Correlated variability modifies working memory fidelity in primate prefrontal neuronal ensembles

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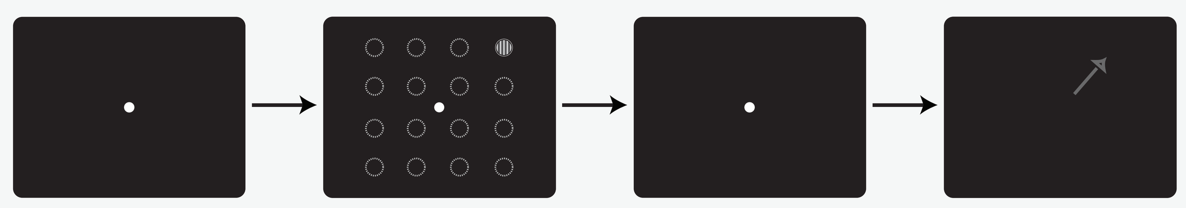
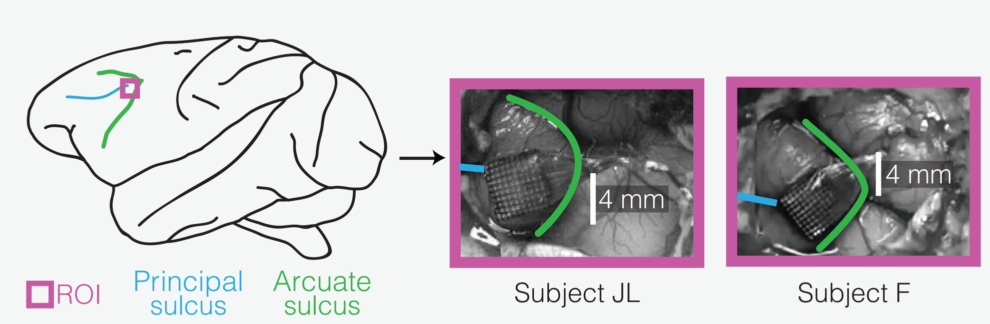
Introduction

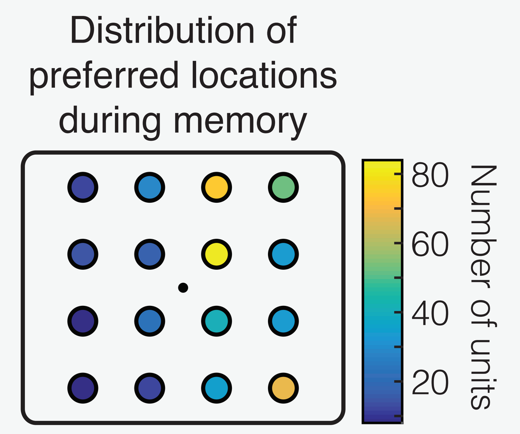
Single neurons in the primate lateral prefrontal cortex (LPFC) are thought to encode working memory (WM) representations via sustained firing, a phenomenon hypothesized to arise from recurrent dynamics within ensembles of interconnected neurons. WM has been extensively studied at the level of single neurons, and pairwise neural recordings indicate that WM maintenance modifies correlated variability between neurons (i.e. noise or spike count correlations—r_{sc}) but **we lack an understanding of how neuronal ensembles represent WM: we do not know if r_{sc} affects WM coding, nor how WM coding properties scale with the size and composition of neuronal ensembles.**

Spatial working memory (WM) task



Multielectrode array recording

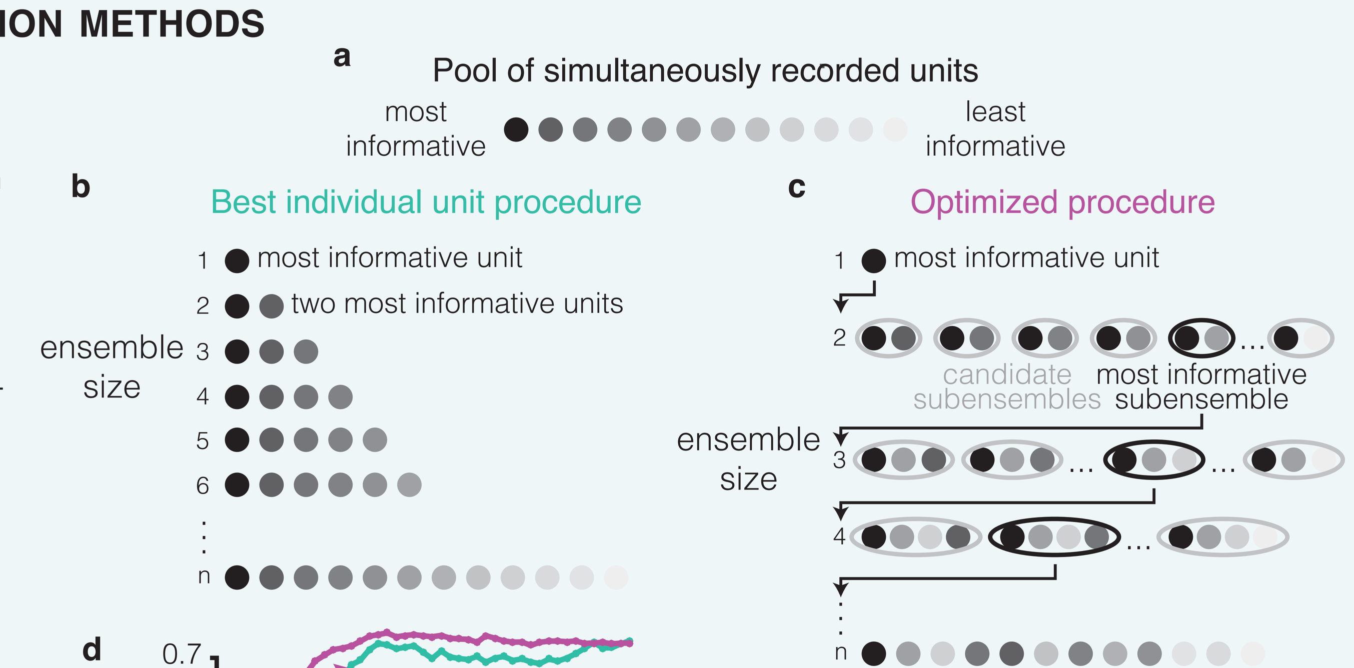


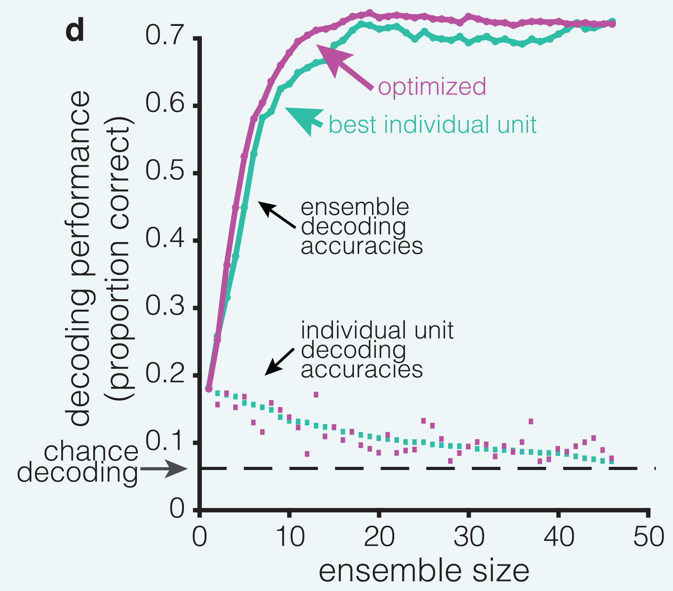


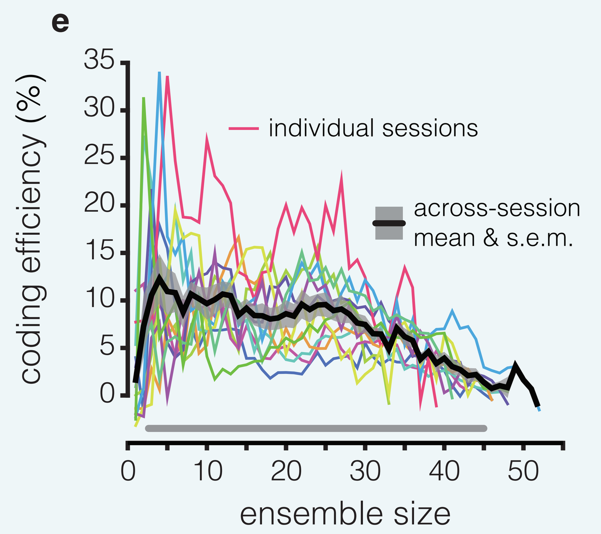
Two *Macaca fascicularis* were implanted with 96-electrode microarrays (Blackrock Microsystems, Utah) in LPFC area 8a. We recorded 545 single- and multiunits across 12 recording sessions. Ensemble sizes ranged from 30-50 units.

Neuronal ensemble construction methods

The effects of the rsc structure have been proposed to increase with ensemble size, but most of our knowledge about these scaling effects is drawn from extrapolations of pairwise recordings. In order to determine how WM coding scales across ensemble configurations, we devised "ensemble construction" procedures: **(a)** First, a linear classifier (a support vector machine—SVM) was used to quantify each unit's WM information during the delay epoch; **(b)** in the **best individual unit procedure**, we iteratively constructed neural ensembles based on the individual units' rank-ordered WM information content; **(c)** in the **optimized procedure**, we used the SVM to find the unit that added the most information when paired with the most informative unit. We then used this "most informative pair" as the basis for finding the trio of units that maximized WM information, then used this trio as the basis for finding the most informative quartet, etc. **(d)** Results for the **best individual unit** and **optimized** procedures, applied to a single example session. **(e)** % change in decoding accuracy (i.e. coding efficiency) of the **optimized** ensembles relative to the **best individual unit** ensembles, across all sessions.

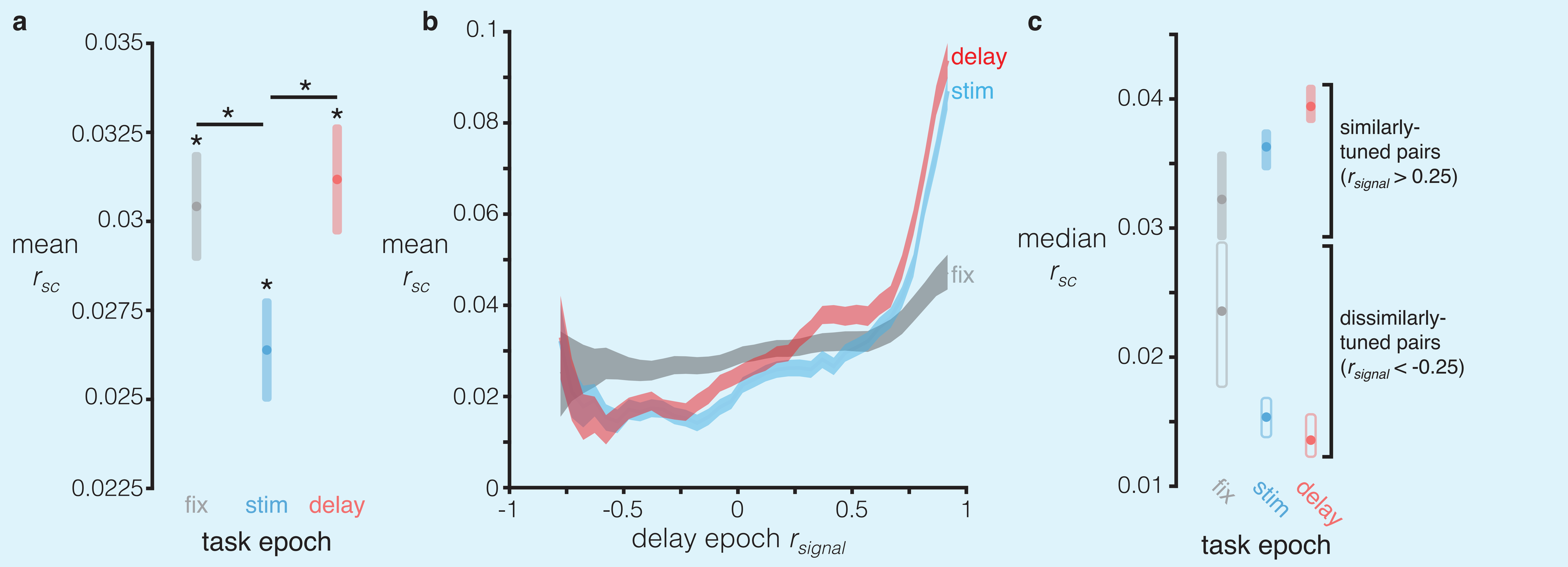






WM maintenance modifies spike count correlations (r_{sc})

We computed r_{sc} between pairs of neurons during the fixation, stimulus, and delay epochs, and found that **(a)** mean pairwise r_{sc} between neurons varies as a function of task epoch; **(b)** the relationship between r_{sc} and pairs of neurons' tuning (as measured using r_{signal}) varies across task epochs; **(c)** median pairwise r_{sc} between similarly-tuned neurons was greatest during the delay epoch, and median pairwise r_{sc} between dissimilarly-tuned neurons was lowest during the delay epoch. These results indicate that WM maintenance modifies pairwise r_{sc} in the LPFC in a manner consistent with a recurrent excitation, lateral inhibition scheme.

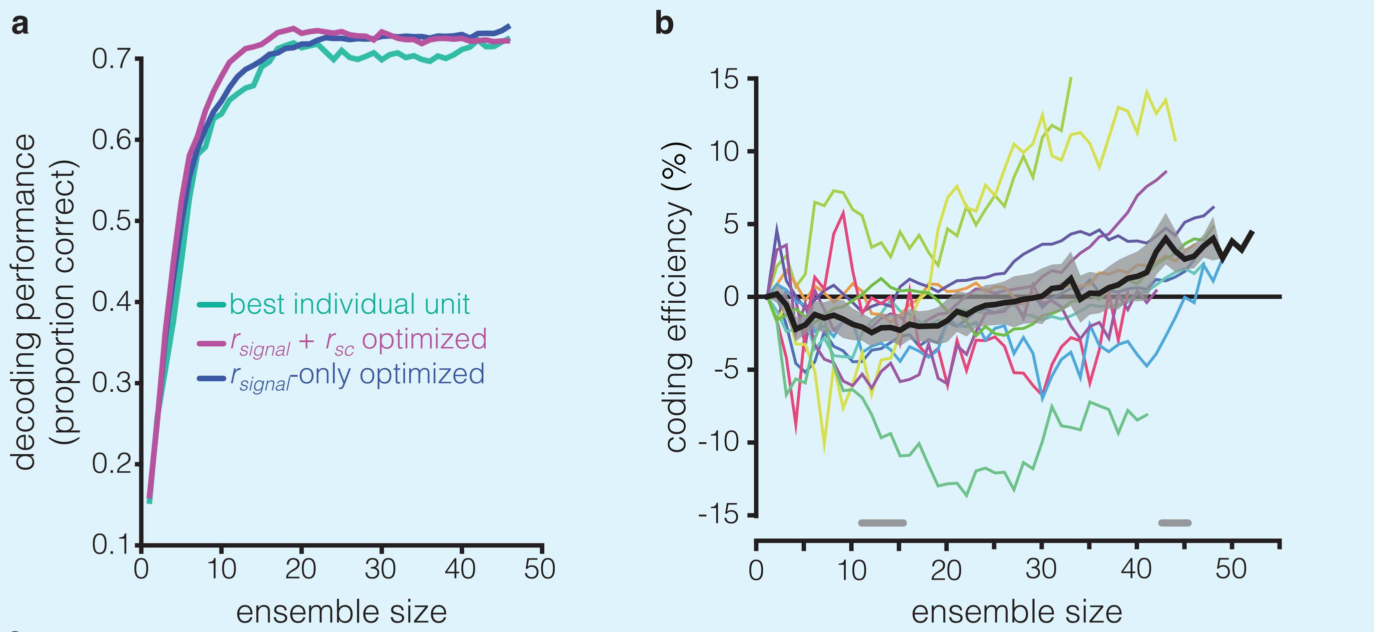


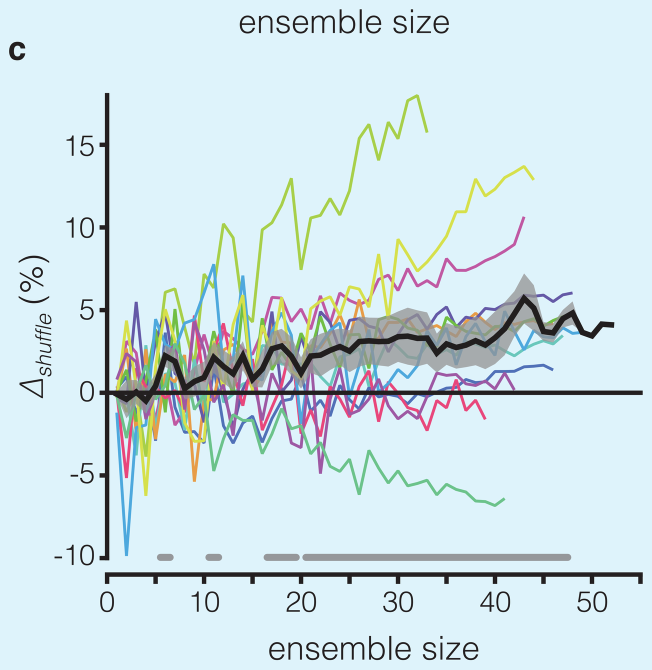
shaded regions = s.e.m (n = 10,535 pairs)
*P < 0.001, bootstrap test

shaded regions = 99.9% bootstrapped CI

Ensemble r_{sc} structure can facilitate or impair WM coding

In order to independently examine the effects of the r_{sc} and r_{signal} structures on WM coding efficiency, we constructed new ensembles using the optimized procedure on firing rate data from which the r_{sc} structure had been removed via shuffling. **(a)** Decoding accuracy for the **best individual unit**, **r_{signal} + r_{sc}**, and **r_{signal}-only** ensembles for an example session. **(b)** Coding efficiency of the **r_{signal}-only** relative to the **r_{signal} + r_{sc}** ensembles. Removing the r_{sc} structure can either impair (at small sizes) or improve (at larger sizes) decoding. It is possible that the observed effects of the rsc structure on WM coding are simply a property of an ensemble's size, regardless of whether the ensemble is optimized for WM representation. We addressed this by comparing the decoding performance of the randomly-built ensembles in which r_{sc} structure was intact vs. shuffled. **(c)** Change in decoding from removing r_{sc} ($\Delta_{shuffle}$) in randomly-built ensembles.

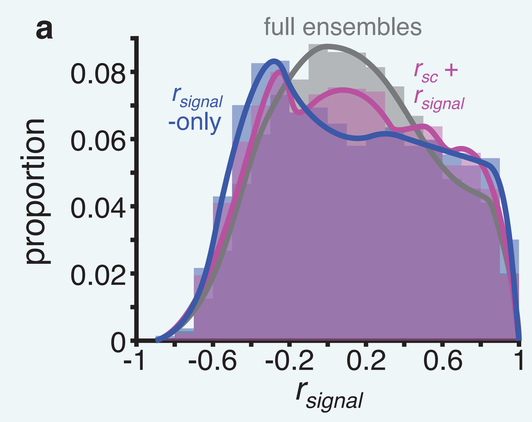




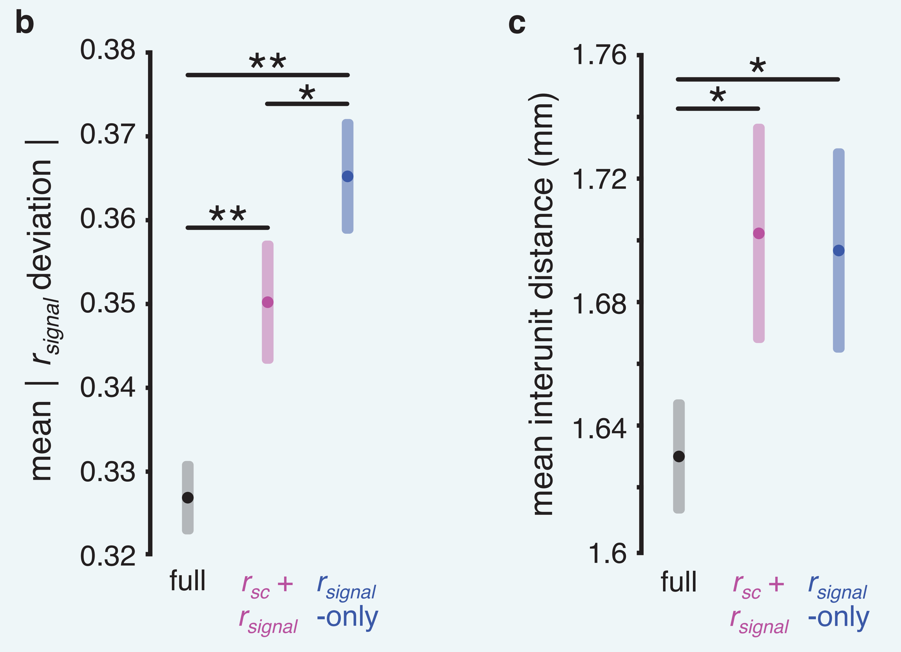
individual sessions — across-session mean & s.e.m.
P < 0.05, paired t-test, Hochberg-corrected

Ensembles optimized for WM representation are r_{signal} diverse and anatomically dispersed

Prior analyses demonstrated that near-maximum decoding performance can be achieved with a relatively small proportion of recorded units. If the WM coding in the optimized ensembles involves maximizing their representation of the stimulus space, their r_{signal} distributions should be broader than those of the full population. **(a)** r_{signal} distributions of the **full ensembles**, **r_{signal} + r_{sc} ensembles** that achieved ≥95% of maximum decoding performance (i.e. near-max ensembles), and near-max **r_{signal}-only ensembles** were all significantly different from each other (P << 0.001, χ2-test, Bonferroni-corrected). **(b)** Mean |r_{signal} deviation|, defined as the difference between a unit pair's r_{signal} and the mean r_{signal} of the ensemble to which the unit pair belongs, is greater in the optimized ensembles compared to the full ensembles. **(c)** Prior studies have reported weak topography for visual and mnemonic space in LPFC. If the optimized ensembles reflect this topography, their broader representation of the stimulus space means they should encompass larger regions of cortex relative to the full recorded ensembles. Indeed, we found that the mean distance between units was larger in the near-max **r_{signal} + r_{sc}** and **r_{signal}-only** ensembles than the full ensembles.



(n = 12,222 unit pairs)
(n = 2,414)
(n = 2,724)



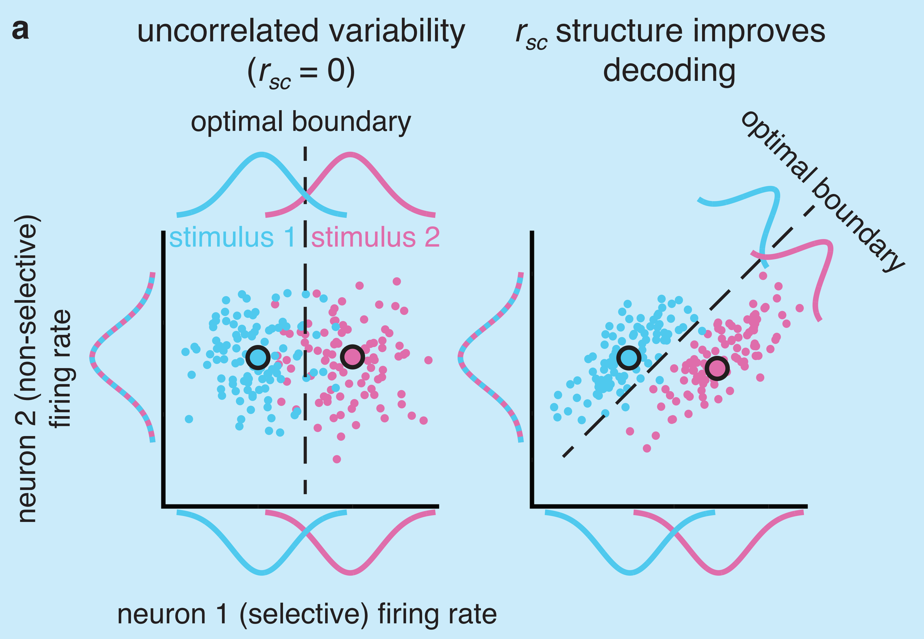
**P << 0.001, *P < 0.01, F-test, Bonferroni-corrected

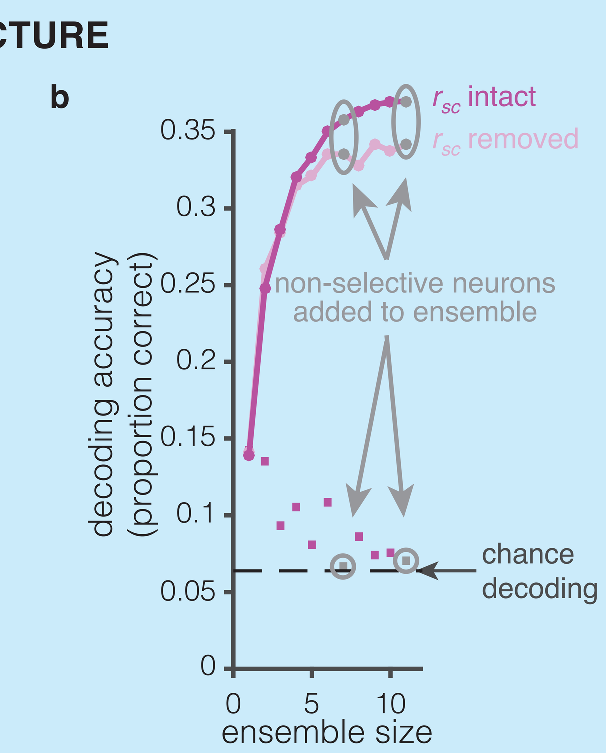
*P < 0.005, F-test, Bonferroni-corrected

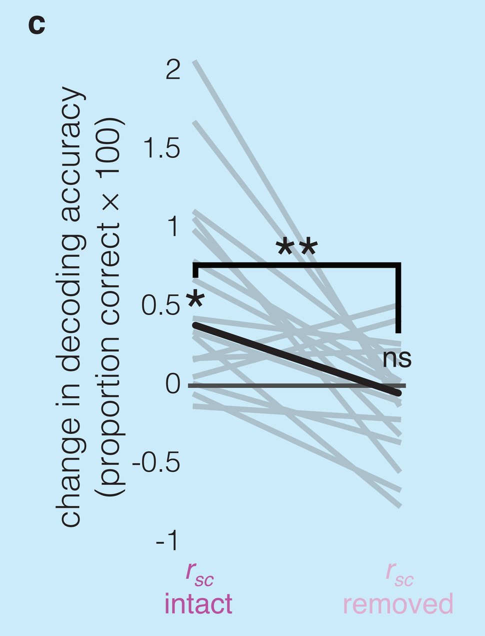
shaded regions = Bonferroni-corrected 95% comparison interval

Non-selective units can improve WM coding by modifying the r_{sc} structure

It is possible that "non-selective" neurons could still contribute to WM coding when part of an ensemble by modifying the r_{sc} structure, as depicted in the model in panel **(a)**. **(b)** An example ensemble that contains multiple non-selective units (defined as P < .05, ANOVA). **(c)** We identified every such instance in which a non-selective unit improved decoding in the near-max ensembles, and then examined their contribution to decoding before and after shuffling the r_{sc} structure. Removing the r_{sc} structure significantly decreased the amount of WM information contributed by these units.







**P < 0.005, paired signed-rank test
*P < 0.005, ns P = 0.43, unpaired signed-rank test

Conclusions

- WM maintenance modifies the ensemble r_{sc} structure in a manner consistent with a recurrent-excitatory, lateral inhibitory connection scheme
- The r_{sc} structure can improve or impair working memory decoding in a neuronal ensemble depending on the size of the ensemble and tuning properties of its constituent neurons
- Ensembles optimized for WM representation are more r_{signal}-diverse and anatomically dispersed than predicted by the statistics of the full recorded population of neurons
- Neurons that do not contain WM information in isolation can still contribute to coding when part of an ensemble by modifying the r_{sc} structure

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