Impact of cortical plasticity on information signaled by populations of neurons in the cerebral cortex

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Submitted 15 November 2010; accepted in final form 2 June 2011

Pita-Almenar JD, Ranganathan GN, Koester HJ. Impact of cortical plasticity on information signaled by populations of neurons in the cerebral cortex. J Neurophysiol 106: 1118–1124, 2011. First published June 8, 2011; doi:10.1152/jn.01001.2010.—The performance of various putative neural codes to represent attributes of sensory signals has been evaluated in the vertebrate peripheral and central nervous system. Here, we determine how information signaled by populations of neurons is modified by plasticity. Suprathreshold neuronal responses from a large number of neurons were recorded in the juvenile mouse barrel cortex using dithered random-access scanning. Pairing of one input with another resulted in a long-lasting, input-specific modification of the cortical responses. Mutual information analysis indicated that cortical plasticity efficiently changed information signaled by populations of neurons. The contribution of neural correlations to the change in mutual information was negative. The largest factor limiting fidelity of mutual information after pairing was a low reliability of the modified cortical responses.

function of calcium imaging; barrel cortex; random-access scanning; mesoscale; spatiotemporal patterns of activity

MATERIALS AND METHODS

Slice preparation. Acute thalamocortical slices were prepared from C57BL/6 mice, aged postnatal day (P)14–P21, as described previously (Agmon and Connors 1991). All procedures were approved by The University of Texas Institutional Animal Care and Use Committee (Austin, TX). Briefly, animals were anesthetized (ketamine/xylazine) and decapitated, and the brain was quickly removed and placed in ice-cold solution (in mM: 2.5 KCl, 1.25 NaH2PO4, 25 NaHCO3, 1 CaCl2, 7 MgCl2, 7 dextrose, and 240 sucrose). The brain was placed on a 10° ramp plate, and a vertical cut was made at 55° from the anterior to the posterior axis. The posterior section was glued on a metal block, and 350–400 μm slices were cut using a vibrating microslicer. Slices were incubated at 35°C for 30 min in extracellular solution (in mM: 125 NaCl, 2.5 KCl, 1.25 NaH2PO4, 25 NaHCO3, 1.7 CaCl2, 1 MgCl2, 10 dextrose, 3 pyruvate, and 1 ascorbate, bubbled with 95% O2, 5% CO2) and stored at room temperature before experiments. All experiments were carried out at 35°C. Neurons in 1–2 mm2 of cortex were stained by several bolus injections (six to 40) of the ester form of a calcium indicator (Oregon Green BAPTA-1 AM, dissolved in 34 μl extracellular solution, 5 μl DMSO, and 20% pluronic) using glass pipettes (>2-μm tip opening).

Focal extracellular stimulation. To evoke suprathreshold electrical activity, localized to a column in the barrel cortex, we placed one theta-glass stimulation electrode (diameter <2 μm) in the ventrobasal nucleus (VB). A second stimulus electrode was placed in the VB or in layer 4 (L4). In each trial, brief electrical stimuli (three to seven, 1 ms, 4–16 μA, average 9.5 μA), at 33–100 Hz, were given, using stimulus isolators. We refer to one such set of stimuli as one input. Stimulation electrodes in the VB were positioned by first testing a fiber bundle in the striatum. An electrode placed in the fibers was moved and stimulation intensity adjusted until the cortical response was restricted to a single barrel/column. We then located the antidromically activated neurons in the VB and placed a stimulation electrode within the activity observed in the VB. Stimulation electrode positions in the VB were fine tuned by minimizing the current required to evoke a cortical
response. We only proceeded with experiments if the thalamic stimulation did not evoke significant responses in L5 or L6.

**Functional calcium imaging (wide-field recordings).** For wide-field fluorescence microscopy a charged-coupled device (CCD) camera (Rolera-XR), an upright microscope (Olympus BX51WI), a 10× water-immersion objective [numerical aperture (NA) = 0.3], and a metal halide lamp were used. Sequences of images (50-Hz frame rate) were analyzed with custom routines in the analysis software Igor Pro. Briefly, fluorescence signals were extracted from images, and the relative fluorescence changes were calculated: \( \Delta F(t) \equiv F(t) - F_0 \). For calculation of baseline fluorescence \( F_0 \), fluorescence in a 1-s time window before a stimulus was averaged. The CCD had a field of view of 890 \( \times \) 670 \( \mu \)m.

**Image analysis (wide-field recordings).** Activity on the larger spatial scale was examined as population averages. Each region of interest (ROI) spanned one layer in one column. For each ROI, the fluorescence signal was averaged over a 2-s time window following a stimulus and all pixels

\[
\int \Delta F = \int_0^{2s} \int dxdy / \int dxdy
\]

Perimeters of columns, layers, and barrels were determined from differential interference contrast images.

**Dithered random-access two-photon scanning.** To record from a population of neurons, we used dithered random-access scanning (Ranganathan and Koester 2010). The scanning system consisted of a high-power, ultrafast-pulsed Titan:Sapphire laser system (Chameleon Ultra II, Coherent, Santa Clara, CA; operated at 880 nm), a custom prechirper system consisting of a prism pair, two acousto-optic deflectors (AODs; ATD-6510CD2, IntraAction, Bellwood, IL), a single reflective diffraction grating (100 grooves/mm, Newport, Irvine, CA), and a fixed-stage microscope (Olympus BX50W). A 40× water-immersion objective (NA = 0.8) was used. Fluorescence was detected using photomultiplier modules (H9305 and R6357, Hamamatsu, Shizuoka, Japan). Two detection units were used to detect epifluorescence and transfluorescence (Koester et al. 1999). The output of the photomultiplier tube modules was converted from a current to a voltage signal and amplified (C6438-01, Hamamatsu), filtered using a 2- or 6-pole Butterworth filter with a cutoff frequency of 100 KHz, and converted to digital signals using a Data Acquisition (D/A) board (PCI-6115, National Instruments, Austin, TX). Deflection angles of AODs were controlled, using voltage-controlled drivers (IntraAction), by the output of the D/A board with a sample and analog output rate of 125 kHz. Data were analyzed and displayed using custom software in Matlab and Igor Pro. In each trial, we recorded 2–5 s of fluorescence, sampled at 651 Hz from 40 neurons. Trials were recorded at ~0.1 Hz.

**Spike detection in small populations of neurons with single-cell and single-spike resolution.** For populations of cortical neurons, where somatic calcium signals are highly correlated with suprathreshold neuronal spiking activity, the somatic calcium signal can be used to detect suprathreshold spiking activity. The high spatial resolution of two-photon excitation used for dithered random-access scanning, the high temporal resolution, and the high signal-to-noise ratio allow one to detect spikes from somatic calcium fluorescence signals. This has been demonstrated by two recent studies that confirmed detection of spikes by simultaneous electrophysiological and optical recordings (Grewe et al. 2010; Ranganathan and Koester 2010). Spikes were deconvolved from fluorescence responses by a maximum-likelihood procedure, resulting in a high-spike detection efficiency (>97% of correctly detected spikes and a low rate of false positives of <0.003 s~1~) (Ranganathan and Koester 2010).

**Significance test.** To determine significance, an unpaired Student’s t-test was used unless stated otherwise. Results are given as mean ± SD unless stated otherwise.

**Mutual information analysis.** Experiments with a large number of recordings (on average, 168) for the responses \( r_1(\text{control}), r_2(\text{control}), r_{\text{ip}}(\text{post}), r_{\text{dp}}(\text{post}) \) were used to calculate mutual information. Mutual information about stimulus identity is given by (Shannon 1948)

\[
I(R, S) = H(R) - H(R|S)
\]

with entropies

\[
H(R) = -\sum P(r) \log_2 P(r)
\]

and

\[
H(R|S) = -\sum P(s) \sum P(r|s) \log_2 P(r|s)
\]

To reduce the finite sampling bias, we used a coverage-adjusted estimator of entropy (Chao and Shen 2003), which adjusts empirical observation frequencies and uses the Horvitz-Thompson general estimator for the population total. This method of reducing the finite sampling bias has been shown to perform well on small sample sizes (Vu et al. 2007).

Because of the large number of simultaneously recorded neurons \( N = 40 \), cardinality in our experiment was high (up to \( 2^{40} \)). Combinatorial explosion rendered an exhaustive calculation of mutual information across all potential ensembles (combinations) consisting of \( M < N \) neurons intractable. Mutual information as a function of ensemble size was therefore calculated as an average of over 1,000 ensembles, drawn at random from all possible combinations of \( M \) out of \( N \) neurons (given by the binomial coefficient). Errors (graphs show ± SD) were calculated from 100 bootstrapped samples. Mutual information was calculated from binary response vectors, where each entry represents neuronal activity across an entire trial binned into a single number. To examine the contribution of spike timing to mutual information, we subdivided each trial into five-time bins (of 0.02 s) and calculated mutual information.

To estimate the residual finite sampling bias, we created surrogate data simulating a large number of recordings (10,000). Surrogate data were constructed such that neurons had the same response probabilities in surrogate and experimental data. For each simulated number of available recordings (trials/input), 1,000 recordings were drawn at random, and mutual information was calculated. From the distribution, we calculated SD to estimate residual finite sampling bias. This method previously has been demonstrated to estimate residual finite sampling bias (Schultz et al. 2009; Schultz and Panzeri 2001).

Changes in mutual information as a result of cortical plasticity were calculated from

\[
\Delta I = I_{\text{post}} - I_{\text{control}}
\]

where \( I_{\text{post}} \) was calculated using the responses \( r_i(\text{post}), r_j(\text{post}) \) and \( I_{\text{control}} \) from \( r_i(\text{control}), r_j(\text{control}) \).

**Contribution of correlations (Icorr)** was calculated as \( I_{\text{corr}} = I - I_{\text{ind}} \) by subtracting mutual information calculated from neuronal responses assuming independence (Latham and Nirenberg 2005; Montani et al. 2007). Briefly, independent response distributions were calculated using

\[
p_{\text{ind}}(r|s) = \prod p(r|s)
\]

where \( p(r|s) \) indicates response probability of neuron \( i \). Mutual information \( I_{\text{ind}} \) was calculated using the independent response distributions \( p_{\text{ind}}(r|s) \) and

\[
p_{\text{ind}}(r) = \sum s p(s) p_{\text{ind}}(r|s)
\]

To estimate the importance of correlations for decoding, we calculated the upper bound on information loss when ignoring correlations by calculating

\[
\text{IInd} = I_{\text{corr}} + I_{\text{ind}}
\]
which represents the Kullback-Leibler divergence ($D_{KL}$) of the two response distributions (Latham and Nirenberg 2005). This is similar to the breakdown of mutual information into the contribution of stimulus-dependent and independent correlations carried out in other studies (Montani et al. 2007; Panzeri et al. 2001).

**RESULTS**

**Changes in cortical responses evoked by thalamocortical inputs.** To measure the impact of cortical plasticity on signaling of information, we recorded cortical responses ($r_1$ and $r_2$) to two different inputs, $s_1$ and $s_2$. One of these inputs was paired with other activity to induce long-lasting changes in the cortical responses to this input (plasticity). With the use of fluorescence calcium imaging, we measured the cortical responses to two stimulation electrodes placed in the thalamus (VB) or in L4. In the first set of experiments, using wide-field fluorescence microscopy (Fig. 1), we verified that our experimental design resulted in long-lasting changes of the cortical responses. We further examined whether the observed changes were specific to the paired input $s_1$. For all experiments, the positions of both electrodes were adjusted so that both electrodes evoked responses within the same barrel (Fig. 1B). The wide-field fluorescence microscopy in this first set of experiments allowed us to quickly localize the responding cortical column because of the large field of view (1.74-mm width) of this technique. This first set of experiments, however, did not resolve cortical responses with single-cell resolution; instead, responses were quantified as population averages.

To induce long-lasting changes in the cortical responses ($r_1$) evoked by one of the inputs ($s_1$), we paired this input with activity evoked by an electrode placed in the cortex ($s_{CI}$). The cortical electrode was placed in L2/3 of the column adjacent to the column activated by the input $s_1$ (Fig. 1, A and B). Under control conditions, the cortical responses to both inputs ($r_1$ and $r_2$) were restricted to a single column (the activated column) and largely to L4 and L2/3 within that column (Fig. 1B). As shown in Fig. 1B, the placement of the stimulation electrodes indeed resulted in activation of the same barrel. The cortical input ($s_{CI}$) and the input ($s_1$) were paired at a small temporal offset, such that the input $s_1$ preceded the $s_{CI}$ by a short time interval $\Delta t$ ($\Delta t = 65$ ms). We refer to this pairing protocol as the “induction” stimulus, $s_{Induct}$. After 100–150 pairings of the inputs $s_1$ and $s_{CI}$ at ~0.1 Hz, the cortical responses to the paired input $s_1$, but not to the unpaired input $s_2$, increased significantly in two out of three experiments ($P < 0.05$). As shown in another study, these changes are long-lasting and do not occur if the N-methyl-D-aspartate receptor blocker N-2-

![Fig. 1. Input sensitivity of cortical plasticity for thalamocortical inputs. A: pictogram on the left illustrates experimental design. Photomicrographs showing layer 4 (L4) of the barrel cortex (top right image) and thalamic ventrobasal nucleus (VB; bottom right image). Rounded boxes illustrate barrels and dotted lines, borders between columns. Two stimulation electrodes were placed in the VB, $s_{CI}$, cortical input paired with $s_1$ (paired) input. $s_2$, unpaired input. B: images show the cortical responses ($\Delta F/F(t)\$ in L2/3 of the paired column. Left traces show responses before (control) and right traces, responses after (post) pairing. Only the cortical response to the $s_1$ displayed a significant change following the pairing, $r_1$ and $r_2$.](http://jn.physiology.org/doi/10.1152/jn.00923.2010)
calculated the change in mutual information as a function of number of neurons in an ensemble (Fig. 3A). For example, for ensemble size two (pairs of neurons), we calculated mutual information for all 780 ensembles, which one can construct from 40 simultaneously recorded neurons. Mutual information before pairing was low. When calculating mutual information from ensembles of two neurons before pairing, the average mutual information was 0.004 ± 0.003 bit (n = 2,340 pairs; n = 3 experiments). Following pairing, the mutual information signaled by pairs of neurons increased significantly by 0.26 ± 0.05 bit (P = 0.005). This increase in mutual information exceeded the finite sampling bias. As expected, the mutual information increased with the number of neurons in an ensemble (Fig. 3A). This result indicates that cortical plasticity changes the suprathreshold activity of populations of neurons and thus what information is signaled by populations of neurons. To analyze the contribution of spike timings on the change in mutual information, we subdivided trials into five time bins. Spike timings did not contribute to the change in mutual information; there was no significant difference in the change in mutual information when binning into one bin compared with five bins (when calculated for pairs of neurons: 0.26 ± 0.05 bit vs. 0.26 ± 0.07 bit; P = 0.89).

Contribution of correlations to change in mutual information. The neuronal responses following the pairing were highly correlated. The correlations for all pairs of neurons in L2/3 for the modified responses of the first input are shown from one example experiment in Fig. 3B. Because one of the underlying mechanisms of the observed change in cortical response was synaptic plasticity, the pairing protocol also changed the correlations among L2/3 neurons. When calculating correlations among pairs of neurons (Pearson’s correlation coefficient) from

Impact of cortical plasticity on mutual information. The information carried by neuronal responses, for example, to differentiate between input signals, can be quantified using information theoretical tools. We calculated Shannon’s mutual information (Shannon 1948). Because of experimental limitations, one can only record a finite number of responses. The limited number of responses may lead to a finite sampling bias when calculating mutual information. To reduce the inherent, finite sampling bias, we used the Chao-Shen estimator of entropy (Chao and Shen 2003). In addition, the finite sampling bias was estimated from surrogate data (see MATERIALS AND METHODS, Mutual information analysis; Fig. 3A). Changes in mutual information were calculated as the difference in mutual information conveyed by the responses to both inputs before pairing (control) and after pairing (post). Of the variability of neuronal responses, information represented by suprathreshold responses of cortical neurons is expected to increase with the number of (observed) neurons. We therefore significantly in three out of four experiments. All further analysis was restricted to these three experiments. Average spike count of the responses to the paired input S1 increased significantly from 0.014 ± 0.016 to 0.53 ± 0.31 (n = 120 neurons; P < 10^{-50}). In contrast, average spike count for S2 did not change significantly (0.015 ± 0.017 compared with 0.012 ± 0.014; P = 0.11). At the end of each experiment, we paired the second input S2 with S_C to verify that the lack of changes of responses to the second input following the first pairing (of S1 with S_C) was not because these responses were not plastic [r_2 changed significantly (P < 0.05) in n = 3 out of three experiments when paired with S_C].

Fig. 2. Impact of plasticity on activity in small populations of neurons. A: pictogram illustrates experimental design. Two stimulation electrodes were placed in L4 to evoke suprathreshold activity. Input S1 consisted of 3 electrical stimulations at 40 Hz of the first stimulation electrode and input S2 of 3 stimulations at 40 Hz of the second stimulation electrode. Middle image shows photomicrograph; right image, fluorescence raster image (region indicated by box in middle image). B: images illustrate examples of cortical responses in 40 neurons recorded simultaneously in L2/3 to both inputs before (control; left 2 images) and after (post; right 2 images) pairing. Traces below images show spike raster plots of detected spikes. t, Time. C: graphs show binary response vectors for all trials recorded for both inputs before and after pairing. Each black dot represents 1 spike.
binary response vectors, the average correlation coefficient for the paired L4 input responses increased significantly from 0.07 ± 0.2 for r1(control) to 0.53 ± 0.20 for r1(post) (n = 2,340 pairs; P < 10^-16). The increase in suprathreshold activity in L2/3 suggests a large contribution of changes in rate of individual neurons to signaling of information. Neural correlations, however, can contribute to signaling of information. The increase in mutual information calculated above includes all contributions of spiking activity to signaling of information, including correlations. To dissect the contribution of correlations to the change in signaling of information, we broke down the mutual information into its components (Montani et al. 2007; Pola et al. 2003; Quiroga and Panzeri 2009; Schneidman et al. 2003). The first step of the breakdown is to calculate mutual information from the measured probability distribution, as calculated above, as well as from the probability distribution assuming independence (see MATERIALS AND METHODS, Mutual information analysis). The difference yields the contribution of correlations to mutual information. Again, we calculated the change in mutual information for different ensemble sizes. The change in mutual information signaled by pairs of neurons assuming independence is shown for all ensembles of size 2 for one example experiment in Fig. 3B. The contribution of correlations was calculated for each ensemble (Fig. 3B). The contribution of correlations to the change in mutual information (ΔICorr) was negative (Fig. 3B), on average, ΔICorr = −0.11 ± 0.05 bit (n = 3 experiments). To further evaluate the importance of correlations, we calculated the upper bound of information loss when ignoring correlations DKL (see MATERIALS AND METHODS, Mutual information analysis). As has been argued before, the Kullback-Leibler divergence between the full and the independent probability distributions represents the upper bound of this loss of information when ignoring correlations (Latham and Nirenberg 2005). This calculation represents a further breakdown of the mutual information into the contribution of stimulus-dependent and stimulus-independent correlations to signaling of information. On average, DKL was just 0.02 ± 0.01 bit, indicating that correlations were not important for decoding information from the modified patterns of activity. These results indicate that the change in suprathreshold responses of a population of neurons in cortical networks efficiently modifies information signaled by spikes (rate code) about the input, but the neural correlations do not contribute to this change in signaling of information.

Low reliability of learned responses limits fidelity of information. A substantial number of trials of the learned responses displayed very low spike counts (Fig. 4) to the degree that no spike was detected in any neuron for that trial (failure). The number of such failures varied from experiment to experiment, with no detectable failures in some experiments (Fig. 4, left graph) and a substantial number of failures in other experiments (Fig. 4, right graph). The substantial number of failures limited the reliability of patterns for r(post). Reliability of patterns was calculated here as the normalized dot product of the binary spike vectors between trials. On average, the reliability for r(post) was 0.43 ± 0.32, which was significantly lower compared with the reliability for the cortical input response (0.83 ± 0.14) and for the induction response (0.85 ± 0.13), respectively. When increasing reliability by removing failures, the change in mutual information asymptotically approached full information (one bit) for larger ensembles and exceeded 90% of maximal information for ensemble sizes of 14 or more neurons. This result indicates that the fidelity of signaling of information was limited by a reliability of r(post), which was low compared with the reliability of all other input signals.

DISCUSSION

Cortical plasticity changes the response properties of cortical neurons in a long-lasting manner. Because synaptic plasticity is one of the underlying learning rules, not only the number of suprathreshold spiking responses (rate) but also the correlations between neurons may change with plasticity. Neural correlations can both contribute to signaling of information as well as limit the fidelity of information (Averbeck et al. 2006). Here, we determined the contribution of correlations to the change in signaling of information in a primary sensory cortex. We measured the impact of plasticity on suprathreshold responses in a small population of cortical neurons. The dithered random-access scanning method used in this study allowed us to characterize population responses with single-cell and single-spike resolution, as shown by rigorous hypothesis testing and simultaneous electrophysiological and optical recordings (Grewe et al. 2010; Ranganathan and Koester 2010). As a result of the input signal-specific change in the cortical responses, the mutual information signaled by neurons in L2/3 increased. Our results demonstrate a high performance of a neural code based on the identity of neurons (patterns of activity) for cortical plasticity. The contribution of correlations to change in signaling of information was negative, indicating a low performance of a neural code relying on correlations for plasticity. The limiting factor of the fidelity of information was the low reliability of the learned responses.

The input specificity was observed for both experimental designs and placement of stimulation electrodes in VB as well as in L4. This indicates that plasticity of intracortical synaptic connections (L4 to L2/3 and within L2/3) rather than thalamocortical synaptic connections contributed to the input-specific changes of population activity. This is in agreement with previous studies that found changes in thalamocortical synapses onto L4 neurons only in very young animals (<P12) (Feldman et al. 1998; Glazewski and Fox 1996) and plasticity of L4 to L2/3 synapses in juvenile and adult animals when inducing map plasticity by manipulation of the sensory inputs (Allen et al. 2003; Drew and Feldman 2009; Shepherd et al. 2003); for review, see Feldman (2009) and Fox (2002).

Previous studies have demonstrated changes in neural activity induced by pairing protocols in vitro (Jimbo et al. 1999; Johnson et al. 2010; Petersen and Sakmann 2001; Shahaf and...
Marom 2001; Wagenaar et al. 2006). This study extends results from previous studies from the single-neuron level to the level of populations of neurons while maintaining cellular resolution and bridges the gap between single-neuron and population recordings that lack cellular resolution (population averages). For example, evaluating the importance of correlations for signaling of information requires simultaneous recordings from multiple neurons. This is important because signaling of information requires many neurons (Petersen et al. 2001) and is often signaled by the precise patterns of activity in populations of neurons (Georgopoulos et al. 1986; Pillow et al. 2008). The purpose of this study was to break down the change in mutual information to evaluate the performance of correlations and independent neural activity for plasticity. In contrast to the large contribution of precise spike timing to mutual information signaled about whisher identity, we do not find any contribution of spike timings to mutual information (Panzeri et al. 2001). In contrast to differentiating between inputs to two different columns, however, in our experimental design, both inputs were to the same cortical column.

**Functional significance.** The performance of different neural codes for signal representation, for example, to represent attributes of sensory inputs, has been evaluated in the peripheral nervous system, as well as in primary sensory and motor cortices. Here, we extend these studies and determine the impact of plasticity on putative neural codes. The input-specific changes in a subset of neurons are an extension of Hebb’s concept (Hebb 1949) of the formation of cell assemblies to subpopulations of neurons embedded in a recurrent network. The results thus demonstrate that a code relying on the identities of neurons has a high performance when cortical responses are modified by plasticity.

The learned response patterns displayed significant correlations. On average, these correlations were higher than those observed for sensory responses in vivo (Kerr et al. 2007). This is not unexpected because of the large difference in background activity in vitro compared with in vivo. The high correlations had a strong negative impact on signaling of information. This is consistent with predictions that pairwise correlations strongly impair the fidelity of a rate code (Mazurek and Shadlen 2002). The high correlations may be a reflection of the gain provided by the intracortical synaptic connections (Feldmeyer et al. 2006; Liu et al. 2007). Rather than reflecting importance for signal representation, correlations therefore may be simply a result of the intracortical gain. This gain in turn may be required to achieve a sufficiently large signal amplitude (average spike count). The single largest factor limiting the fidelity of information was the low reliability of the modified responses. The low reliability found here does not only limit a spatial pattern code but also any other spike-dependent coding mechanisms because of the low spike count of a number of responses (failures). In contrast to the performance of putative neural codes evaluated in the peripheral nervous systems to represent attributes of sensory signals and behavioral output (Jacobs et al. 2009; Pillow et al. 2008), we find here that correlations do not contribute to the performance of a neural code for learning and memory. The performance of a rate code for plasticity, which takes into account neuron identity and does not simply pool over all neurons, is thus in agreement with a low contribution of correlations to signal representation in the cerebral cortex (Panzeri et al. 2001) and the prediction of a low performance of a correlation-based code in cortical networks based on the high sensitivity of cortical networks to perturbations (London et al. 2010).

**ACKNOWLEDGMENTS**

We thank Brett Johnson for assistance with programming the custom scanner-control software. We thank Drs. Daniel Johnston, Richard Aldrich, Nicolas Priebe, and Hiroshi Nishiyama for comments on the manuscript.

**GRANTS**

This work was supported by the Alfred P. Sloan Foundation and the Whitehall Foundation and startup funds from The University of Texas at Austin.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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