripathi et al., 2010, 2013). Core neurons exhibit elevated firing rates during self-administration behaviors (Ghitza et al., 2004) and VPdl

neurons primarily exhibit decreased firing rates during the cocaine self-administering response (Root et al., 2013), likely resulting from GABAergic core projections to VPdl. In the same issue of *The Journal of Neuroscience* as the article by Leung and Balleine (2013), Stefanik et al. (2013) found that optogenetic inhibition of the core–VPdl GABAergic projection blocked reinstatement of drug-seeking behavior induced by cocaine and drug-related cues. That is, the decreased firing rates of VPdl neurons during the drug-seeking response (Root et al., 2013) were prevented, and this blocked reinstatement. Considering all these results, it is becoming increasingly clear that shell–VPvm and core–VPdl circuits differentially participate in motivated behaviors, providing a foundation to delineate the unique contributions of several neuronal circuits involved in reward-seeking behaviors.

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