

# Unpacking self-ordered sequences

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In this issue of *Neuron*, Chiang et al. examine population coding of self-ordered sequences in prefrontal cortex. They find better decoding, more distributed information, and less variability when order is consistent. Consistent ordering produces reliable population response patterns that may aid planning and memory.

The tasks we perform in daily life frequently rely on a series of related actions: for example, packing each item in a bag when preparing for a trip. The steps in these tasks can be executed in any order, but must all be completed to successfully reach the end goal. These tasks impose a higher cognitive burden than isolated actions, since they require us to keep track of which steps have been completed and which remain to be done. Addressing this challenge effectively may depend on the behavioral strategy used for the task. If you use an established sequence order—always putting toothpaste in your suitcase after your shoes—knowing which item you *just* packed lets you know *all* those completed. This strategy also always gives you a prompt for the next item, minimizing your chances of missing it. Accordingly, well-trained animals will often choose to execute repeated sequences, and settle on highly efficient ones, even when there is no requirement to do so (Desrochers et al., 2010).

Chiang et al. (2021) examine how population activity in macaque lateral prefrontal cortex (LPFC) corresponds to behavior in a self-guided sequential saccade task (Figure 1A). In this task, monkeys were presented with six targets at different locations on the screen and moved their eyes (saccaded) to each target without repeats, returning to a central spot between each item. While monkeys performed well, they often made errors later in the sequence, returning to previously visited targets—somewhat like packing a second tube of toothpaste when you've already put one in your bag. Error frequency depended on monkeys' behavioral patterns across trials (Chiang and Wallis, 2018). More consistent saccade

sequences produced better performance, and vice versa.

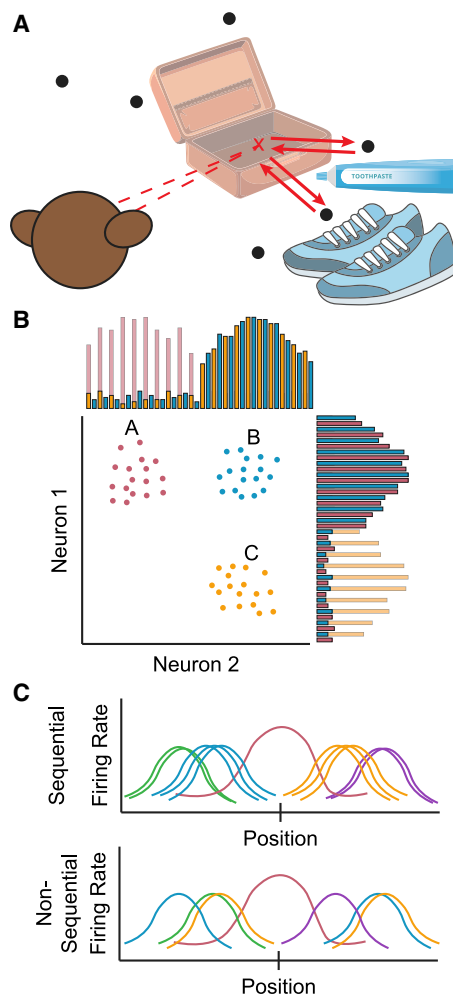
In a previous analysis, Chiang and Wallis (2018) were left with a puzzle as to how LPFC neurons were tuned to target locations. Other experiments have found that better behavioral performance correlates with sharper tuning. This phenomenon has been observed in primary sensory cortices (Ollerenshaw et al., 2014), high-level visual neocortical areas (Britten et al., 1992), and, more recently, the striatum during more efficient sequential performance (Desrochers et al., 2015). In contrast, Chiang and Wallis found that *less* sharp spatial tuning in LPFC correlated with better performance and more consistent saccade sequences. These results reversed the previously observed relationship between tuning and behavior, and raised the question of how behavior in this task improved when the specificity of single neuron responses decreased.

To address this puzzle, Chiang et al. conducted an ambitious set of population analyses. As they note, task performance depends on the entire network of neurons, not only single cells. The distribution of activity across neurons affects population-level information in ways that are not obvious in single cells (Figure 1B) (Quiroga and Panzeri, 2009). Chiang et al. used multi-class linear discriminant analysis (LDA) to evaluate how well ensembles of neurons could distinguish the target location and sequence position of saccades. LDA finds the weighted sum of activity that best separates different categories of data using all recorded neurons. The resulting weights are then used to “decode” individual target locations or sequence positions, and the proportion of correct classifications measures the infor-

mation about these variables in the population response.

The results revealed a solution to the neural tuning puzzle: decoding accuracy was higher in more stereotyped sequences even though single-neuron tuning was weaker. In other words, the population as a whole had more information about target locations and sequence position when sequence order was more consistent. Further, they found a wider distribution of information across the population in stereotyped sequences: individual neurons had less influence, but a greater number of them contributed to decoding, improving accuracy overall.

These results raised the question: what neural response features affected decoding accuracy and behavioral performance? One possibility was population response variability. Decoding relies on the ability to separate response patterns associated with different targets. Variability in responses to the same target can blur the boundaries between categories, reducing accuracy and leading to inconsistent classifications. The same factor might affect information decoding in the brain, contributing to behavioral errors. The authors examined variability using population dimensionality and found that it was higher for later sequence positions and less stereotyped sequences, when animals' performance was worse. These differences were interpreted as a signature of working memory load. This explanation is appealing, because working memory load is presumably higher later in the sequence with more previous targets to recall. Consistent saccade ordering may reduce that load: the association of a saccade target with a specific time in the sequence could provide an additional memory cue, and repeating



**Figure 1. Task and neural coding concepts from Chiang et al. (2021)**

(A) Monkeys performed self-guided saccades to six targets, returning to a central spot between targets. An analogous task, packing a suitcase for a trip, is also depicted (images from Vecteezy.com). In commonly performed tasks, even ones like packing a bag that do not have an intrinsic order, repeating a self-generated sequence can be advantageous.

(B) Higher-dimensional analyses provide information that is not available from single cells. A two-dimensional case is illustrated: Neuron 1 responds strongly to targets A and B, while Neuron 2 responds to targets B and C. Individually, neither neuron's response can uniquely identify target B (histograms on top and right axes), but when both neurons are combined in a two-dimensional space, all targets are easily distinguished.

(C) Hypothetical responses across five sequence steps for consistent and inconsistent sequences. Colors represent neurons with five different preferred targets (green, blue, red, yellow, and purple). When sequence order is consistent (top), overlapping responses to past and future targets provide information about the current state. For example, moderate activation in the blue and yellow neurons indicates that it is the third step in the sequence and the current target is red. If order is random (bottom), each target can come before or after any other, so overlapping activation is uninformative.

saccade order may decrease interference across trials.

Other factors may also contribute to the observed differences in dimensionality. Previous analyses from Chiang and Wallis (2018) showed that LPFC neurons encode information about past and future saccades in addition to the current target. Such layering of information, where paral-

lel planning of multiple steps gives rise to the appearance of differential coding, has been observed in the frontal eye fields (Basu et al., 2021) and motor cortex (Zimnik and Churchland, 2021). Responses to previous and upcoming targets could explain differences in dimensionality. When target order is stereotyped, responses to past and future targets will

overlap with each other in consistent ways on each trial (Figure 1C, top). These activations can, in turn, provide an informative cue for behavior due to their predictability. In contrast, when saccade order varies, responses to past and future targets will change across trials, increasing variability in the response pattern (Figure 1C, bottom). These signals are then less informative for behavior and decoding. Future work will be needed to determine whether parallel processing of past and future actions improves performance during stereotyped sequences and how this process interacts with working memory.

The results of this study raise important questions about the nature of behavioral sequences. In previous studies of action sequences, animals' strategies evolved to become more stereotyped over time (Desrochers et al., 2010). In contrast, animals in this study showed different degrees of stereotyped behavior across sets, but their use of these strategies did not appear to change with time. This may be because the variety of displays and their frequency of use did not encourage more habit-like behaviors as in Desrochers et al. (2010). Instead, sequential performance in this task may reflect a heuristic to simplify the repeated performance of similar actions without necessarily optimizing long-term efficiency. This difference raises the intriguing possibility that this task may reflect a distinct element in the taxonomy of sequential behaviors, opening a promising path for further research.

Along with these questions, there are a few caveats to consider. First, decoding methods impose categorical boundaries that may not reflect the structure of data. While not a critique of the current study, this limitation will be important to keep in mind for future experiments. Second, it is unclear from the current study whether the use of stereotyped sequences reflects an explicit strategy, as opposed to random variation or implicitly learned behavior. This distinction may go beyond semantics when considering that different neural systems may be engaged in sequences that are executed implicitly and explicitly. Despite these points of uncertainty, these findings are important for how we think about the relationship between neural coding and behavior in the

frontal cortex and potentially elsewhere in the brain.

Integrating these findings into the context of broader cognitive processes and neural systems will be a key direction for future research. Elements of planning, memory, and choice may all contribute to the observed neural signals in LPFC, and disambiguating these processes will be important for understanding high-dimensional data. LPFC is also connected through well-known anatomical and functional loops with basal ganglia structures thought to be responsible for habitual behaviors (Graybiel, 2008). Apparent differences in tuning between the striatum (Desrochers et al., 2015) and LPFC (Chiang et al., 2021) during sequential actions may result from behaviors that are not quite habitual, or, perhaps more intriguingly, might be a feature of their cooperative function. Sharper tuning in single striatal neurons could give rise to more distributed, flatter coding in the LPFC that could be considered more general and enable parallel planning. In combination with causal manipulations, answering these questions will be essen-

tial for determining how components of neural activity contribute to sequential behavior and understanding how sequential behaviors are planned and executed.

Ultimately, this study raises new ways that sequential behavior (goal-directed or not) can aid behavioral performance, connect to memory processes, and shape the response structure of neurons in the brain. Chiang et al. have decoded the key to keeping track of the items we put in our suitcases: following the same order every time.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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## Weighing the evidence in sharp-wave ripples

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In this issue of *Neuron*, Krause and Drugowitsch (2022) present a novel approach to classifying sharp-wave ripples and find that far more encode spatial trajectories than previously thought. Their method compares a host of state-space models using what Bayesian statisticians call the model evidence.

Imagine you are navigating a large Scandinavian furniture store. You find yourself in the *Children's Rooms* section with who-knows-how-many miles to go before checkout. It didn't take so long last time you were here... You recall weaving your way through *Kitchen and Dining* into *Home Office* and *Children's Rooms*, and then you remember. There was a shortcut, hidden behind a brown-black

lacquered wardrobe, that led straight to the exit!

What neural mechanisms might facilitate the recollection of past experiences and the formation of mental models of the environment? Rodents performing spatial navigation tasks, albeit in less-enriched environments, seem to perform similar mental computations. As animals move through their environment, place

cells in the hippocampus fire in a spatially localized manner to represent the animal's current location. Every so often, when the animal pauses, there are brief bursts of spikes in the hippocampus that give rise to sharp-wave ripples (SWRs) in the local field potential. In a fraction of SWRs, the burst involves a sequence of spikes across neurons with adjacent place fields. In other words,

