

inhibitory DREADDs to reduce LC activation during fear conditioning. When testing for feeding suppression during the fear retrieval test, they found that mice with inhibited LC did not display the expected feeding suppression. Down-regulation of CB1Rs on CeA neurons recapitulated this effect, establishing the importance of cannabinoid-mediated CeA synapses on PBN neurons in the appetite-suppressive response to LC input.

This work fills gaps in the scientific knowledge of LC-PBN-CeA connectivity and provides important information on the complex neurocircuitry underlying a relatively complex behavior. Most research investigating the relationship between fear/stress and feeding behavior has focused on the observation that chronic stress increases appetite, with only limited explicit inves-

tigations of fear-induced appetite suppression. The results from Yang et al. are consistent with a wider literature suggesting that hyperactivity of the locus coeruleus underlies hypervigilance, a symptom observed in patients with post-traumatic stress disorder. Further, the authors integrate observations in the LC with those in lateral PBN, contributing to ongoing efforts to understand how the brain functions as a system. Finally, although not the focus of the study, Yang and colleagues also make a significant contribution to the understanding of complex neural systems by detailing both new evidence of noradrenaline and glutamate co-transmission and its possible consequences. The ultimate functional outcomes of this co-transmission have yet to be determined and present an intriguing path for future research.

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# Anterior cingulate and putamen neurons flexibly learn whether a hot dog is a sandwich

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**Policy search lets you discover rules and adapt behavior. In this issue of *Neuron*, Cohen et al. (2021) demonstrate that the dynamics of neurons in primate anterior cingulate cortex and putamen indicate when a correct policy is discovered and confidence in executing decisions under that policy.**

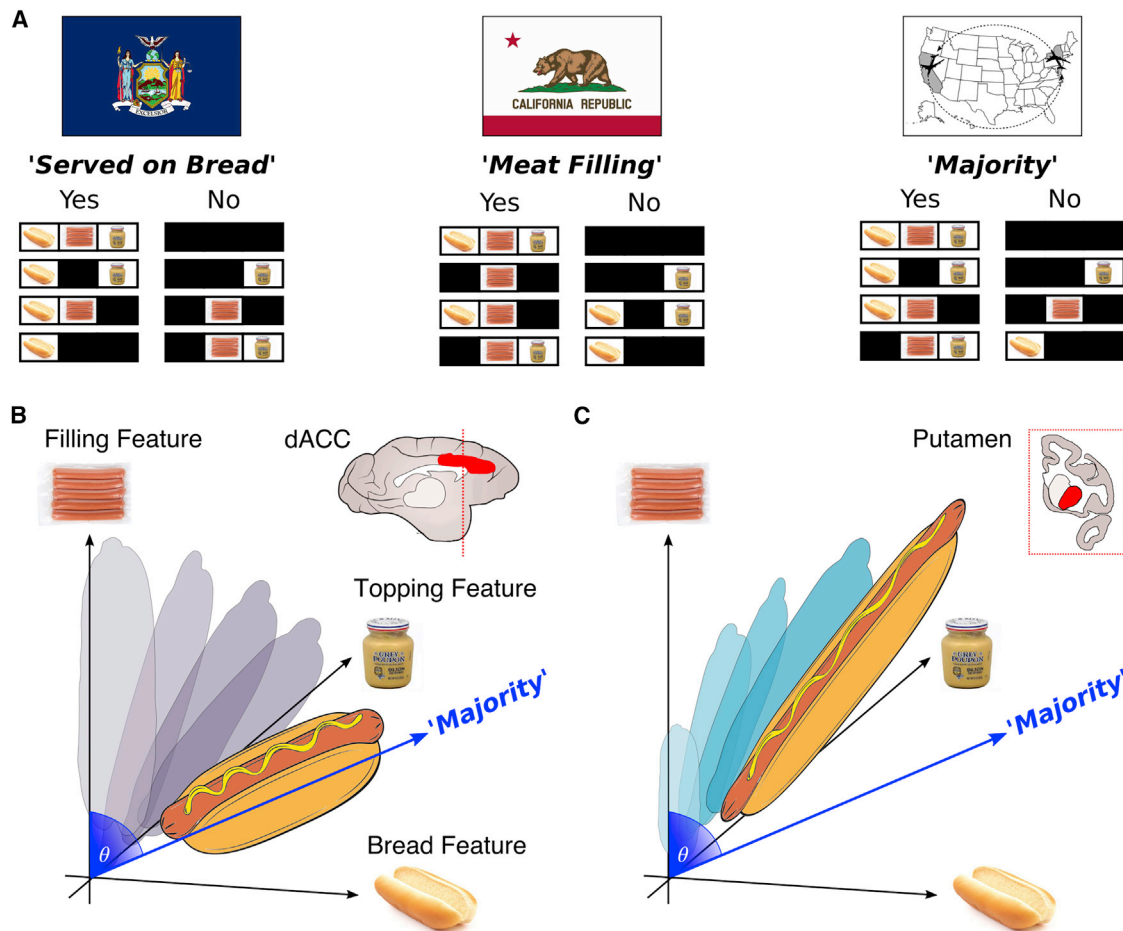
The hot dog is an American cultural and culinary institution, but is a hot dog a sandwich? One reason this question remains hotly debated is that there are many rules surrounding what constitutes a sandwich in the United States. A hot dog ordered in New York is legally categorized as a sandwich as long as it is served on bread. A hot dog ordered in California is categorized as a sandwich if the sausage casing contains a meat filling (Park, 2019). If you want to know which rule to follow, you must learn which fea-

tures of a hot dog indicate whether it is a sandwich or not (Figure 1A). But not all rules are defined by single features, and learning more complex rules can be useful for generalizing across contexts. For instance, another useful rule for categorizing a hot dog is whether a majority of its features overlap with those of a sandwich.

While frontostriatal circuits are known to contribute to behavioral flexibility and category learning after extensive training (Miller and Cohen, 2001; Mansouri et al.,

2020), the neural dynamics of individual neurons in cortex and striatum during the acquisition of newly learned rules remains largely unknown. In this issue of *Neuron*, Cohen and colleagues (Cohen et al., 2021) demonstrate a geometric way of representing the activity of individual neurons in the primate dorsal anterior cingulate cortex (dACC) and putamen that reveals the contributions of each region to category learning. By mapping neural activity into a multidimensional space where a rule is represented as a





**Figure 1. Geometric representations of neural dynamics in dACC and putamen during rule learning**

(A) A schematic for answering whether a hot dog is a sandwich based on three key features whose relevance varies across contexts.

(B) The neural vector representing the activity of dACC neurons (shown as a hot dog) is projected into the geometric space where the rule vector used to categorize whether a hot dog is a sandwich is defined. While searching for the correct rule, changes in neural activity cause the neural vector to rotate toward the rule vector.

(C) As confidence grows that the correct rule has been found, the neural vector representing the activity of putamen neurons increases in magnitude. In both (B) and (C), the light-to-dark changes in the hue of the hot dog contours reflect the change in neural vector dynamics over time.

weighted combination of multiple features, they show that the activity of individual neurons in the dACC reflects the monkeys' search for a new decision policy (Figure 1B), whereas the activity of individual neurons in the putamen reflects the monkeys' confidence in that same policy (Figure 1C).

In each session, the monkeys played a game where they were shown a cue made up of three features (i.e., bits) that could be turned on and off in various combinations on each trial. The monkeys viewed each combination of features and had to press a left or right button according to a rule they needed to learn. The rules could be simple, like

those used to decide whether a hot dog is a sandwich in New York or California (i.e., relying on only one feature). But the monkeys also attempted to learn more complex policies, like the majority rule, which categorizes an empty hot dog bun slathered in fancy mustard as sandwich (Figure 1A). The elegant task design allows the researchers to use the same set of three-bit patterns to probe learning of rules that are unique relative to each other. What this means is that perfect learning of one rule did not aid the monkeys' learning of additional rules.

Expectedly, the monkeys were better at some rules over others. Cohen et al.

(2021) took advantage of variability in the monkeys' performance by splitting the sessions into easy versus hard rules. This was done under the assumption that if the animals are learning more successfully during the easy sessions, greater learning-related changes in neural activity should exist. These changes should be most obvious at the end of the session when the animals have the most experience with the current rule. When the activity of dACC and putamen neurons at the end of the session was contrasted with activity at the beginning of the session, more neurons responded in ways that reflected the correct rule. As the monkeys' performance improved so

did the percentage of rule-encoding neurons in each brain region.

But how did the neurons actually change their encoding to signal the new rules? The experimenters take a geometric approach to representing neural correlates of learning by establishing a multidimensional feature space defined by possible patterns of the three-bit stimuli. Each rule can be represented as a “rule vector” projecting into this feature space (blue line in [Figures 1B](#) and [1C](#)). Then, the activity of individual neurons in response to each three-bit pattern was used to project a “neural vector” (hot dog contours in [Figures 1B](#) and [1C](#)) into the feature space. If the neuron responded in a selective way to patterns that matched a particular rule, its neural vector should be aligned with the correct rule vector.

[Cohen et al. \(2021\)](#) exploited this geometric framework to quantify *de novo* rule learning. They tracked how the rotation and magnitude of the neural vector changed relative to the rule vector over the course of learning. Rotation of the neural vector toward the rule vector decreased the angular distance between the two vectors. When the angular distance between the vectors decreased, it indicated that a neuron is adapting its response to each cue to be more selective for a particular rule policy. These rotational dynamics allow tracking of the monkeys’ search for a new decision policy at the individual neuron level.

The neural vector not only rotates, but it can also be extended ([Figure 1C](#)). Changes in the magnitude of the neural vector reflect increasing responsiveness to one or more features. [Cohen et al. \(2021\)](#) interpret these changes in neural vector magnitude as reflecting a change in the monkeys’ confidence in applying a particular rule. Neural vector magnitudes were larger in easy versus hard rules, but only in the putamen, and were correlated with a reduction in reaction times. These results support the idea that changes in vector magnitude reflect confidence in rule usage. It is important to note that changes in the rotation and magnitude of the neural vector can vary independently and that it is possible that different neural systems mediate the search for a new policy versus signaling confidence in executing that policy.

What does this geometric representation tell us about the neural underpinnings

of learning? In the dACC and putamen, strings of successful trials were followed by neural vector rotation toward the rule vector, and this was more common when monkeys learned easy versus hard rules. This shows that as the animals begin to formulate a new decision policy, neural representations in the dACC and putamen adapt accordingly. These results complement evidence that population vector coding by ensembles of amygdala neurons undergo a rotation and lengthening during fear learning and extinction ([Grewe et al., 2017](#)). An important question moving forward is in determining how the dynamics of neurons involved in learning new rules influences population-level representations of category learning, especially given evidence ([Sadler et al., 2014](#)) that monkeys find it difficult to learn rules that are misaligned with the intrinsic dynamics of a neural population. In the current study, there was no clear explanation for why the monkeys found it easier to learn certain rules over others. While behavioral training history might play a role, one possibility is that harder rules were constrained by the intrinsic dynamics of neural activity in the dACC and putamen. Determining how geometric representations of learning scale up from neurons to populations will therefore be informative in identifying general neural constraints on learning.

Neural vector rotations in the dACC tended to precede magnitude lengthening in the putamen by approximately three trials, suggesting that the policy search process is established in the dACC and then transferred to the putamen where confidence in the rule is strengthened with positive feedback. While prior studies have demonstrated incremental or hierarchical processing of the same computation (i.e., value) across multiple brain regions during learning ([Costa et al., 2019](#); [Klavin et al., 2013](#); [Morrison et al., 2011](#); [Rudebeck et al., 2013](#)), the current work is notable for its demonstration of both distributed and sequential processing of multiple computations fundamental to rule learning. But given that learning-related changes in the dynamics of dACC and putamen neurons slightly lagged changes in behavior, an important question remains. What brain regions are

involved in acquiring the rule such that their activity might *lead* behavior? Likely candidates are the dorsolateral prefrontal cortex or orbitofrontal cortex given their known roles in categorical learning, exploratory decision making, and behavioral flexibility ([Mansouri et al., 2020](#)).

If changes in the dynamics of individual neurons persist and reflect a long-term learning process, it should be possible to measure the angular distance between the neural vector at the end of session and the rule vector the monkeys would have to learn the next day and predict how quickly the monkeys would acquire the new rule. This relationship was evident for neurons in the putamen, but not in the dACC. From one day to the next, how quickly the monkeys learned the new rule was predicted by how closely the neural vectors of putamen neurons that encoded the rule on the previous day were aligned with the current rule vector. One implication of this finding is that geometric representations of neuronal activity during learning could be used to predict the persistence of adaptive or maladaptive rule usage. Such a metric might be especially important in predicting whether cognitive and behavioral interventions will reliably counteract maladaptive, habitual behaviors commonly observed in mental health and substance abuse disorders. For instance, endlessly ruminating on the question of whether a hot dog is a sandwich.

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