PV cells are 30%–50% of all inhibitory interneurons (Gonchar and Burkhalter, 1997), and that 90% of PV cells were virally infected (88% ± 6%; n = 5 mice), a simple calculation reveals that the observed change in PV cell firing rate should result in a 13% ± 8% change in inhibition, consistent with the experimentally observed 10% reduction in synaptic inhibitory current (Figure 5A). Moreover, since our perturbation of PV cells was chosen to be moderate, and thus fall within the range of firing rates spanned by these neurons during awake-behaving states in mice (Niell and Stryker, 2010), we believe that PV cells are likely to exhibit a similar level of control over visually evoked responses during naturally occurring behavioral states and visual environments.

While changing the firing rate of the PV cells by 3–4 spikes/s (~40%) resulted in an opposite change in layer 2/3 Pyr cell responses by ~0.5–1 spikes/s (~40%; Figures 2F, 2G, and S2), a small fraction (<10%) of Pyr cells exhibited "paradoxical" effects. That is, upon photo stimulation of Arch-expressing PV cells these Pyr cells were also suppressed rather than activated, or upon photo stimulation of ChR2-expressing PV cells Pyr cells were activated rather than suppressed (Figures 2F, 2G, and S2). These paradoxical effects in Pyr cells probably occur because a small subset (<10%) of PV cells also exhibited paradoxical effects. That is, upon photo stimulation, a few visually identified Arch-expressing PV cells were activated rather than suppressed or ChR2-expressing PV cells were suppressed rather than activated (Figures 2E and S2A). This may be explained by the fact that PV cells not only contact Pyr cells but also inhibit one another (Galarreta and Hestrin, 2002). Thus, in a fraction of PV cells the changes in synaptic inhibition caused by perturbing PV cell activity may outweigh the direct effects of opsin activation. The potential for paradoxical effects during optogenetic manipulation further highlights the importance of directly quantifying the impact of the perturbation.

Perturbing PV Cells Affects Synaptic Inhibition with Little Change in Excitation

We find that PV cells substantially impact the response of layer 2/3 Pyr cells to visual stimuli. In principle, this action can occur via two mechanisms: the direct reduction in synaptic inhibition and, due to the recurrent nature of the layer 2/3 circuit, the indirect increase in excitation. Whole-cell recordings from Pyr cells upon photo suppression of PV cell activity revealed a systematic, yet relatively small, decrease in synaptic inhibition and negligible changes in excitation. This underscores the exquisite sensitivity of cortical sensory responses to even small changes in synaptic inhibition. The fact that synaptic excitation did not change in a consistent manner, despite clear increases in Pyr cell spiking, implies that recurrent excitatory connections between layer 2/3 Pyr cells contribute little to the overall excitatory input onto these cells during visual stimulation, as suggested by a recent study (Hofer et al., 2011).

PV Cells Linearly Transform Visual Responses of Pyr Cells

The computation performed by PV cells, i.e., how these neurons control the visual responses of layer 2/3 Pyr cells, is quantitatively summarized by a simple linear equation, both additive and multiplicative with a threshold (which accounts for the spiking threshold of neurons). While Pyr cell responses are most significantly transformed by the multiplicative factor, which has no impact on tuning properties, the small additive component of this transformation accounts for the minor changes in overall selectivity (quantified by OSI and DSI) while leaving tuning sharpness unchanged.

The simplicity of this transformation relies in part on the fact that, in mice, PV cells generate inhibition that varies little with orientation (Figure 1; Sohya et al., 2007; Niell and Stryker, 2008; Kerlin et al., 2010; Ma et al., 2010). Accordingly, within each condition (control or Arch or ChR2 stimulation), as long as the stimuli were presented at constant contrast (Figure 4) the activity of PV cells must have been approximately constant, regardless of stimulus orientation. In other species, like cats, where due to the presence of large orientation domains the responses of inhibitory neurons are tuned to orientation (Anderson et al., 2000) (although PV cells are likely to be less turned than other neurons; Cardin et al., 2007; Nowak et al., 2008), more complex models may be necessary to describe their impact on visual responses (Ferster and Miller, 2000; Katzner et al., 2011). In the primate, however, where orientation domains have an anatomically smaller scale (Nauhaus et al., 2008), individual PV cells may sample excitation from several domains and, hence similar to mice, control gain by generating orientation invariant inhibition.

Interestingly, despite the fact that cortical responses as a function of contrast and cortical responses as a function of orientation are independent of each other (Niell and Stryker, 2008; Finn et al., 2007), PV cell perturbation affected both responses linearly and in a quantitatively similar fashion (i.e., PV cell suppression multiplied both responses by ~1.4 and added a small offset). This further demonstrates that PV cells are ideally suited to globally modulate gain.

Modulation of Pyr Cell Response without Systematic Changes in Tuning Sharpness

How can PV cell perturbation so robustly modulate Pyr cell response without systematically affecting tuning sharpness? Based on the classical "iceberg" model of a cell's membrane potential tuning (Carandini and Ferster, 2000) this seems counterintuitive. The iceberg model illustrates the fact that, due to the spike threshold, the spike output of the neuron is generally more sharply tuned than the underlying membrane potential (where a mountain shaped iceberg is the membrane potential tuning curve and the water level is the spike threshold). According to this model, depolarization of the membrane (e.g., by decreasing inhibition through PV cell suppression) is like lowering the water level around the iceberg and results in a broader spiking response as a function of orientation, i.e., a decrease in tuning sharpness. Importantly, this model implies that some of the iceberg is under the water level, i.e., that some of the membrane potential tuning curve is below threshold for spike generation. This is clearly the case in Pyr cells, like the one illustrated in Figures 1E and 1F, that do not generate any spike to stimuli of the nonpreferred orientation. However, such cells are the exception rather than the rule. The average tuning curve of layer 2/3 Pyr cells (e.g., Figure 1D inset and Figure 4)