Supporting information

Buckley CL, Toyoizumi T (2018) A theory of how active behavior stabilises neural activity: Neural gain modulation by closed-loop environmental feedback. PLoS Comput Biol 14(1): e1005926. https://doi.org/10.1371/journal.pcbi.1005926

Contents

S1 Supplementary whisker data

We analyze if sensory input through infraorbital nerve (ION) plays a role in coordinating whisking behavior, thalamic spiking activity, and cortical local field potential (LFP). Previous results based on simultaneous recording from whisker, thalamus, and cortex exhibited that thalamic spiking rate increased and low frequency power of cortical LFP decreased during whisking behavior. Here, we reanalyze this data set and quantify cross-correlation functions between (1) 5-20 Hz power of the whisker position, denoted by *Whisker*; (2) thalamic spiking rate computed with 20 ms averaging window, denoted by *Thalamus*; (3) and 1-20 Hz cortical LFP power, denoted by *Cortex*, recorded from ION-intact animals (n=22) and ION-cut animals (n=19). Raw recordings and the three processed traces are shown in Fig. S1A for an example animal. We chose the 1-20 Hz range for the analysis of cortical LFP power because notable brain-state-dependent changes were previously observed in this range [1]. The spectrogram was computed using 2 s window to reliably estimate the predominant 1Hz power in cortical LFP and the window was gradually shifted in 20 ms steps.

Next, we computed cross-correlation functions between these 3 quantities: *Whisker-Thalamus*, *Whisker-Cortex*, and *Thalamus-Cortex*. While the resulting cross-correlation functions were noisy in each animal, a mean cross-correlation function averaged over each animal group exhibited clear common properties. In both ION-intact and ION-cut animals, whisking behavior lead correlated increase in the thalamic activity and decrease in the cortical slow oscillations. Consistent with this result, the thalamic activity was negatively correlated with the low-frequency cortical LFP fluctuations (Fig. S1B).

Notably, the position of the mean cross-correlation peaks was significantly shifted in ION-cut animals relative to the ION-intact animals (Fig. S1B). Specifically, the peak of the *Whisker-Thalamus* cross-correlation was delayed for 400 ms ($p=0.02$, bootstrap test) and the peak of *Whisker-Cortex* cross-correlation was delayed for 200 ms ($p=0.03$, bootstrap test) in ION-cut animals. However, the temporal relationship between the thalamic spiking activity and the

low-frequency cortical LFP power was not significantly altered as assessed by the *Thalamus-Cortex* correlation function ($p>0.05$, bootstrap test). The bootstrap statistics were computed by randomly resampling animals from the two groups, assuming a null hypothesis that the two animal groups are the same (see, the inset panels for the bootstrap statistics about the difference of the cross-correlation peak locations).

These analyses suggest that the brain state transition was delayed after a whisking onset in ION-cut animals relative to ION-intact animals. Thus, while sensory input is not necessary for the brain state transition, it was necessary for inducing short-latency brain state transitions.

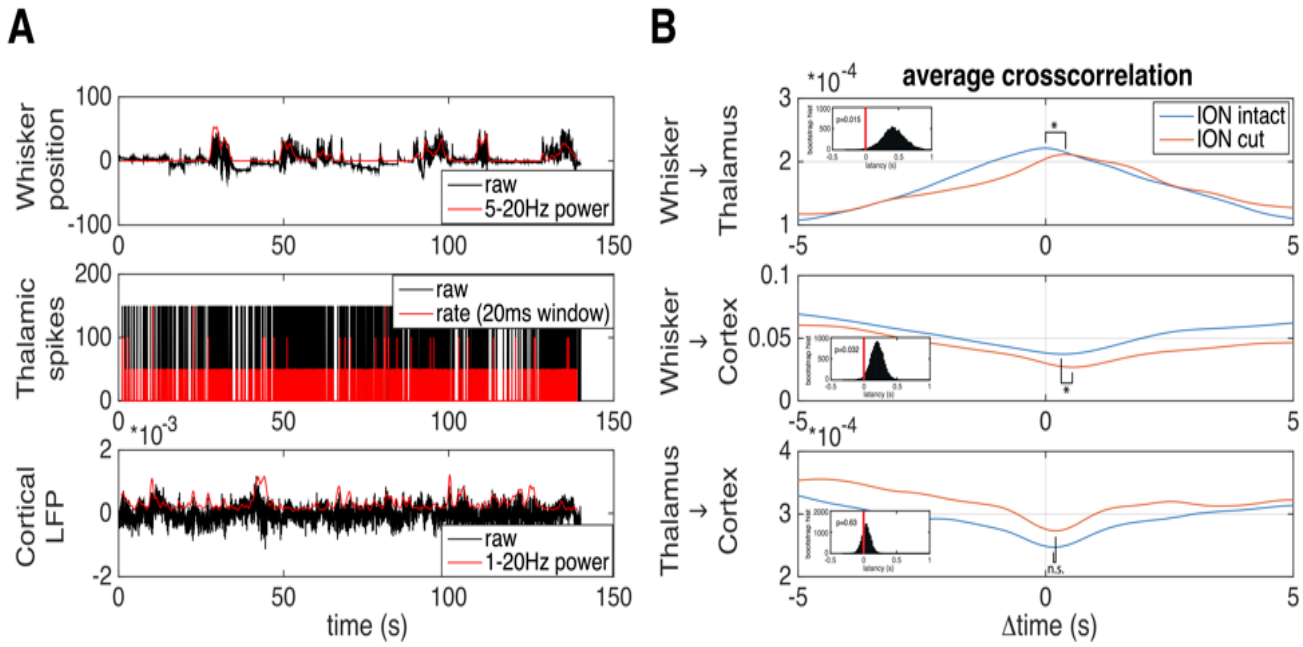


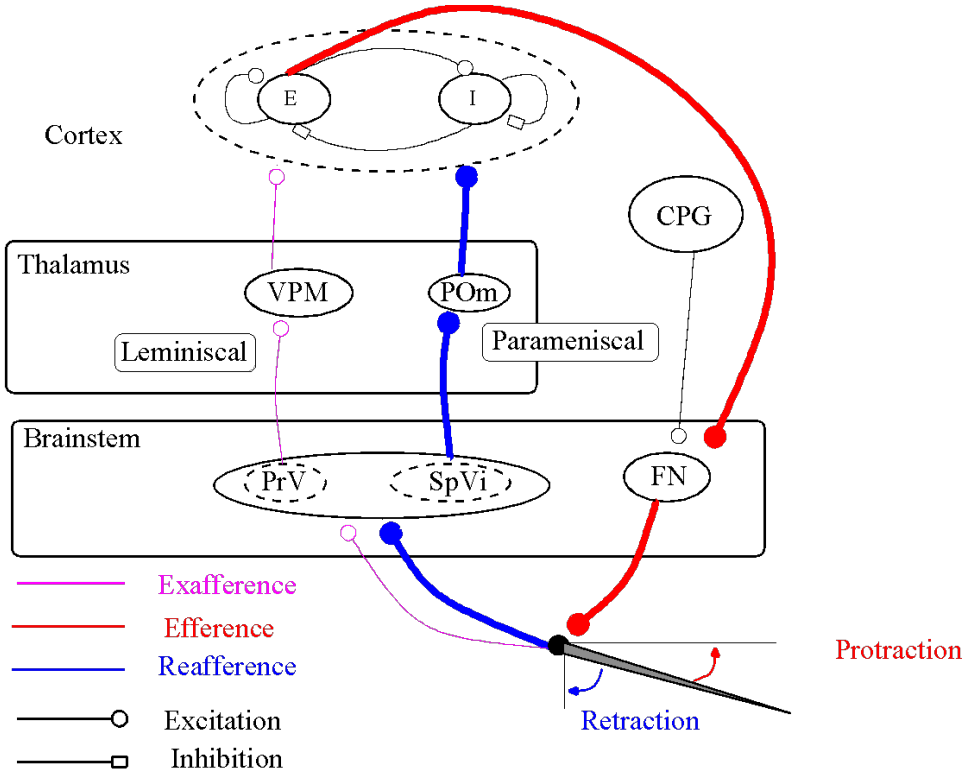
Fig. S1 | (**A**) A simultaneous recording of whisker position (Top), thalamic spikes (Middle), and cortical LFP (Bottom) in an example animal [2]. Based on these raw traces (black), brain-state-relevant quantities (red) are computed and shown in each panel: 5-20 Hz power of the whisker position (Top), thalamic spiking rate (Middle), 1-20 Hz power of the cortical

LFP (Bottom). (**B**) A cross-correlation function between *Whisker* and *Thalamus* (Top), *Whisker* and *Cortex* (Middle), and *Thalamus* and *Cortex* (Bottom) for ION-intact animals (blue) and ION-cut animals (red), where the inset panels show the bootstrap statistics about the difference of the cross-correlation peak locations. The *Whisker-Thalamus* and the *Whisker-Cortex* correlation functions were significantly shifted by the ION cut.

1. Poulet JFA, Petersen CCH. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. Nature. 2008;454: 881–885.
2. Poulet JFA, Fernandez LMJ, Crochet S, Petersen CCH. Thalamic control of cortical states. Nat Neurosci. 2012;15: 370–372.

S2 Alternate schemes for sensory feedback in the whisker system

A



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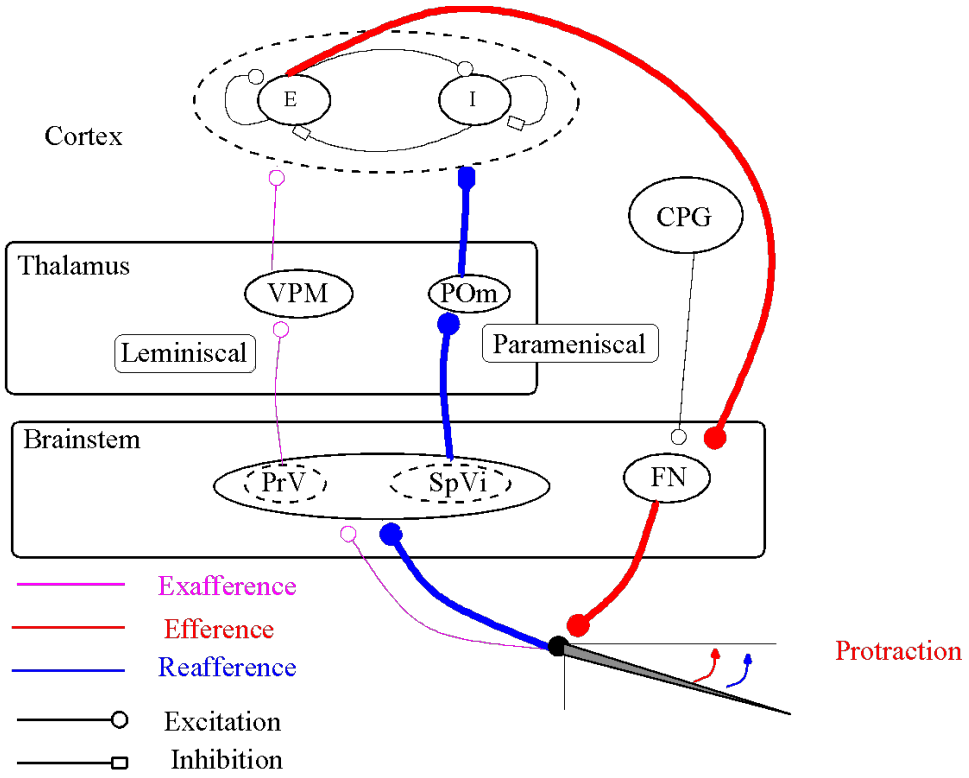

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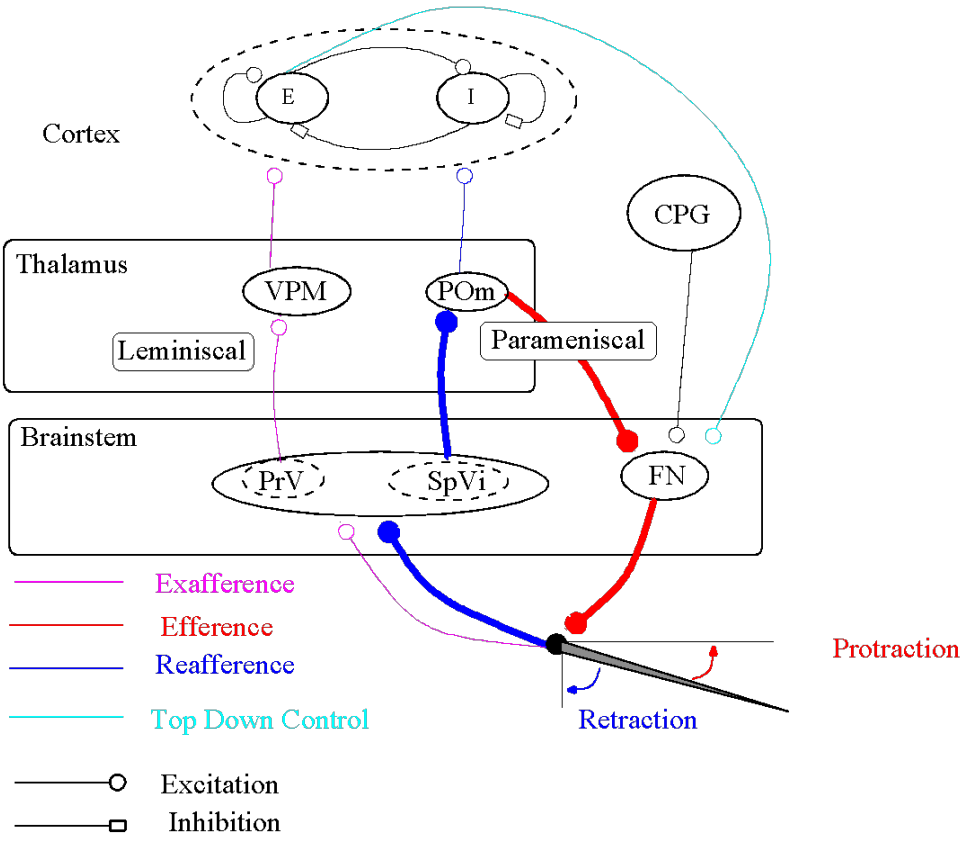

Fig. S2: Three models for whisker circuits mediating a negative closed-loop sensory feedback. (**A**) Net activation of the modeled cortical population drives neurons in the facial nucleus (FN) to drive whisker protraction. This in turn reduces excitatory sensory input to the modeled cortical population because this is driven by retraction. Here negative feedback is mediated implicitly at the periphery. (**B**) Protraction information could be conveyed along the full pathway but net inhibitory input to the modeled cortical population result because POm inhibits the cortex. In either model circuit, the initial activation of cortical neurons causes subsequent suppression of their activity by feedback through the whisker circuit, constituting a negative sensory feedback loop. These two hypotheses are testable but not necessarily mutually exclusive. (**C**) An alternative hypothesis is the whisker feedback is completed in the brain stem and changes in cortical activity are driven by activity changes in the thalamus.

Fig. S2: Three models for whisker circuits mediating a negative closed-loop sensory feedback. (**A**) Net activation of the modeled cortical population drives neurons in the facial nucleus (FN) to drive whisker protraction. This in turn reduces excitatory sensory input to the modeled cortical population because this is driven by retraction. Here negative feedback is mediated implicitly at the periphery. (**B**) Protraction information could be conveyed along the full pathway but net inhibitory input to the modeled cortical population result because POm inhibits the cortex. In either model circuit, the initial activation of cortical neurons causes subsequent suppression of their activity by feedback through the whisker circuit, constituting a negative sensory feedback loop. These two hypotheses are testable but not necessarily mutually exclusive. (**C**) An alternative hypothesis is the whisker feedback is completed in the brain stem and changes in cortical activity are driven by activity changes in the thalamus.

Our whisker model remains abstract in terms of known vibrissa system anatomy and, in particular, the relay stations between the cortex and a whisker. The exact concordance of the model with known vibrissa system anatomy is beyond the scope of this paper, but we provide a more detailed to demonstrate a possible anatomical explanation of our model and provide a means for the research community to experimentally examine closed-loop sensory feedback in specific biological circuits.

In our model (Fig. S2A), we assume that projections between regions are largely excitatory (c.f.[1]). Importantly, we distinguish two subcortical pathways that signal afferent input to cortical neurons - one for transmitting reafferent input and the other for transmitting exafferent input. This distinction could reflect the separation between a parameniscal pathway i.e., via thalamic POm, conveying reafferent signals, and a lemniscal pathway, i.e., via thalamic VPM, conveying exafferent input [2,3]). Accordingly, we modeled exafferent input to cortical neurons by using a stereotypical pulse upon each whisker contact and brief deflection, and reafferent input proportional to whisker angle reflecting motor efference [4]. Regardless of how the properties of reaffererent input - whisking phase, absolute position, or

their temporal derivatives - are encoded by the pathway they do not change the main conclusion of our model as long as the closed-loop sensory feedback constitutes net negative feedback.

In agreement with the anatomy, we assume that cortically generated motor signals modulate whisking behavior by acting on the facial nucleus (FN) [1]. Because whisking behavior persists after sensory denervation [5] , cortical ablation [6], or decerebration[7], we explicitly modeled a central pattern generator (CPG) that autonomously generates whisking patterns locating exogenous to the cortical-whisker loop [8]. Thus, the FN receives input from both the cortical population and CPG and moves the whisker in the reafference model.

We cannot rule out other biological pathways for negative closed-loop sensory feedback. For example, negative feedback can also be mediated by dominant cortical inhibition to the modeled population of cortical neurons (Fig. S2B). In agreement, thalamocortical connections strongly innervate fast spiking neurons and consequently implement strong feedforward inhibition to the cortex[9]. Other potential models arise from heterogeneity in cortical populations. For example, negative closed-loop sensory feedback can be mediated by neurons in the barrel cortex that directly drive whisker retraction with extremely short latencies [10].

Alternatively, the dominant negative feedback loop could be subcortcial, Fig. S2C. Here the dynamics of the cortex only indirectly reflects the stabilization of the thalamus. This scheme is also consistent with reduced thalamic activity during whisking [11]. It is important to note that this implementation also fundamentally relies on stabilisation of neuronal activity by negative closed-loop sensory feedback.

At the level of the whole vibrissa system, there are likely multiple parallel and nested feedback loops, both positive and negative [1]. However, we assume that the overall or net feedback mediated by the cortical-whisker circuit during corresponding behavior is negative

in sign which we empirically demonstrate the presence of negative closed-loop sensory feedback in zebrafish active sensing. These models are experimentally testable. For example, a group of neurons that encode aspects of reafferent input, such as whisker protraction, could be genetically labeled and used for anatomical tracing studies. We can moreover study the physiological role of these neurons by optogenetically silencing them during active whisking and study how brain state as well as the animal's behavior may be altered. This specific neuronal population could also be optogenetically activated and the ensuing behaviors and changes in vibrissae information processing pathways studied.

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S3 Supplementary fish data

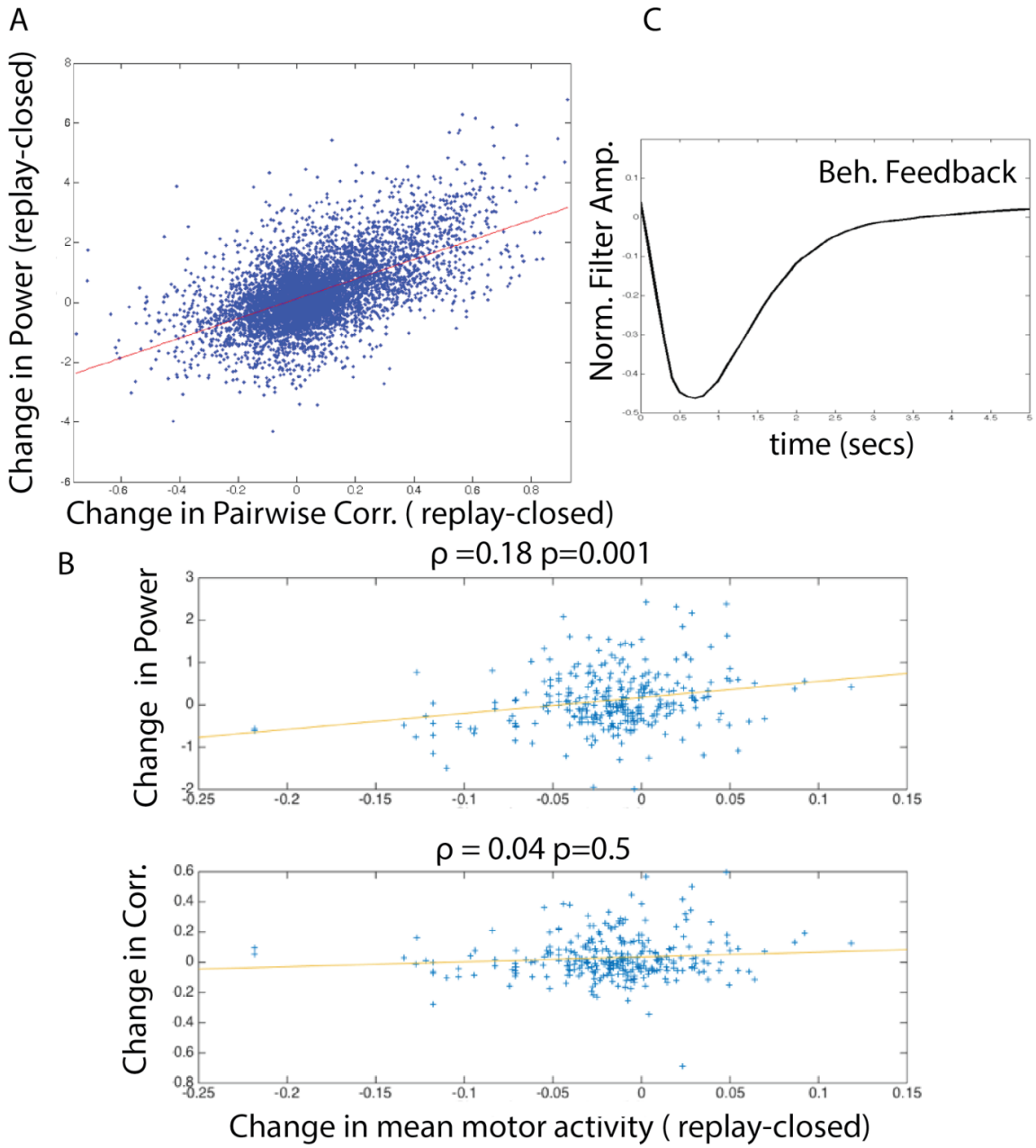

Fig. S3 | (**A**) The decorrelation effect is not an artifact of measurement noise. Changes in pairwise correlations (replay-closed and change in log low frequency power (replay-closed, mean over interval [0.01 0.15] Hz) were highly correlated in the recorded neurons even when the calcium traces (both cells and motor neurons) were thresholded (the threshold was equal to the mean plus one standard deviation of the calcium signal measured over both replay and closed loop conditions) (Spearman's rank correlation $\rho=0.57$, $p<10^{-8}$). (**B**) The increase of motor activity in the closed-loop condition does not easily explain reduction in

neural fluctuations and correlation. (**B**,top): Changes in mean motor activity (replay-closed) and change in log low frequency power (as in **A**), averaged over all cells within a given trial are positively correlated ($r=0.18$, $p<10^{-2}$, Spearman's rank correlation). Specifically, on a cell-by-cell basis increases in low frequency fluctuations are correlated with increases in motor activity (replay-closed) despite the fact that on average motor activity was higher during closed-loop behavior and low frequency fluctuations were reduced. **B**(bottom): Furthermore changes in mean motor activity (replay-closed) and changes in pairwise correlations (replay-closed) (averaged over all pairwise interactions in a given trial) are not significantly correlated ($r=0.03$, $p>0.5$, Spearman's rank correlation). (**C**) Filter describing behavioral feedback**.** A linear filter that describes *behavioral feedback* (E→E') is also strongly negative. Following the kernel method outlined in the methods section we calculated the behavioral feedback as a direct filter between the closed loop environment and environment in the replay condition (E→E'). This also indicates that the closed-loop sensory feedback is negative. Note: the magnitude of this closed-loop sensory feedback estimated from the behavior is much greater than the cell self-feedback, reflecting the fact that cellular variability was much greater than variability across animals.