

Segregated Neuronal Populations in Prefrontal Cortex Encode Task Variables during Working Memory

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Abstract

Mixed selectivity, with neurons responding to diverse combinations of task-relevant variables, has been proposed as a key mechanism to enable flexible behavior and cognition. However, it is debated whether neural population responses in prefrontal cortex are better described as random mixed-selective or as non-random, that is, in terms of multiple subpopulations with stereotypical response profiles. Here, we show that neural activity in macaque prefrontal cortex during a working memory task is organized into subpopulations that provide a comprehensive description of the low-dimensional population dynamics. Using demixed-PCA and model-free clustering, we find that stimulus identity, task condition and elapsed time are encoded in the population activity with a significant degree of clustering, incompatible with random mixed selectivity. Examining the contribution of stimulus-selective neurons to task condition-related variance reveals two contrasting activity profiles that correspond to functionally different populations, one responding during visual stimulation and the other one during memory maintenance. Finally, the observed neural geometry explains how stable task and stimulus information can be read out from the population response. Our results highlight that despite the heterogeneity of prefrontal responses during working memory, neurons do not represent random mixtures of task features but are structured according to neural subpopulations.

Keywords: working memory; prefrontal cortex; neural population code

Encoding of task variables in PFC

We used demixed-PCA (Kobak et al., 2016) to understand how different task variables (cue stimulus, task condition, and elapsed time) are represented in the PFC population activity during working memory and visual tasks (Markowitz, Curtis, & Pesaran, 2015) (Fig. 1). As has been observed previously, two stable stimulus components reflect the two-dimensional task geometry, yielding a stable representation of the x and y coordinates of the visual cues (Fig. 1b). The neural activity

along the task dPC shows that the neural representation during the memory and visual conditions diverges at cue offset when both experimental conditions become distinguishable. The three non-selective time dPCs reflect firing rate changes during the cue period and ramping activity before the cue and during the delay. Together, these six most-variance-explaining dPCs account for 43.9 % of the variance.

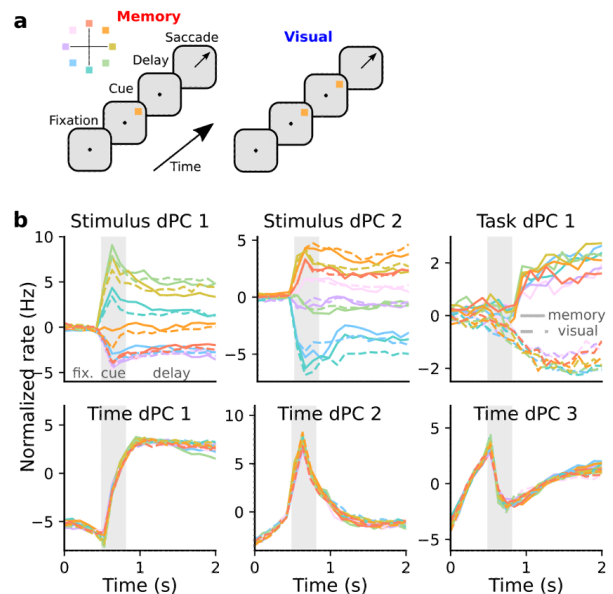


Figure 1: Encoding of task variables in PFC. **a**, Task design, with memory trials (0.3 s cue period and 1.2 s delay) and visual trials in which the cue is presented the whole trial. **b**, Time-course of the demixed PCs. The data were projected onto the respective dPCA decoder axis, so that there are 16 lines (8 cue locations and 2 task conditions).

Non-random population structure

We found that individual neurons express these task-related features in a structured manner. We measured the distribution of selectivity to task variables with the elliptical Projection An-

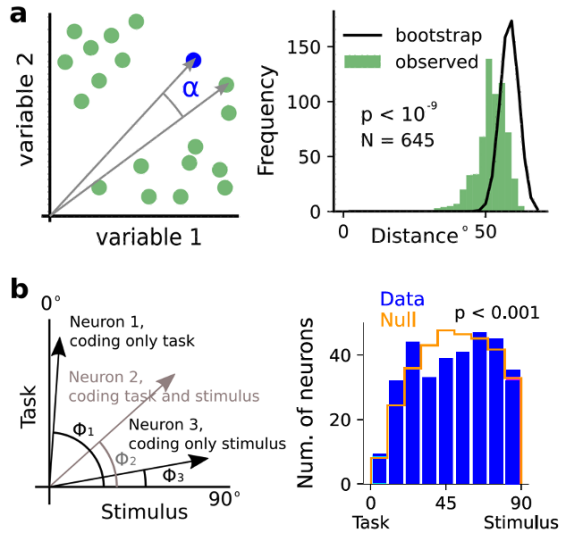


Figure 2: Neuronal activity modes in PFC are supported by distinct neuronal populations. **a**, The ePAIRS test compares the distribution of angular distances α between nearest neighbors (left panel) to a null distribution. Right: A lower mean α of the data is indicative of significant clustering. **b**, Distribution of stimulus and task selectivity. Left: the degree of mixed selectivity specifies an angle ϕ in the task-stimulus plane. Right: data and null distributions. Note the null distribution is not flat because we combine the two orthogonal stimulus dimensions.

gle Index of Response Similarity test (ePAIRS; (Raposo, Kaufman, & Churchland, 2014; Hirokawa, Vaughan, Masset, Ott, & Kepecs, 2019)). This measure compares the distribution of angular distances between neurons, given by their contribution to different task variables (dPC weights), to a null distribution generated by bootstrapping from a multivariate distribution with the same covariance (Fig. 2a). The test robustly indicates that neuronal selectivity to stimulus identity, task condition, and elapsed time is non-randomly distributed across the prefrontal neurons ($p < 10^{-9}$ for taking between 6 and 20 PCs, the latter explaining 67.4 % of the variance). To gain a more detailed insight into the population structure, we measured the degree of mixing between selectivity for stimulus identity and task condition among the neurons. We computed the distribution of angle ϕ , which is 0° for purely task-selective and 90° for purely stimulus-selective neurons (Fig. 2b). We observe fewer mixed neurons (with angles ϕ around 45°) than would be expected by chance. Consequently, neuronal selectivities for stimulus and task are distributed (mixed) in a non-random, structured manner.

Geometry of population activity

Next, we show that a subpopulation of *cue* and one of *memory* neurons are crucial for understanding the low-dimensional neural representation and decoding. We selected 156 neurons that show structured mixed (distributed) selectivity for

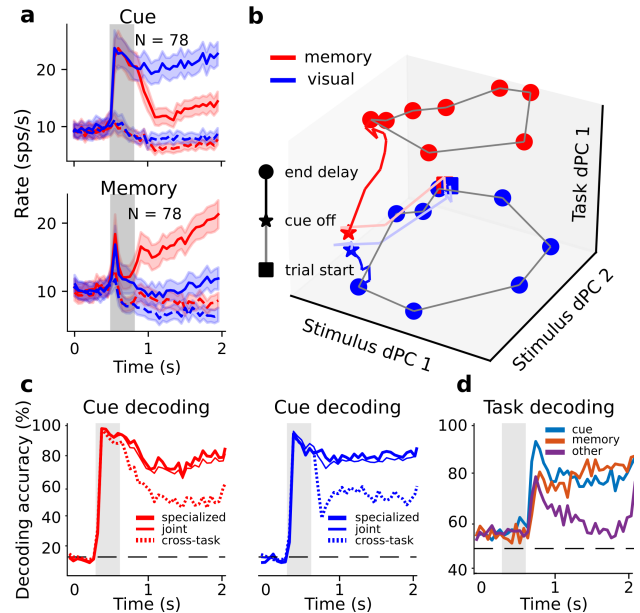


Figure 3: Structure of population activity. **a**, Average firing rates of neurons classified by their dPCA weights of the task component. Solid lines indicate preferred and dashed lines non-preferred cues. **b**, Geometry of the neural representation at the end of the delay for memory and visual trials (red and blue circles) and representative trajectories for one cue, obtained from demixed-PCA (Fig. 1b). **c**, Decoding of cue and task information from the population activity ($N = 650$ neurons) using a linear SVM decoder. **d**, Decoding of task condition from different neuronal groups (each cue and memory: $N = 78$, other: $N = 494$ neurons).

stimulus and task condition (Fig. 2b) and divided them in two groups according to the sign of their weight on the task dPC. The average firing rates of these populations shows how the selectivity for task and stimulus is distributed among the prefrontal neurons (Fig. 3a). Cue neurons respond during stimulus presentation (during the cue period in the memory task and until the end of the trial in the visual task) and they reduce activity during the delay in the memory task. In contrast, memory neurons sustain the stimulus during the delay in the memory task and show only weak activation during the visual task. The presence of cue and memory neurons helps to understand the neural trajectories in a 3-dimensional space, spanned by the 2 stimulus-related dPCs and the task dPC (Fig. 3b). These low-dimensional trajectories capture the essential task dynamics: at the beginning, all stimulus and task conditions are equivalent; when the cue is presented, trajectories split according to cue location along the stimulus axes, and finally, at the moment when the cue is removed in the memory task, the trajectories corresponding to different tasks diverge along the task-relevant dimension (Fig. 3b). The geometry of the neural representation suggests that a single decoder should be able to read out the cue information for both

tasks. Indeed, a decoder trained on both memory and visual trials achieves the same decoding performance as two separate decoders for each task (Fig. 3c). The separate decoders, on the other hand, do not generalize to the other task which is explained by the contrasting activity profiles of the cue and memory neurons. Finally, the task condition can be reliably decoded from the activity of either the cue or the memory neurons, which are task-selective but not from all the remaining neurons (Fig. 3d).

Conclusion

We have shown that in macaque prefrontal cortex stimulus and task information during working memory is encoded in a distributed, non-random way in neural populations with different response profiles. Our results suggest that cortical populations responses in basic working memory tasks may share the same organization principles across primates and rodents (Yang, Tipparaju, Chen, & Li, 2022).

Acknowledgments

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References

- Hirokawa, J., Vaughan, A., Masset, P., Ott, T., & Kepecs, A. (2019). Frontal cortex neuron types categorically encode single decision variables. *Nature*, *576*(7787), 446–451.
- Kobak, D., Brendel, W., Constantinidis, C., Feierstein, C. E., Kepecs, A., Mainen, Z. F., ... Machens, C. K. (2016). Demixed principal component analysis of neural population data. *eLife*, *5*, 1–36.
- Markowitz, D. A., Curtis, C. E., & Pesaran, B. (2015). Multiple component networks support working memory in prefrontal cortex. *Proceedings of the National Academy of Sciences*, *112*(35), 11084–11089.
- Raposo, D., Kaufman, M. T., & Churchland, A. K. (2014). A category-free neural population supports evolving demands during decision-making. *Nature Neuroscience*, *17*(12), 1784–1792.
- Yang, W., Tipparaju, S. L., Chen, G., & Li, N. (2022). Thalamus-driven functional populations in frontal cortex support decision-making. *Nature Neuroscience*, *25*(10), 1339–1352.