



Geometrical representation of serial order in working memory

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Summary

Encoding a sequence relies on one's memory for ordinal succession of events and is critical for episodic memory, spatial navigation, language, and other cognitive functions. Investigating the neural mechanisms underlying sequence working memory in the macaque prefrontal cortex, Xie et al. (*Science*, 375, 632–639, 2022) uncovered a novel integrated representation of temporal and spatial information in different subspaces of a high-dimensional neural state space, offering broad implications across comparative cognition and neuroscience.

Keywords Neural manifold · Prefrontal cortex · Episodic memory · Temporal structure · Sequence memory

Sequences are central to many human activities. For example, a sequence of remembered actions is used in cooking. Similarly, to dial a phone number you need to remember the numbers in the correct order. Our personal memories also comprise sequences of events that unfold over time.

Despite the ubiquity of ordinal information in our lives, little is known about how the brain encodes and stores this information. One theoretical possibility is that sequence representations are factorized, where individual items are separated from their ordinal rank within the sequence and stored in distinct memory slots, like theories of cardinality or object file representations (e.g., Hauser & Carey, 2003). Sequences can be factorized into representations of temporal order and spatial location. For sequence working memory (SWM), separate representations for temporal structure and events allow for consistent ordinal components of a sequence to change while others remain intact, leading to faster generalization and novel inferences. For example, when rhesus monkeys engage in a simultaneous chaining task in which they select images on a touch screen in particular order (A→B→C→D→E), they show a “learning to learn” effect, in which acquisition increases with each newly introduced list (e.g., Templer et al., 2019). Numerous cognitive and neural findings suggest that absolute ordinal positional information is extracted and coded separately in slots, such that information about distinct items can fill the same slot, creating faster generalization. Yet slot-based views cannot account for all

the effects of working memory. Indeed, working memory is capacity limited, perhaps due to the number of slots (slot-based views) or the processing resources available (resource-based views), or some combination of both (Ma et al., 2014). Regardless of the extent to which slot-based views apply in serial contexts, how neural activity supports such a sequence memory that consists of temporal, ordinal, or spatial information remains obscure. A recent study by Xie et al. (2022) provides exciting evidence that there are population codes with distinct subspaces for each rank in a sequence. Their paper provides a vivid picture of what neural representation of temporal and ordinal information looks like in the brain.

Xie et al. (2022) uncovered a novel neural representation for sequences in the prefrontal cortex. Two macaques were trained on a delayed spatial sequence-reproduction task (see Fig. 1A in Xie et al., 2022) in which monkeys were presented with sequences of two or three spatial locations of a circular array on a screen. After a brief delay, monkeys reproduced this sequence by making saccades to locations presented during the sample phase in the correct order. Sequence recall decreased with sequence length, was highest for items presented at the start of the sequence (primacy effect), and fell to chance at the third item.

Two-photon calcium imaging was used to record from thousands of neurons in the lateral prefrontal cortex (LPFC), a principal area associated with working memory, to uncover the organization of neural codes maintaining this serial information. Using dimensionality analyses, they decomposed the population activity observed at the end of the delay period before monkeys had to respond, uncovering subspaces for each position in the sequence. Further, each subspace contained a ring-shaped manifold, or low-dimensional structure in the subspace, that represented the different targets in the circular array. In other words, the similarities in shape between the circular array on the screen and the shape of these manifolds reveal the preservation of the geometric relations of the stimuli presented during

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the sample phase of the task. The size of this ring decreased for each position in the sequence, correlating with a decrease in encoding strength. Further, on trials in which monkeys were incorrect, the representational ring structure did not appear.

The remarkable geometric structure displayed during the delay was stable throughout single trials, across trials and even across days, suggesting long-term stability of the code. The authors observed multiplicative gain modulation at a population level, meaning that large populations of neurons were responsible for combining multiple pieces of information such as item and order. Though this binding of item and ordinal information has been proposed to be accomplished by PFC neurons before (Botvinick & Watanabe, 2007), Xie et al. (2002) showed that this gain modulation occurs at a collective level. They were therefore able to reject a single neuron account, which would indicate individual neurons have fixed spatial tuning curves.

Temporal-spatial associations were found at the population level, suggesting that the integration of order and space occur collectively, in overlapping neural activity within the LPFC. Mirroring the behavioral pattern of higher accuracy at the beginning of sequence, the researchers found that more neurons contributed to rank 1, then rank 2, and rank 3, suggesting that perhaps less attention or more confusion occurs later in the list. Indeed, at the neural population level there was confusion of nearby locations and overlap with adjacent subspaces as shown by ordinal rank error patterns, which were less frequent at the beginning of the sequence. The finding that errors associated with overlapping subspaces is an especially powerful result because it suggests that these representations are being used to guide behavior; however, the authors did not directly examine this correlation. They also confirm classical behavioral effects in serial recall while providing a mechanistic explanation for recall of sequences in working memory. There was more overlap in subspaces as the rank increased, reflecting Weber's law, which is classically observed across a broad range of ordinal tasks. Like erring when dialing the last few digits of a phone number, transposition errors are more likely to occur later in the number sequence. Though it is well known that monkeys (and other species) display Weber's law in a variety of ordinal tasks including similar sequence reproduction tasks (e.g., Akre & Johnsen, 2014), the authors did not test for Weber-like effects. However, they show for the first time that these behavioral effects correspond to exactly what we see at the neural population level.

The findings from Xie et al. (2022) are compelling for multiple reasons. The authors extend population state space approaches to cognition by finding evidence for storing information in distinct subspaces of the same neural population activity. Not only do the authors provide a novel neural correlate for sequence representations using population subspaces, but they also provide evidence that each subspace contains a manifold that mirrors the geometric properties of the stimuli to be recalled. Sustained spatially overlapping patterns of brain activity reflected monkeys' memory for item position and order, suggesting that our inner representations of the world may be constructed to mirror our outer perceptions.

While the data provided by Xie et al. (2022) are revelatory, caution is advised in using these results to further theories of cognition and behavior. While Xie et al. uncovered a startling representational mechanism for sequence memory that utilizes distinct subspaces in high-dimensional neural population activity, the computational operations performed on such representations remain to be elucidated. The behavior in the task was not modeled. Without such behavioral modeling, the computations underlying performance remain unclear; in particular, the ramifications of their results for understanding whether working memory is capacity-limited in the number of slots or resource-limited in the distribution of attention or other cognitive factors remains unresolved. Regarding slot-based views, Xie et al.'s results tantalizingly suggest that the function of slots can be performed by a single population by representing distinct items in different subspaces of the same population activity. But their results are also consistent with resource-based views, as the quality of subspace representations clearly degrades across the items in a sequence, or with a combination of resource- and slot-based views, where the subspaces are noisy slots. Additionally, there are many types of sequence tasks in the comparative cognition and neuroscience literature, and it is unclear if the geometry of disentangled representations would extend to other ordinal paradigms. The task presented in Xie et al. is relatively simple and it will be exciting for investigators to use similar methods in tasks that capture other elements of ordinality such as with fixed orders that are either learned or inferred (e.g., Templer et al., 2019). Notably, more work is required to determine the joint neural and cognitive mechanisms responsible for SWM. By combining powerful neuroscience analyses, like those discussed here, with rigorous behavioral work and carefully considered test paradigms, it will be possible for us to better understand the mechanisms of and computations for ordinal SWM.

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