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Supplemental Information

Combined Phase-Rate Coding by Persistently Active Neurons as a Mechanism for Maintaining Multiple Items in Working Memory in Humans

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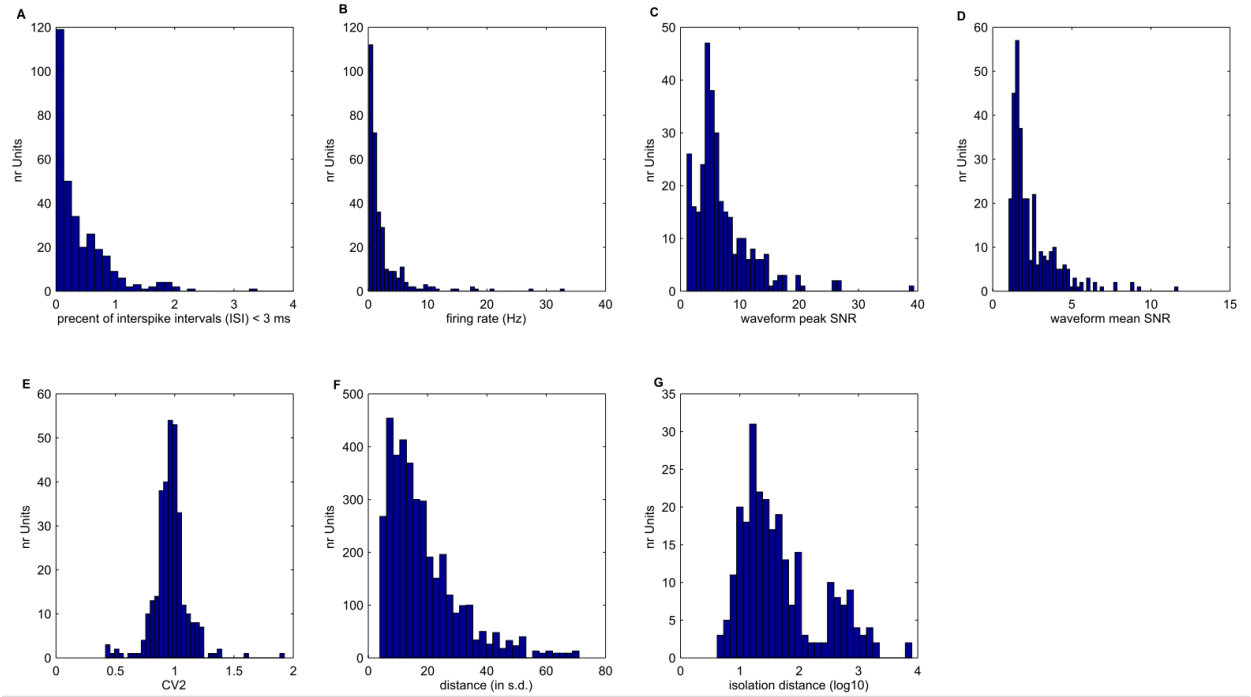

Figure S1. **Spike-quality metrics for all identified putative single-cells (clusters). Related to STAR Methods - Spike sorting and quality metrics of single units.** (**A**) Histogram of proportion of inter-spike intervals (ISIs) that were shorter than 3ms. On average, 0.42% ± 0.79% of ISIs were shorter than 3sm. (**B**) Histogram of mean firing rate. (**C**) Histogram of the signal-to-noise ratio (SNR) of the peak of the average waveform (average 6.96 ± 4.88). (**D**) SNR of the entire waveform of all units. (**E**) Histogram of the coefficient-of-variation (CV2), computed from the spike train of each neuron (average 0.96 ± 0.14). (**F**) Pairwise distance, estimated using the projection test. The pairwise distance was estimated between all possible pairs of neurons on all wires on which at least two clusters were isolated (13.28 ± 7.66). (**G**) Isolation distance for all neurons for which this metric was defined (median = 31, N=259). The isolation distance quantifies how far away a clusters if from all other detected spikes on a cluster (including the noise cluster).

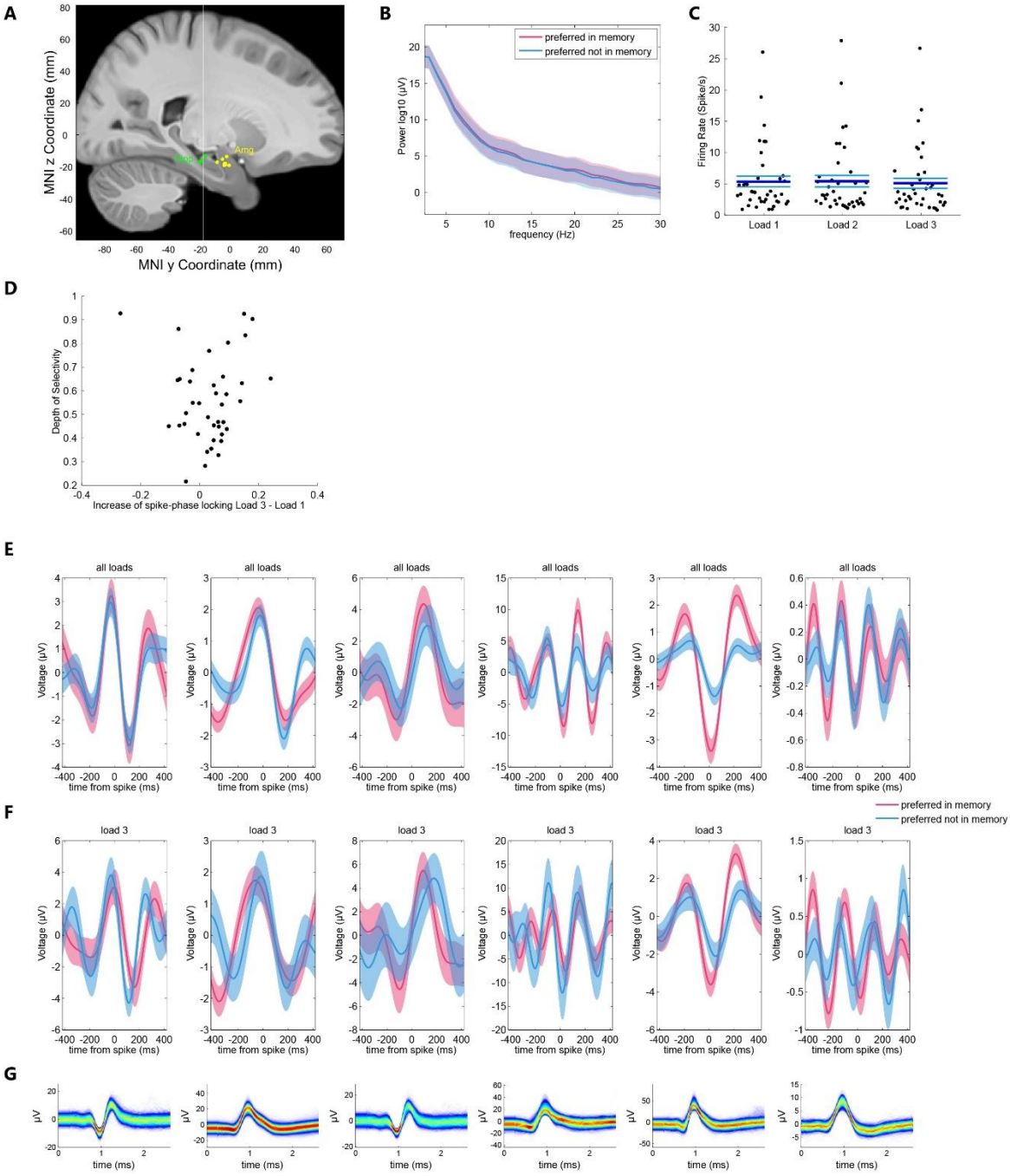

Figure S2. **Additional results on spike-phase locking strength during WM maintenance. Related to Figure 3.** (**A**) Recording locations of all selective cells included in the analysis (N=40), plotted on the same brain as Fig. 1C. (**B**) Average spike triggered power (STP), computed from the ±450 ms long LFP snippets extracted around each spike. Shaded areas represent s.e.m. There was no significant difference between when the preferred image of a cell was held in vs. not held in memory. (**C**) Firing rate of selective neurons as a function of load during trials in which the preferred stimulus of a cell was not held in memory (N=40). There was no significant difference. The three bars mark represents, from top to bottom, upper s.e.m., mean, and lower s.e.m. (**D**) Correlation between Depth of selectivity (DOS, which measures how selective the response of a given neuron is) and the extent of the change in

spike-phase locking strength between load 1 and 3 when the preferred image was not in held in WM. There was no significant correlation (r=0.05; p=0.72). (**E-G**) Example Spike Triggered Averages for six different individual cells. Traces were filter in the preferred subband identified for each cell (1-2, 2-3, 3-4, 4-5, 5-6, or 6-7Hz). Shaded areas represent s.e.m. (**E**) shows loads 1-3 pooled, (**F**) shows only load 3, and (**G**) shows the spike waveform of each neuron.

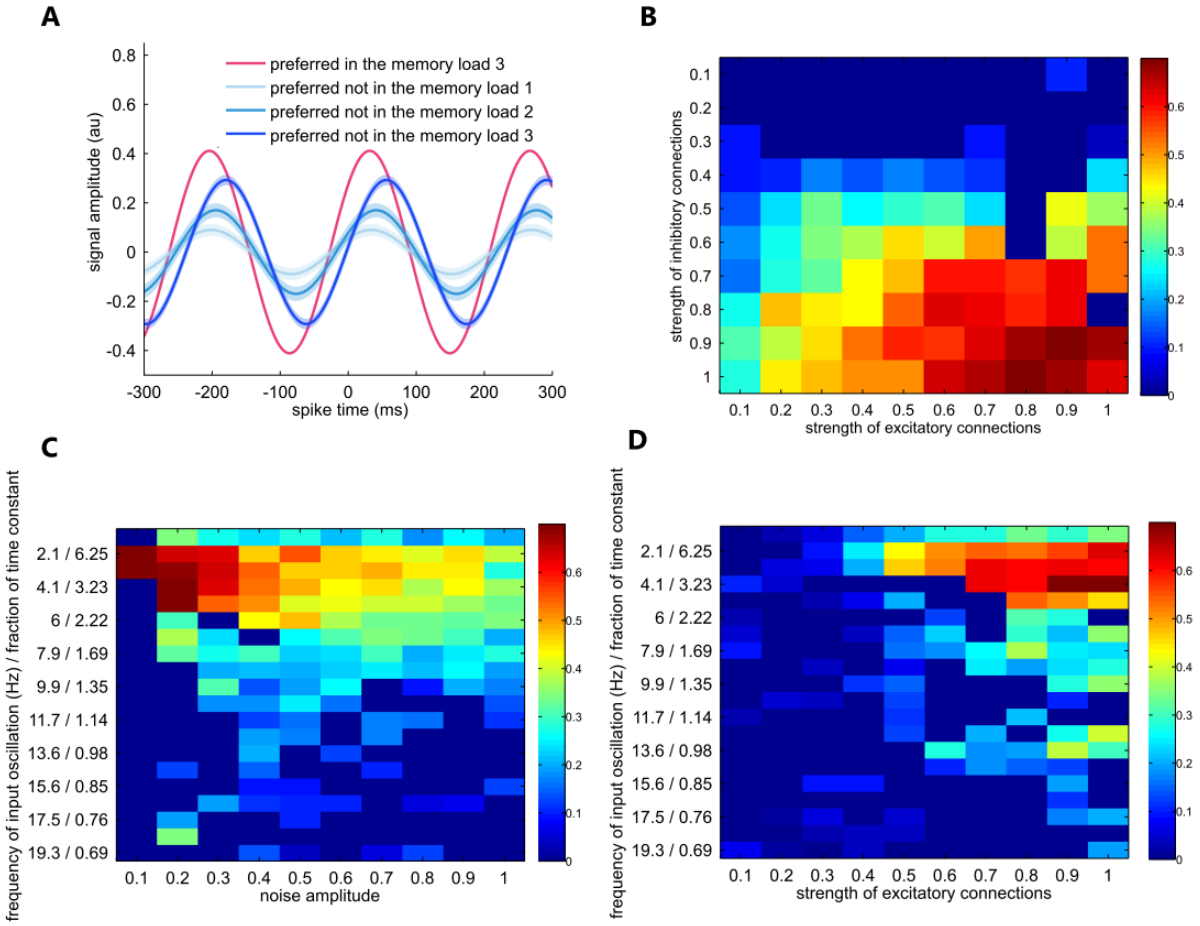

Figure S3. Model results are robust for a range of parameters. Related to Figure 4. (**A**) Spike-Triggered Average (STA) of the simulated excitatory neurons (extracted by averaging activity in a window of ±300 ms centered on each spike). Shaded areas represent s.e.m. (**B**,**C**,**D**) The maximal amplitude of the STA when the preferred image is not held in memory as a function of different parameters. The color scale represents the ratio between the maximum amplitude of the STA in trials in which the preferred image is not in memory divided by when the preferred was held in memory. Parameter combinations for which the phase difference between conditions was not at least 40 degrees are zeroed out **(B)** Inhibitory vs. excitatory connection strength plot reveals a wide range in which the network performs well in the sense that phase-locking strength was maximally different between when the preferred image of a cell was vs. was not held in memory. **(C-D)** Network performance as a function of frequency of oscillatory input and noise (**C**) and excitatory connection strength. The frequency of the external input is reported both in units of Hz as well as in units of the time constant of the network. Note how the network performs best in the 2-5 Hz frequency band.

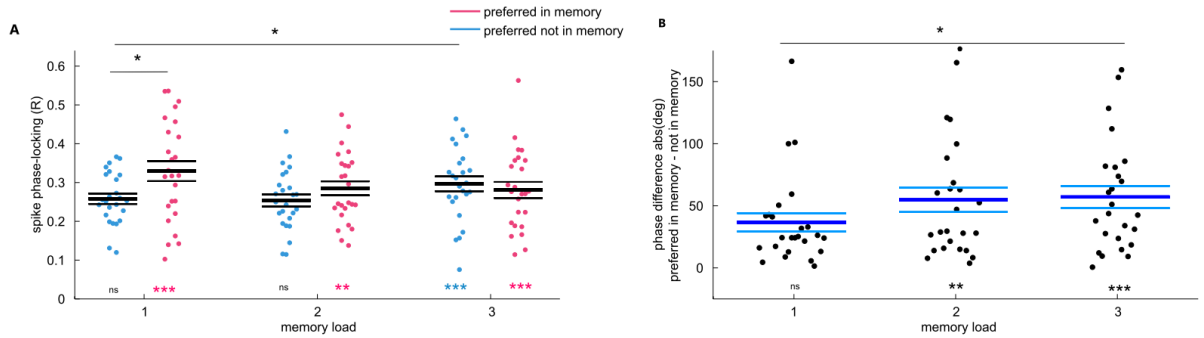

Figure S4. **Spike phase-locking of WM content by neurons without rate coding (confirmation of model prediction). Related to Figure 4.** All analysis in this figure is based on the N=25 selective neurons that did not exhibit significant rate coding for memory content during WM maintenance. (**A**) Average spike-phase locking strong as a function of load and memory content (preferred or non-preferred image of the cell) for neurons which were stimulus selective during encoding but not during maintenance (N=25). Neurons showed significantly stronger phase locking during trials in which the preferred stimulus of a cell was held in WM in load 1, but not loads 2-3. (**B**) Absolute spike-phase difference between spikes in trials in which the preferred stimulus was held in WM vs. when it was not (see Fig. 3B for details). Neurons fired spikes at significantly different phases as a function of whether the preferred stimulus was held in WM or not in loads 2-3, but not load 1 (load 1: p= 0.6356; load 2: p=0.005; load 3: p=0.002, compared to scrambled data). Also, the absolute phase differences were significantly different with moderate significance between loads 1 and 3 (one-sided permuted t-test, t[24]=1.86, p=0.042). For (A and B) the three bars mark represents, from top to bottom, upper s.e.m., mean, and lower s.e.m.

Table S1. List of subjects recorded. Related to STAR Methods - Experimental Model and Subject Details. Age is at the time of recording. The diagnosis listed (focal epilepsy) was determined as a result of depth electrode monitoring. Cell counts denote number of selective neurons in the analysis (5th column) and all recorded neurons that were considered for the analysis after applying the exclusion criteria (>0.1 Hz mean firing rate and not located in the hemisphere that contained the seizure onset zone; 6th column). As a control, note that the principle results hold after excluding the patient with most neurons (P39; remaining N=17, 13 in Amygdala). After this exclusion, the spike-phase locking strength for loads 1-3 when the preferred image was in memory was: 0.31, 0.29, and 0.28, respectively; and when preferred image was not in memory: 0.25, 0.24, and 0.30. During load 1, phase-locking strength during trials in which the preferred image of a cell was in memory was significantly larger than when it was not (permuted t-test t[16]=2.48; p=0.029). Similarly, for trials when the preferred image was not in memory, phase-locking was significantly different between load 1 and 3 (permutated t-test t[16]=2.37; p=0.037). The average absolute difference in spike phases between when the preferred image was in memory vs. not were 35.4, 56.1, 57.6, for loads 1-3. Lastly, as in the main result (Fig. 3B), for loads 2 (p=0.007) and 3 (p=0.004), these phase differences were larger than expected by chance.

ID	Age	Sex	Epilepsy Diagnosis	# selective neurons in analysis	# recorded neurons considered
P31	32	M	Left Temporal Neocortical		0
P32	19	M	Not localized	5	16
P33	44	F	Right Temporal		2
P34	70	M	Bilateral Temporal		0
P35	63	M	Left Temporal Neocortical		12
P36	45	M	Right Hippocampus	3	24
P37	33	F	Right Hippocampus		0
P39 (2)	26	M	Right Insula	8 (15)	34 (35)
P40	25	M	Right Motor Cortex	1	34
P42	25	F	Not localized		8

P43	42	F	Left Hippocampus		13
P44	53	F	Right Medial Temporal		1
P47	32	M	Right Medial Temporal	2	33
P48	32	F	Left Medial Temporal		19
P49	24	F	Left Medial Temporal		1
P47 HMH	20	M	Right Amygdala		0
P48 HMH	54	M	Left Temporal	2	24
P49 HMH	54	F	Right Medial Temporal		1
P51 HMH	24	M	Not localized	4	63