SUPPLEMENTARY TEXT

Modeling Results

Our electrophysiological findings support a specific role for the NMDA receptor on FS-PV interneurons in the emergence of gamma rhythm. First, in PV-Cre/NR1f/f mice we observed enhanced baseline cortical gamma oscillations, both in the anesthetized and awake state (Figure 2a, b and 3b). In a model of reciprocally coupled excitatory and inhibitory neurons, decreasing the excitability of FS-PV cells, as would be expected in the absence of slow excitatory NMDA currents, during conditions of noisy background excitatory drive, led to decreased spontaneous asynchronous activity in these interneurons. This reduction in asynchronous inhibition in turn increased activity in the excitatory population, and enhanced the emergence of synchronous activity in the excitatory network. Model interneurons with reduced excitability required more synchronous input from the excitatory population in order to fire, and because of their reduced sensitivity to background asynchronous activation, they in turn provided more synchronous inhibition to the network, enhancing gamma range activation (Supplementary Figure 3a). This mechanism is closely related to the "suppression boundary" described in (1).

Second, we observed a significant reduction in gamma-band activity following MK-801 administration in PV-Cre/NR1f/f mice (Figure 3d-g). In contrast, MK-801 application in control mice led to enhanced gamma activity (Figure 3d-g) which may be due to reduced activity of the inhibitory populations (2). MK-801 application in PV-Cre/NR1f/f mice, which already have suppressed NMDAR activity in the FS-PV

population, could be expected to experience a decrease, rather than an increase in gamma power. MK-801 would actually serve to suppress activity of excitatory cells, in addition to the previously suppressed FS interneurons, and thus reduce the synchronous excitation onto inhibitory neurons required for gamma emergence. This hypothesis is supported in our model, which shows a decrease in gamma power when application of MK-801 to PV-Cre/NR1f/f mice is modeled by reducing excitability in excitatory cells in addition to the previously suppressed inhibitory population (Supplementary Figure 3b).

Third, we observed decreased enhancement of gamma oscillations under optogenetic drive of FS-PV interneurons in PV-Cre/NR1f/f mice compared to in control mice (Figure 2d and e). We also found from tetrode recordings that although FS-PV interneurons in PV-Cre/NR1f/f mice are as likely to respond to light drive as FS-PV interneurons in control mice, their spiking responses are later and show more variance (Supplementary Figure 2b, c, g) compared to in control mice (Supplementary Figure 2e-g). This increase in latency and variation in the FS-PV response to light drive may be responsible for the decreased enhancement of gamma power, as decreased inhibitory synchrony is known to undermine gamma generation in computational models (1, 3). Our modeling indicates that decreased interneuron excitability due to removal of NMDA from the FS-PV population may directly generate this increase in FS-PV spike latency and variation in response to optical stimulation in the PV-Cre/NR1f/f mice. In a second model of inhibitory cells responding to periodic excitatory input, we found that a uniform reduction in interneuron excitability led to a 83 % increase (3.0463 ms to 5.5658 ms) in latency and a 4.43-fold increase (0.0209 to 0.0926) in the standard error of the drive response time in a 200 ms trial with 10 cells receiving 40 Hz excitatory input

(Supplementary Figure 3c). These changes are comparable to our tetrode data which shows a 73 % increase in latency and a 1.83-fold increase in standard error at low light drive (Supplementary Figure 2g). The discrepancy in the absolute value of standard error between the model and data is due to the high level of heterogeneity in recorded cells, which is not completely reproduced in the model. Thus, our modeling predicts that the general slowing of the FS-PV response to light drive is due to a decrease in excitability caused by reduction of NMDA currents, while the increase in variation is due to transfer to a dynamic regime where small reductions in excitability can increase variation in response time.

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3. Tiesinga PH, Fellous JM, Salinas E, Jose JV, Sejnowski TJ. Inhibitory synchrony as a mechanism for attentional gain modulation. *J Physiol Paris* 2004 Jul-Nov; **98**(4-6)**:** 296-314.