

to express an association between two events separated in time. Specifically, Guo et al. (2019) propose that cholinergic neurons support learning by providing information about both conditioned and unconditioned stimuli as well as providing ongoing activity spanning the time until the outcome. These observations raise several questions, especially related to the sustained activity within BF after days of conditioning. For example, how does the BF, itself, learn this association between the CS and US? Are cholinergic cells a substrate for learning, or are they inheriting information learned elsewhere in the brain? Additionally, fiber photometry allows researchers to measure population activity, but it does not offer insight as to what individual cells are doing. Is the sustained cholinergic tone the result of individual neurons remaining active across an interval, or are individual cells “tiling” the time interval? Furthermore, after these many days of conditioning, are neurons in A1 also subtending the interval (as would be predicted from studies in V1; Hussain Shuler, 2016)? If so, does the incoming cholinergic signal influence circuit mem-

bers to allow for such plasticity? To answer these questions, future researchers should take inspiration from this current work and use multiple, cutting-edge techniques to gain insight into brain function.

Together, this comprehensive set of experiments advances cholinergic BF neurons as a crucial player in learning and expressing associations between cues and the behaviorally relevant events that they predict.

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## Why Are Sequence Representations in Primary Motor Cortex So Elusive?

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<https://doi.org/10.1016/j.neuron.2019.09.011>

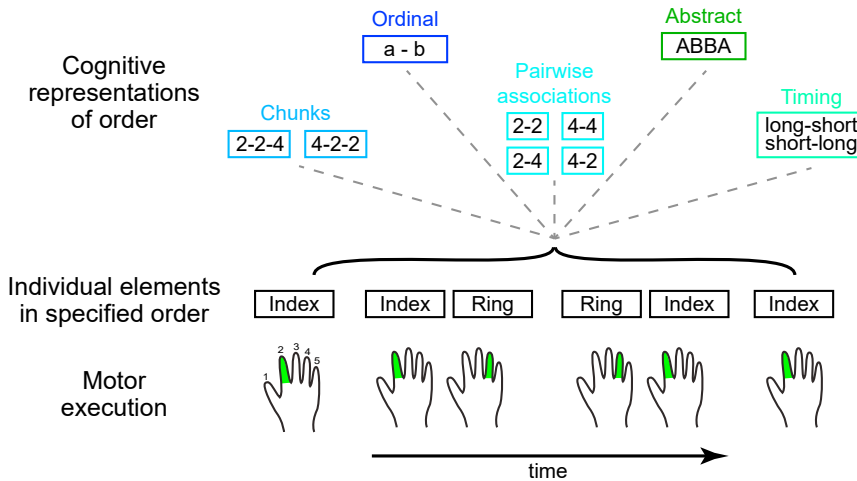
In this issue of *Neuron*, Yokoi and Diedrichsen (2019) use a finger keyboard task to show that sequences are widely represented across cortex but that only single elements are represented in primary motor cortex. These results suggest that sequence tasks primarily probe the ability to order discreet actions rather than to execute a skilled continuous sequential action.

Whether anticipating the next word in a sentence, an opponent’s upcoming move, or the timing of a green traffic light, we are constantly trying to predict and respond to what will happen next. Predicting future events enables quick re-

sponses—in some cases, even circumventing inherent sensory delays in order to initiate responses simultaneously with the upcoming event. This results in the tendency to treat sets of spatial and temporal events as ordered sequences, or to

learn the likelihood of associations between two or more events, in order to make inferences about the future. Many daily actions are also organized into sequences, ranging from key presses when playing the piano to the routine of





**Figure 1. Cognitive Representations of Event Order Support Motor Sequences**  
Hierarchical information ranging from pairwise transitions and timings to abstract representations of events and chunks together determine the sequential order in which individual movements are to be executed.

making a cup of tea. Performing events in the wrong order can lead to unfortunate consequences, such as a cacophony of noise or a cup of cold, unbrewed tea. This inherent preference for detecting, remembering, and performing sequences has given rise to the strong interest in studying the process by which they are learned, executed, and represented.

One area that has shed light on how individuals predict subsequent sequential events is the study of motor sequence learning. Such tasks have been taken to be, at least in part, a model for studying sequential continuous actions, such as the smooth multi-componential motion of a tennis serve or the well-timed agonist-antagonist bursts of muscle activity during a simple reach. The assumption is that such continuous behaviors arise by merging together motor primitives in the proper order to create a new behavior. Thus, in an effort to investigate how such skilled sequential actions are learned, researchers have turned to discrete action sequences such as learning to press keys in the proper order (e.g., [Robertson, 2007](#)).

A potential concern, however, is that discrete action sequences are learned by assembling a set of individual actions that are, in and of themselves, already part of the existing movement repertoire. Thus, discrete action sequences may only reveal how people learn to specify in-

dividual components in the proper order and how that *order* is represented ([Krakauer et al., 2019](#)). Indeed, behavioral evidence from motor sequence tasks suggests that any performance advantages associated with executing sequences over random movements arise from knowledge of the sequence order ([Wong et al., 2015](#)) and its temporal structure. Such knowledge can generalize across effectors as well as to sequences that retain the same stimulus order even if the movements associated with those stimuli change (for review, see [Krakauer et al., 2019](#)). In contrast, in a continuous sequential action for which the subcomponent boundaries are not readily discernible, the concern is largely with how the motor system executes the proper time-varying, continuous motor command. Critically, in this latter case, the individual subcomponents and their order may not need to be overtly represented; instead, there might be a distinct signature for the entire compound behavior in primary motor cortex (M1) after the continuous sequential action has been overlearned, a point we will return to later.

In discrete action sequences, knowledge of sequence order is largely thought to be organized hierarchically. Small sets of single events are organized as chunks, which in turn may be grouped into sets of chunks and so forth until ultimately the

entire sequence is represented. Interestingly, when the notion of chunking was introduced, chunks were defined as abstract representations of the subcomponent items rather than actual movements ([Johnson, 1970](#)). Hence, a “motor” chunk, rather than being a single movement consisting of an amalgamation of simpler motor primitives, is better thought of as a cognitive fragment of ordinal abstractions of these actions ([Figure 1](#))—that is, chunks and higher-order sequence representations encode *information* about movement order in an abstract sense. This enables efficient storage and recall of the entire sequence rather than having to laboriously recall the individual movement elements and their pairwise transitions each time the sequence is to be produced. At the behavioral level, systematic changes in reaction time are often cited as evidence for chunking: reaction times between successive movements in a sequence are typically longer across chunk boundaries than within chunks, with inter-chunk reaction times generally increasing with the number of elements in the chunk. Moreover, rearranging the order of chunks in a sequence allows individuals to retain a performance advantage over performing a completely novel movement sequence. However, because this evidence of chunking is expressed as fragments of movement sequences, it has been challenging to distinguish whether we are examining the consequences of abstract representations of sequence order (i.e., chunking) or the merging of component movements into a continuous sequential action.

The body of work from [Diedrichsen](#) and colleagues has made important strides toward distinguishing whether sequence tasks capture either learning of discrete sequence order or construction of continuous sequential actions. In the study in this issue of *Neuron*, they examined the neural representation of individual sequence elements and of higher-order sequence units such as chunks and whole sequences ([Yokoi and Diedrichsen, 2019](#)). Importantly, [Yokoi and Diedrichsen \(2019\)](#) found a clear segregation in how sequences are represented. M1 appears to represent individual movement elements (i.e., finger presses) but contains no chunk or sequence representations

(see also [Beukema et al., 2019](#)). That is, M1 is concerned only with executing discrete movements, and despite clear signs of sequence learning, there is no evidence of a new representation arising from consolidation of those discrete movements into a single continuous sequential action. Nor is there evidence that spatiotemporal sequence information is represented in M1. Instead, information about the order in which those discrete actions are to be executed is represented outside M1: chunk and whole-sequence representations were only found in premotor and parietal cortices. In line with these findings, dynamical systems analysis has revealed that whereas M1 is primarily concerned with representing the current movement event to be executed, higher-order motor areas such as the SMA can keep track of the number of repetitions of that event (i.e., temporal and ordinal structure) ([Russo et al., 2019](#)). Such analyses also reveal that within M1, execution and planning can occur simultaneously in separate neural subspaces ([Ames et al., 2019](#)); consequently, whereas neural activity corresponding to the preparation of the first movement would be distinct, executing ongoing movements would blur the neural signature of planning future actions, potentially contributing to the prominence of the first-finger representation in M1 ([Yokoi and Diedrichsen, 2019](#)).

[Yokoi and Diedrichsen \(2019\)](#) demonstrated that information about sequence order is maintained across a large swath of the cortex. In a sense, this is not surprising. As we noted above, the brain is largely concerned about predicting upcoming spatial and temporal events; hence, it stands to reason that a fair share of neural resources would be devoted to various aspects of this task. The importance of anticipating event order is highlighted by the fact that two of the most prominent learning signals in the brain—reward prediction errors in the basal ganglia and sensory prediction

errors in the cerebellum—compare real-time observations with predictions about those events. Such predictions are supported by the ability to represent sequences comprised of stimuli, actions, and outcomes in several unique formats ([Dehaene et al., 2015](#)) ([Figure 1](#)) ranging from concrete transitions between specific events (e.g., a series of precise finger presses) to abstract sequence-element relationships (e.g., an alternating pattern of two different types of action events). In line with this variety of order representations, [Diedrichsen and colleagues](#) have previously demonstrated that the temporal and ordinal structure of sequences are represented separately in the brain ([Kornysheva and Diedrichsen, 2014](#)). This suggests that the reason [Yokoi and Diedrichsen \(2019\)](#) observed numerous cortical regions outside M1 that each represented chunks and whole sequences to different extents is because these regions are concerned with different temporal and spatial aspects of the sequence order at different levels of abstraction.

This work critically demonstrates that lab-based motor sequence tasks, as we have argued previously ([Krakauer et al., 2019](#); [Wong et al., 2015](#)), largely probe the brain's ability to represent the spatial and temporal ordering of discrete events. Indeed, the clear distinction between single-finger representations in M1 and higher-order sequence representations throughout frontoparietal regions of cortex imply that motor sequence tasks are predominantly cognitive tasks, which stress the ability to learn abstract structure or probabilistic associations, combined with sequence-independent practice executing the individual elements. Whether the representation of continuous sequential actions, such as a tennis backhand, is comparable to that of sequences of discrete actions is an empirical question, but our guess is that it will not be. Instead, discrete motor sequence tasks are better suited for

providing insight into the cognitive question of how we represent the spatiotemporal ordering of events in order to anticipate the future. In light of these results, the next challenge will be to devise a finger-based task that captures acquisition of the ability to execute a skilled sequential action, thereby making it more likely to depend on the intrinsic dynamics of primary motor cortex.

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