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Priming Spatial Activity by Single-Cell Stimulation in the Dentate Gyrus of Freely Moving Rats

Highlights

- Spike trains were evoked in silent granule cells during exploratory behavior
- Theta-rhythmic trains can induce spatial firing in previously silent neurons
- Place-field induction is most effective under novelty

Authors

Maria Diamantaki, Markus Frey, Patricia Preston-Ferrer, Andrea Burgalossi

Correspondence

andrea.burgalossi@cin.uni-tuebingen.de

In Brief

Diamantaki et al. have discovered that, under novelty, single trains of action potentials can be sufficient for recruiting silent dentate gyrus neurons into the coding population. These findings provide insights into the cellular mechanisms by which fast representations of the environment can be generated within dentate gyrus circuits.

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Priming Spatial Activity by Single-Cell Stimulation in the Dentate Gyrus of Freely Moving Rats

Maria Diamantaki,[1,2] Markus Frey,[1] Patricia Preston-Ferrer,[1] and Andrea Burgalossi[1,*]
[1]Werner-Reichardt Centre for Integrative Neuroscience, Otfried-Müller-Strasse 25, 72076 Tübingen, Germany
[2]Graduate Training Centre of Neuroscience, IMPRS, 72074 Tübingen, Germany
*Correspondence: andrea.burgalossi@cin.uni-tuebingen.de
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SUMMARY

An essential requirement for hippocampal circuits to function in episodic memory is the ability to rapidly disambiguate and store incoming sensory information [1]. This "pattern separation" function has been classically associated to the dentate gyrus, where spatial learning is accompanied by rapid and persistent modifications of place-cell representation [2, 3]. How these rapid modifications are implemented at the cellular level has remained largely unresolved. Here, we tested whether plasticity-inducing stimuli—spike trains—evoked in postsynaptic neurons are sufficient for the rapid induction of place-field activity in the dentate gyrus. We juxtacellularly stimulated 67 silent granule cells while rats explored a maze for the first time. Spike trains with different characteristics (e.g., number of spikes, frequency, and theta-rhythmicity) were evoked at randomly selected spatial locations. We found that, under novelty, ~30% (10/33) of the stimulated neurons fired selectively at the "primed" spatial location on subsequent laps. Induced place fields were either transient or persisted for multiple laps. The "priming" effect was experience dependent, as it was less frequently observed in habituated animals (3/34 neurons), and it correlated with the number of spikes and theta-rhythmicity of the stimulus trains. These data indicate that, albeit with low efficiency, evoked theta-rhythmic spike trains can be sufficient for priming spatial activity in the dentate gyrus and thus recruiting silent granule cells into the coding population.

RESULTS

Extracellular recordings in the dentate gyrus (DG) have shown that granule cells' discharges are spatially modulated and often entrained by local field potential theta-oscillations (4–12 Hz) [2–4]. In order to fire neurons at physiologically relevant theta-bursts, and hence mimic the natural discharge patterns of active granule cells, we developed a novel juxtacellular stimulation procedure (Figure 1); we found that, under juxtacellular configuration, a brief current pulse (1–3 ms; ~30–100 nA) can evoke spike trains that are entrained by the endogenous theta-rhythmicity of the individual neurons. Figure 1 shows examples of silent granule cells (Figure 1A) stimulated in vivo under urethane theta-oscillations [5]. A single stimulation pulse provided transient and partial access to the cell's membrane potential—indicated by a small hyperpolarizing shift of the voltage signal—which was followed by rapid resealing (Figure 1B). As a result, spike trains evoked by single stimuli often carried a significant amount of theta-rhythmicity (Figure 1C). In anesthetized animals, stimulation did not alter baseline firing rates of granule cells (Figures 1D and S1), e.g., stimulated silent neurons rapidly returned to baseline activity (i.e., no spiking) even after multiple stimulations (Figure S1), consistent with previous observations that juxtacellular stimulation does not alter spontaneous firing rates or the physiological properties of the stimulated neurons [6, 7].

Next, we applied these single-cell stimulation procedures to freely behaving rats. By means of a miniaturized micromanipulator [8], we recorded single neurons in the DG while rats explored an elevated "O" maze. The granule cell layer could be easily identified by characteristic patterns of local field potential activity [9] (see Supplemental Experimental Procedures). In a subset of recordings, the anatomical location was verified by juxtacellular labeling, and in all cases (n = 7), morphologically mature granule cells were recovered. In line with previous work [1, 4, 10, 11], the large majority of neurons within the granule cell layer was silent during exploration (~87%; see Supplemental Experimental Procedures).

After a juxtacellular recording from a silent neuron was established, we tested whether spike trains, evoked at randomly selected spatial locations ("primed locations") were able to induce place-field activity. Recordings were initiated while rats explored the maze for the very first time (day 1) and on few consecutive sessions (on days 2 or 3). We will refer to these recordings as the novelty dataset (Table S1). We found that spike trains evoked by single stimulations can be sufficient for priming spatial activity in silent granule cells, as shown in the representative recording in Figure 2. In this silent neuron, a theta-rhythmic spike train (Figures 2A and 2B) was induced at a randomly selected spatial location (Figure 2C); on subsequent laps, the neuron fired spontaneously at the primed location (Figures 2C and 2D) and a place field emerged.

Altogether, 54 spike trains were fired in 33 silent neurons during exploration of a novel arena. Firing was induced after rats had visited on average approximately three times the primed

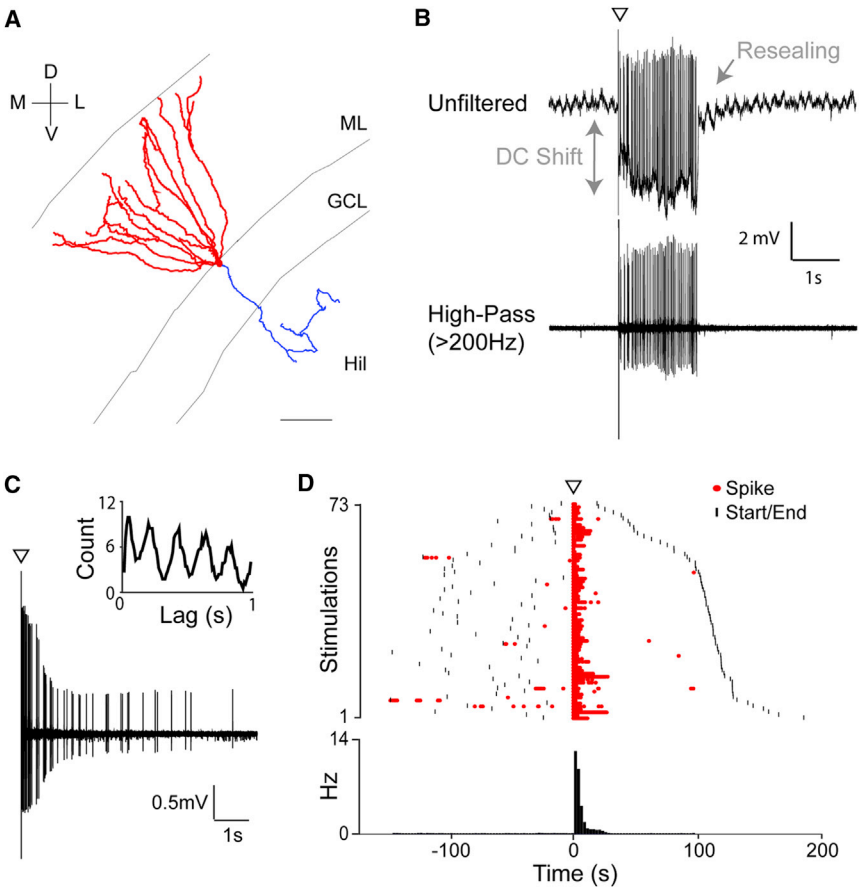

Figure 1. Single-Cell Stimulation in the Dentate Gyrus of Anesthetized Rats

(A) Reconstruction of the dendritic (red) and axonal morphology (blue) of a granule cell, stimulated under anesthesia. GCL, granule cell layer; Hil, hilus; ML, molecular layer. The scale bar represents 100 μm.

(B) Representative raw (top) and high-pass-filtered (bottom) spike traces, showing a typical stimulation procedure of a silent granule cell during urethane/ketamine theta oscillations. A single current pulse (arrowhead) induced a transient negative shift of the recorded voltage (double-headed arrow). Resealing occurred rapidly and led to cessation of spiking.

(C) Representative theta-rhythmic spike train evoked by a single current pulse (arrowhead) and corresponding spike autocorrelogram (top inset). Note the prominent rhythmicity in the theta-frequency range (~4–6 Hz under urethane/ketamine anesthesia).

(D) Raster plot (top) and average firing rate histogram (bottom) for all trains evoked in silent DG neurons under anesthesia (n = 73 stimulations). Red dots indicate spikes; black lines mark the start/end time of each recording. Recordings are aligned by the first spike of each stimulus train (arrowhead).

See also Figure S1.

locations (mean laps = 3.27 ± 3.19), and all stimulated neurons were silent before stimulation (see Table S1). Of these neurons, 23/33 remained silent after stimulation, whereas 10/33 fired spontaneous spikes (median = 16; range 1–382 spikes) after the stimulus trains. In the latter group, we observed a striking spatial specificity, as firing occurred at the primed location on subsequent laps (Figure 3A) with short latencies following stimulation (35.0 ± 16.9 s). To quantify the spatial selectivity of these responses, we calculated the mean distance of all spontaneous spikes from the stimulus locations; in all cases (11 stimulations in 10 neurons; Figure 3A), mean distances were <10 cm (Figure S2A), indicating a tight clustering of spontaneous activity around the primed areas (Figure 3A). In a subset of these neurons (n = 5), multiple stimulations were performed at the same or a different location (Figure S2A; see Figures S2B and S2C for the distribution of firing locations across all cells). Within this limited dataset, we did not observe an obvious correlation between the number of stimulations and the priming effect, with most spatial responses occurring as a result of a single stimulation (Figure S2).

Although the limited recording durations (190.5 ± 109.3 s) and total number of laps (7.7 ± 5.1) prevented rigorous assessment of long-term effects, we next sought to determine the stability of the induced spatial activity across consecutive laps. For this purpose, we restricted the analysis to the subset of recordings where rats visited the primed location more than three times following stimulation (n = 8). In three of the eight cases, induced place fields persisted till the end of the recording sessions (9–28 total laps; Figure S2A) and their properties were similar to previously described DG place fields (e.g., place-field size, 314.5 ± 141.1 cm^2; peak rates, 8.7 ± 7.0 Hz) [4, 10]. In the remaining cases (n = 5), the effect appeared to be transient, lasting for one or two laps following stimulation. In some of these neurons (n = 4), an additional stimulation at the same location (Figure S2A) failed to reinstate spatial firing. We note that this evidence rests on a small number of observations; further work will thus be required for systematically exploring the impact of additional stimulations on evoked spatial activity [12, 13].

Next, we sought to determine which spike train parameters were most efficient for inducing a spatial response. We found that the 11 trains that evoked spontaneous spikes at the primed locations ("effect" trains; Figures 3A and S2A) contained a significantly higher number of spikes compared to the trains (n = 43) that did not evoke spiking (effect = 72.2 ± 76.4 spikes; "no effect" = 34.7 ± 44.6 spikes; p = 0.040; Figure 3B), whereas average firing rates did not differ (effect = 23.9 ± 16.3 Hz; no effect = 22.8 ± 23.1 Hz; p = 0.50; Figure 3B). Second, effect trains were significantly more theta-rhythmic than no effect trains (theta indices; effect = 4.23 ± 3.24; no effect = 1.69 ± 1.62; p = 0.036; Figure 3C). These conclusions were supported by a support vector machine (SVM) approach: a SVM classifier trained solely on the number of spikes and theta-rhythmicity of the stimulus trains was able to assign them to the effect class with high accuracy (87.5%; see Supplemental Experimental Procedures). Thus within the frequency range of our stimulus trains,

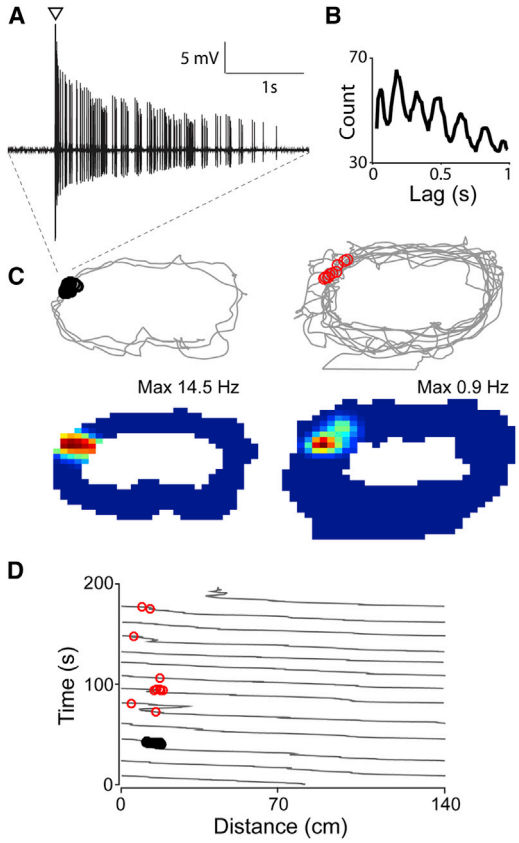

Figure 2. A Place Field Evoked by Single-Cell Stimulation in the Dentate Gyrus of a Freely Moving Rat

(A) Representative high-pass-filtered voltage trace, showing a spike train evoked in a silent granule cell in a freely moving animal.

(B) Spike-autocorrelogram for the train shown in (A). Note the prominent rhythmicity in the theta-frequency range (~6–12 Hz during awake behavior).

(C) Spike-trajectory plots (top) and rate maps (bottom) before and during stimulation (left) and after stimulation (right). Spikes of the stimulus train (black circles), spontaneous spikes after the stimulation (red circles), and maximal firing rates are indicated.

(D) Lap-by-lap analysis for the recording shown in (C). Stimulus spikes (black circles) and spontaneous spikes (red circles) are indicated. The induced place field was stable for the entire recording (approximately nine laps after the stimulus train).

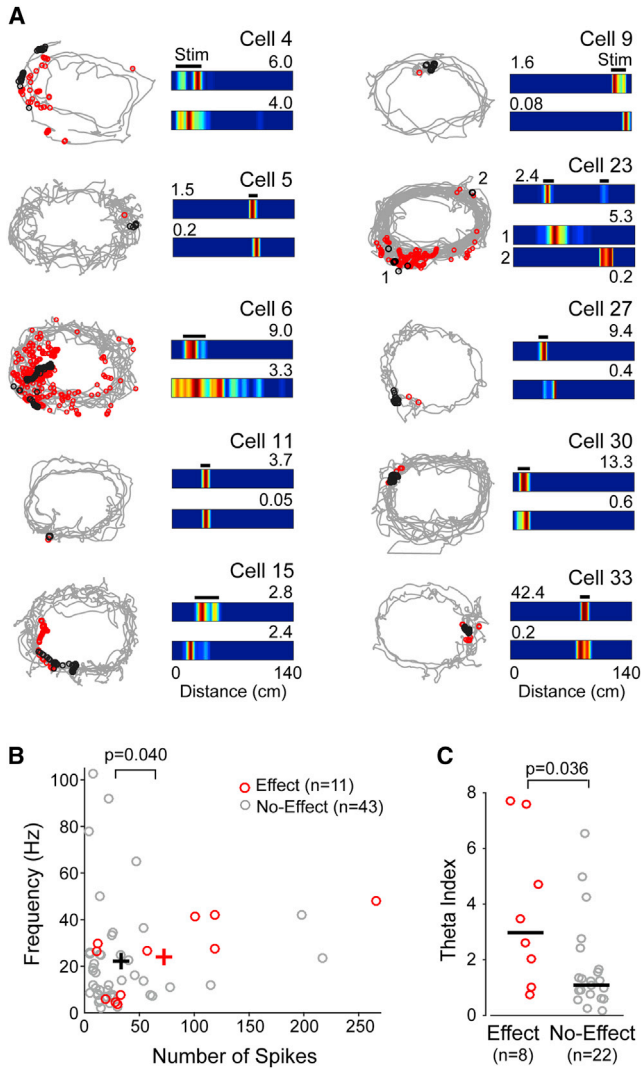

Figure 3. Novelty Dataset: Effect Stimulations and Spike Train Characteristics

(A) Spike-trajectory plots (left panels) showing the location of stimulus spikes (black circles) and spontaneous spikes (red circles) for the ten neurons (11 stimulations), which showed stimulation-induced spatial activity under novelty. (Right panels) Linearized rate maps for the data in the left panels are shown. The location of the stimulus train (black lines), cell ID, and maximal firing rates are indicated. In one neuron (cell 23), a spatial response was observed at two different locations: a long-lasting place field at location 1 and a transient response at location 2 (see also Figure S2).

(B) Scatterplot showing the firing frequencies and the number of spikes for all effect (n = 11; red circles) and no effect trains (n = 43; gray circles) and the corresponding means (red and black crosses). The p value for the comparison of number of spikes (top) between effect and no effect trains is indicated (Mann-Whitney U test).

(C) Theta indices of effect and no effect trains (see Supplemental Experimental Procedures). Black lines represent medians, and the p value is indicated (Mann-Whitney U test).

the total number of spikes and theta-rhythmicity correlated significantly with the effect.

We next asked whether the efficiency of single-cell stimulation in priming a spatial response is experience dependent. To this end, we performed a subset of experiments (60 stimulations in 34 neurons; see Figure S3) in rats that were extensively habituated to the recording environment prior to the experiments (>5 days; see Supplemental Experimental Procedures). We will refer to these recordings as the familiar dataset (Table S1). We found that, in habituated animals, 10/34 stimulated neurons fired spontaneous spikes after the stimulus trains—a similar proportion compared to the novelty dataset (Figure 3B). However, whereas under novelty, spontaneous spikes were clustered around the primed areas (median distance = 3.4 cm; range 0–8.7 cm; n = 11 stimulations in 10 neurons; Figure 3A), in habituated animals, they were more dispersed (median distance = 45.8 cm; range 0–65.7 cm; n = 13 stimulations in 10 neurons; p = 0.005; Figure S4). For a statistical comparison of the two datasets, we defined effect trains as evoking spontaneous spikes

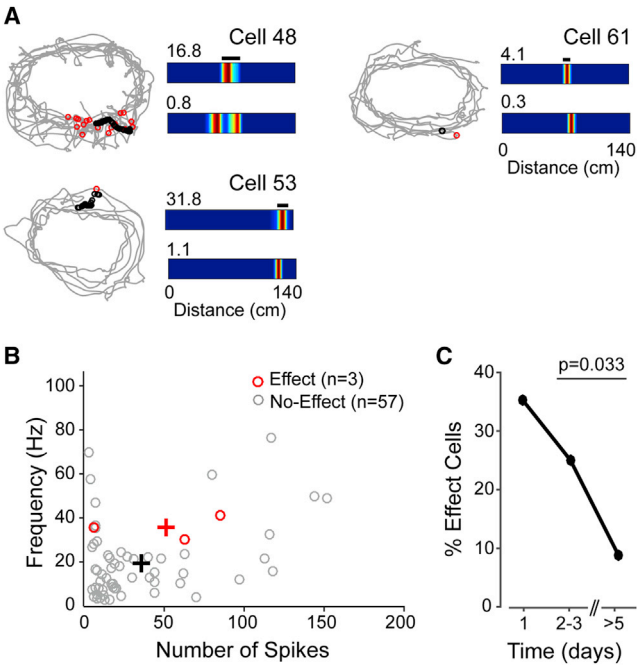

Figure 4. Familiar Dataset: Effect Stimulations and Experience Dependency of the Priming Effect

(A) Spike-trajectory plots (left panels) showing the location of stimulus spikes (black circles) and spontaneous spikes (red circles) for the three neurons, which showed stimulation-induced spatial activity in the familiar dataset. (Right panels) Linearized rate maps for the data in the left panels are shown. The location of the stimulus train (black lines), cell ID, and maximal firing rates are indicated. Note the correspondence between the evoked (top) and spontaneous (bottom) spatial activities.

(B) Scatterplot showing the firing frequencies and the number of spikes for all effect (n = 3; red circles) and no effect trains (n = 57; gray circles) and the corresponding means (red and black crosses).

(C) Fraction of effect cells as a function of experience. The p value of the Fisher's exact test is indicated (novelty versus familiar comparison; see also Table S1).

with short mean distances from the primed area (<10 cm; see Supplemental Experimental Procedures and Figure S4). In habituated animals, three neurons met these criteria (shown in Figures 4A and S3), significantly less than under novelty (3/34 versus 10/33 neurons, respectively; p = 0.033; Fisher's exact test; Figures 4B and 4C). These differences were not accounted for by biases in spike train parameters (average firing rates: novel, 23.05 ± 21.78 Hz, familiar, 20.83 ± 17.06 Hz, p = 0.87; number of spikes: novel, 42.39 ± 54.01, familiar, 35.4 ± 38.18, p = 0.34; theta-index: novel, 2.24 ± 2.14, familiar, 1.81 ± 1.74, p = 0.65) or in the distribution (Figures S2 and S3) and number of stimulations (Table S1) between the two datasets. Altogether, these data indicate that the efficiency of single-cell stimulation in priming spatial responses changes as a function of experience, with granule cells being recruited more efficiently into the coding population under novelty.

DISCUSSION

Extracellular recordings in the DG have revealed that only a small fraction of granule cells are active during behavior, while the large majority remains silent [4, 10, 11]. Such sparse coding scheme is thought to be crucial for disambiguating similar input patterns ("pattern separation") before memory storage [2, 3, 14, 15]. Whether (and how) silent neurons can be recruited into the coding population has remained matter of speculations [16, 17].

Here, we applied novel juxtacellular stimulation procedures (Figure 1) for evaluating the effect of physiologically patterned spike trains in silent DG neurons during free behavior. We provide the first evidence that place-field activity in the DG can be biased by single spike trains and that higher stimulus "intensities" (i.e., duration and number of spikes) are more likely to induce spatial responses in previously silent neurons (Figure 3B). We speculate that longer spike trains could be more efficient than shorter ones in triggering dendritic Ca^{2+} signals and associative synaptic plasticity during behavior [18, 19], in line with previous in vitro work [20]. The temporal structure of evoked postsynaptic spiking in the theta-range also correlated with place-field plasticity (Figure 3C), in line with the higher efficiency of theta-patterned stimuli in potentiating perforant path-granule cell synapses [21–24]. In a number of stimulated neurons, spatial responses closely resembled place-field activity [4, 10], whereas in others, they appeared to be short lasting (Figures S2 and S3); at present, we do not know whether these transient spatial responses can be converted into stable place fields—for example by multiple consecutive stimulations [13]—and whether/how they could impact hippocampal physiology. Such transient effects could result from short-lasting changes in the resting membrane potential of the stimulated cells—a manipulation known to promote spatial firing in silent CA1 pyramidal neurons [25]. Future intracellular recordings will be required for resolving the underlying mechanisms. Notably, the efficiency in evoking a spatial response appeared to be much lower than in CA1 [13, 25], possibly reflecting intrinsic differences between pyramidal and granule-cell circuits in the propensity to express spatial firing [1, 4, 10, 11]. The efficiency was however higher under novelty (Figure 4C), in line with the lower threshold for the induction of synaptic plasticity under reduced GABAergic inhibition [26] and enhanced dopaminergic transmission [27–29], which occur under novelty [30–32].

An open question is the cellular identity of the neurons that showed a spatial response following stimulation. The fact that (1) all recovered neurons were morphologically mature granule cells and that (2) all included neurons were initially silent—a feature classically associated with mature neurons [17, 33–35]—suggests that our recordings are most likely to stem from the mature granule cell population. Future work should however explore the possibility that effect and no effect neurons might correspond to different cell types within the DG network.

Place-field plasticity and the rapid formation of spatial maps in novel environments [36–38] are thought to be a neural reflection of the automatic recording of ongoing experiences by the hippocampus [39]. Such plastic modifications occur most prominently in the DG, where minimal changes in sensory inputs can lead to drastic changes in population responses [2, 3]. Our results offer a potential mechanism for the fast plasticity of spatial maps in the DG, with single spike trains being able to bias the rapid formation of new place fields. Under natural conditions, such trains could be intrinsically [25] or behaviorally driven [40]

and/or induced by co-active sets of spatial inputs [41, 42]. Such localized events could then prime the formation of new activity patterns in the DG, a necessary requirement for the hippocampus to disambiguate similar experiences during episodic memory formation.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.12.053.

AUTHOR CONTRIBUTIONS

A.B. conceived, designed, and supervised the study. A.B., M.D., and P.P.-F. performed experiments. M.D. and M.F. analyzed data. A.B. wrote the manuscript with input from all authors.

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