SI Appendix

Detailed methods.

Experiment: Transverse medial entorhinal cortical (mEC) slices (450 μm) were prepared from adult Wistar rats, during ketamine (100 mg/kg) and xylazine (10 mg/kg) anaesthesia, and maintained 34°C at the interface between a continuous stream (1.2 ml/min) of aCSF (in mM: 126 NaCl, 3 KCl, 1.25 NaH_2PO_4, 24 $NaHCO_3$, 1.2 $MgSO_4$, 1.6 $CaCl_2$, and 10 glucose) and warm, moist carbogen gas (95% O_2 – 5% CO_2). Previous studies using 2 mM $[Mg^{2+}]_o$ revealed a mean decrease in frequency of gamma rhythms that was not significant[S1]. Here we use a lower concentration of extracellular magnesium ions to enhance this effect. Drugs were all bath-applied at known concentrations: kainate (2S,3S,4R)-carboxy-4-(1methylethenyl)-3-pyrrolidineacetic acid), 200–400 nM (Ascent Scientific, UK); ketamine ((±)-ketamine hydrochloride) 10-25μM (Sigma, UK). Extracellular field potentials were recorded from superficial (LII-III) medial entorhinal cortex with glass electrodes (1–2 MΩ) filled with aCSF (composition above), intracellular recordings were taken with glass electrodes (70–130 MΩ) filled with 2M KCH_3SO_4. Four types of neuron were recorded from superficial layers of the medial entorhinal cortex:- stellate cells, with cell bodies predominantly in LII, LIII pyramidal cells, LII fast spiking interneurons (type-1, basket cells generating gamma frequency spiking in control conditions) and LIII fast spiking interneurons (type-2, goblet cells generating bursts of theta frequency spiking in control conditions). Frequency and power values were obtained from power spectra from 60s epochs of field potential data (Axograph, Axon Instruments, Foster City, CA). All values are given as mean ± SE. The kinetics of IPSPs and EPSPs were measured using MiniAnalysis (Jaejin Software, Leonia, NJ), and >200 IPSPs were obtained per slice and pooled for additional analysis.

Modeling: To investigate the mechanisms for the experimentally observed rhythmic activity patterns, we modeled a local region of the superficial layers of

the entorhinal cortex with a network consisting of a population of 100 pyramidal cells (E), a population of 10 LII basket cell interneurons, corresponding to type 1, basket interneurons (I), a population of 10 theta-producing interneurons, corresponding to type 2, goblet interneurons (G), and a population of 20 stellate cells (S), (Fig. 3a, ref S2) Each neuron was modeled as a single compartment using biophysically-based Hodgkin-Huxley type equations. All four cell types were endowed with the standard sodium, potassium, and leak currents as well as certain additional currents. The model for the E cells[S3] possessed an afterhyperpolarization (AHP) current while the model for the S[S4] and G cells were endowed with an h-current (hyperpolarization activated inward current) and a persistent sodium current. We noted that the goblet cells had responses to current injection similar to stellate cells and were thus modeled with the same intrinsic dynamics as the stellates (except a weaker h-current), but with the same synaptic dynamics as the I-cells. Heterogeneity was introduced to each cell population via variable tonic drives chosen randomly from a gaussian distribution. The E cells were also endowed with cycle by cycle white noise chosen from a gaussian distribution. The presence of kainate was modeled by endowing the E and I cells with a depolarizing tonic drive while the presence of NMDA receptor antagonists was modeled by the removal of depolarizing tonic NMDA drive to I-cells. The network was able to recreate a wide range of physiological behaviors with a manageable set of parameters and was thus simple enough to illustrate clearly the mechanism at work behind the switches in activity while still maintaining high physiological relevance. Code for the simulations was written in C++, and the system of ODEs for the model was solved using a fourth-order Runge-Kutta algorithm[S5] with a time step of .02 ms. Simulations were plotted using Matlab (The Mathworks, Natick, USA).

The various neuron types are modeled using Hodgkin-Huxley type equations. The models for the E and I cells are based on the biophysically-based model[S4]. The E cells have the standard sodium, potassium, and leak currents as well as an afterhyperpolarization (AHP) current. The model equations are:

$$C\frac{dv}{dt} = -g_{Na}m^3h(v-E_{Na}) - g_K n^4(v-E_K) - g_L(v-E_L) - g_{AHP}w(v-E_{AHP}) + I_{APP} - I_{Syn}$$

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m$$

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n$$

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h$$

$$\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_w(v)}$$

$$\frac{ds}{dt} = \alpha_s(1+\tanh(v/4))(1-s) - \beta_s s$$

where C the membrane capacitance (μF/cm^2), v is the membrane potential (mV), I_{syn} is the sum of synaptic currents (μA/cm^2), g is conductance (mS/cm^2), and time is measured in ms. The default parameters for the system are:
$C = 1, g_{Na} = 100, E_{Na} = 50, g_K = 80, E_K = -100, g_{AHP} = .4, E_{AHP} = -100, \alpha_s = 5, \beta_s = 0.5$.
For the gating variables, the voltage dependent rate constants (α_x and β_x) and voltage dependent steady-state values (w_∞) and time constants (τ_w) are given by:

$\alpha_m(v) = 0.32(v+54)/(1-\exp(-(v+54)/4))$,
$\beta_m(v) = -0.28(v+27)/(1-\exp((v+27)/5))$,
$\alpha_n(v) = 0.032(v+52)/(1-\exp((v+52)/5))$ and $\beta_n(v) = 0.5\exp(-(v+57)/40)$,
$\alpha_h(v) = .128\exp(-(v+50)/18)$ and $\beta_h(v) = 4/(\exp(-.2(v+27))+1)$,
$w_\infty(v) = 1/(\exp(-.1(v+35))+1)$,
$\tau_w(v) = 400/(3.3\exp(0.05(v+35)) + \exp(-0.05(v+35)))$.

The I cells have identical equations except that there is no AHP current and the synaptic turn-on and turn-off rates are given by $\alpha_s = 2$ and $\beta_s = 0.1$.

The model for the S and G cells are based on the biophysically-based model by Acker et al. (ref S4). The model for the S cells is given by:

$$C\frac{dv}{dt} = -g_{Na}m^3h(v-E_{Na}) - g_K n^4(v-E_K) - g_L(v-E_L) - g_{Nap}p(v-E_{Na}) - g_h(0.65hf + 0.35hs)(v-E_h) + I_{app} - I_{Syn}$$

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m$$

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n$$
$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h$$
$$\frac{dp}{dt} = \frac{p_\infty(v) - p}{\tau_p(v)}$$
$$\frac{dhf}{dt} = \frac{hf_\infty(v) - hf}{\tau_{hf}(v)}$$
$$\frac{dhs}{dt} = \frac{hs_\infty(v) - hs}{\tau_{hs}(v)}$$
$$\frac{ds}{dt} = \alpha_s(1+\tanh(v/4))(1-s) - \beta_s s$$

where the units are as for the E cell model. The default parameters for the system are: $C = 1.5, g_{Nap} = 0.5$, $g_{Na} = 52$, $g_K = 11$, $g_L = 0.5$, $g_h = 1.5$, $E_{Na} = 55$, $E_K = -90$, $E_L = -65$, $E_h = -20, \alpha_s = 11, \beta_s = 0.19$.

The voltage dependent rate constants (α_x and β_x) and voltage dependent steady-state values (x_∞) and time constants (τ_x) are given by:

$$\alpha_m(v) = -.1(v+23)/(\exp(-.1(v+23)) - 1),$$
$$\beta_m(v) = 4\exp(-(v+48)/18),$$
$$\alpha_n(v) = -.01(v+27)/(\exp(-.1(v+27)) - 1),$$
$$\beta_n(v) = .125\exp(-(v+37)/80),$$
$$\alpha_h(v) = .07\exp(-(v+37)/20),$$
$$\beta_h(v) = 1/(\exp(-.1(v+7)) + 1),$$
$$p_\infty(v) = 1/(1+\exp(-(v+38)/6.5)),$$
$$\tau_p(v) = 0.15,$$
$$hf_\infty(v) = 1/(1+\exp((v+79.2)/9.78)),$$
$$\tau_{hf}(v) = 0.51/(\exp((v-1.7)/10) + \exp(-(v+340)/52)) + 1,$$
$$hs_\infty(v) = 1/(1+\exp((v+71.3)/7.9)),$$
$$\tau_{hs}(v) = 5.6/(\exp((v-1.7)/14) + \exp(-(v+260)/43)) + 1.$$

The G cells have identical equations except that $g_h = 1.45$ and the synaptic turn-on and turn-off rates are given by $\alpha_s = 2$ and $\beta_s = 0.1$, which matches those of the I cells.

Heterogeneity and noise is present in the model. To introduce heterogeneity, we choose I_{het} randomly from a gaussian distribution with mean 0. To introduce

noise, we choose I_{noise} randomly from a gaussian distribution with mean 0 at each time step. For E cells, $I_{APP} = I_{tonic} + I_{kainate} + I_{het} + I_{noise}$ where $I_{tonic} = 0$, $I_{kainate} = 1.2$ and I_{het} and I_{noise} correspond to standard deviations of 0.05 and 1.35, respectively. For I cells, $I_{APP} = I_{tonic} + I_{NMDA} + I_{kainate} + I_{het}$ where $I_{tonic} = -3.1$, $I_{kainate} = 0.1$ and I_{het} corresponds to a standard deviation of 0.01, and $I_{NMDA} = 0$ or 3.0, depending on whether NMDA receptor block is present. For G cells, $I_{APP} = I_{tonic} + I_{het}$ where $I_{tonic} = -1.5$ and I_{het} corresponds to a standard deviation of 0.015. For S cells, $I_{APP} = I_{tonic} + I_{het}$ where $I_{tonic} = -2.0$ and I_{het} corresponds to a standard deviation of 0.01.

All-to-all coupling is used between populations and there is no coupling within individual populations. Let S_X denote the sum of the values of the gating variables s of the X cells where $X = E, I, G,$ or S and let $E_{synE} = 0$ and $E_{synI} = -80$. For E cells, $I_{syn} = g_{IE} S_I (v - E_{synI}) + g_{GE} S_G (v - E_{synI})$ where $g_{IE} = 0.48$ and $g_{GE} = 0.16$. For I cells, $I_{syn} = g_{EI} S_E (v - E_{synE}) + g_{GI} S_G (v - E_{synI}) + g_{SI} S_S (v - E_{synE})$ where $g_{EI} = 1.23, g_{GI} = 0.4$, and $g_{SI} = 0.1$. For G cells, $I_{syn} = g_{EG} S_E (v - E_{synE}) + g_{IG} S_I (v - E_{synI}) + g_{SG} S_S (v - E_{synE})$ where $g_{EG} = 1.3, g_{IG} = 0.8$, and $g_{SG} = 0$. For S cells, $I_{syn} = g_{IS} S_I (v - E_{synI}) + g_{GS} S_G (v - E_{synI})$ where $g_{IS} = 0.1$ and $g_{GS} = 0$.

Using this model we were able to accurately reproduce both the global network dynamic changes (the change in power and frequncy of gamma rhythms, fig 3b) by reducing only the NMDA drive to basket cells (I-cells). In addition the model reproduced the cell type-specific changes in spike rates in each interneuron cell class studied (fig. 3c,d), as well as the increase in spike rates seen for the two principal cell populations – pyramidal cells (E-cells) and stellate cells (S-cells) as illustrated in supplementary figures 1a,b. The model demonstrated dynamics that were critically dependent on NMDA drive to basket cells over a broad range of values for this papameter, as summarised in supplementary figure 1c. The critical features of the network, predicted by the model) for the change in power, frequency and differential interneuron spike rates in the control and 'ketamine' conditions included: a) The presence of strong I-G inhibitory synaptic coupling; b) A lower strength of G-E and G-S compared to I-E and I-S.

Supplementary figure legends.

Supplementary figure 1. Changes in neuronal subtype spike rates are accurately reproduced using a 4-subtype analytical model. Using the network structure illustrated in fig.1. ketamine effects were modeled by a single manipulation – reduction in tonic drive to fast spiking basket cells. This change alone predicted the pattern of spike changes in all cells seen in experiment. **a**. 1 second epoch, example traces from a stellate cell recorded in control experimental conditions and in the presence of ketamine. Graphs below show the percentage of stellate cells (s-cells) spiking at any given time during a 1 second simulation using the model. Note both experiment and model show large increase in spike rates for this cell type. **b**. 1 second epoch, example traces from a LIII pyramidal cell recorded in control conditions and in the presence of ketamine. Graphs below show the percentage of pyramidal cells (E-cells) spiking at any given time during a 1 second simulation. Note, as with stellate cells, both experiment and model show large increase in spike rates in the presence of ketamine. Changes in spike rates for goblet (G) and basket (I) cells are shown in detail in figure 3. **c**. Summary of the spike rate changes in each of the 4 cell subtypes used to construct the model. For a range of I-NMDA drive scales from 0 ('ketamine' condition) to 3.0 ('control' condition) a gradual increase in basket cell spike rates was seen. This increase in the degree of fast inhibition in the model network was accompanied by a decrease in spike rates for each other cell type (pyramidal cell, stellate cell and goblet.

Supplementary figure 2. **Characterisation of basket and goblet interneurons. a**. Superimposed traces normalized for amplitude demonstrate that action potentials in goblet cells (red) are characterized by their longer duration and are followed by a longer AHP as compared to those in basket cells (black). **b**. Voltage–current relationship for basket (black, $n = 5$) and goblet (red, $n = 5$) cells, data is represent at each point as mean ± s.e.m. Scale bars represent 10 mV and 2 ms.

Supplementary references

S1. Cunningham, M.O. et al (2006) Region-specific reduction in entorhinal gamma oscillations and parvalbumin-immunoreactive neurons in animal models of psychiatric illness. *J Neurosci* 26: 2767-76.

S2. Jalics J, Cunningham MO, Kispersky TJ, Whittington MA, Kopell N (2006) Activation of different gamma-generating microcircuits in entorhinal cortex is NMDA receptor dependent. *Soc. Neurosci. Abs*. 36: 635.18.

S3. Kopell N, Ermentrout GB, Whittington MA, Traub RD (2000) Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. USA* 97: 1867-72.

S4. Acker CD, Kopell N, White JA (2003) Synchronization of strongly coupled excitatory neurons: relating network behavior to biophysics. *J. Comput. Neurosci*. 15: 71-90.

S5. Burden RL, Faires JD (2005) Numerical Analysis, 8th. Ed. Thomson Brooks/Cole.