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SYMPOSIUM REPORT

Mechanisms of response homeostasis during retinocollicular map formation

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The mechanisms of Hebbian synaptic plasticity have been widely hypothesized to play a role in the activity-dependent development of neural circuits. However, these mechanisms are inherently unstable and would lead to the runaway excitation or depression of circuits if left unchecked. In the last decade, a number of elegant studies have demonstrated that homeostatic plasticity mechanisms exist to stabilize neural networks and maintain the constancy of neuronal output in response to changes in activity levels. These include synaptic scaling, sliding threshold models of synaptic plasticity, dynamic regulation of the number and strength of synapses, and bidirectional control of intrinsic excitability. Recently, we showed that the total synaptic input onto individual neurons of the mouse superior colliculus is preserved regardless of the size of their visual receptive fields, a phenomenon we term 'response homeostasis'. Here, we argue that regulating the capacity for synaptic plasticity and controlling the number and strength of retinocollicular inputs can preserve collicular neuron output, and we present evidence that changes in intrinsic excitability are not associated with response homeostasis. We also review findings from a number of different mutant mice and discuss whether and how different cellular mechanisms may underlie response homeostasis. Combined with other studies, our work reveals an important role for homeostatic mechanisms in regulating functional connectivity during the construction of receptive fields and the refinement of topographic maps.

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Neuronal activity is thought to play an instructive role in regulating the functional connectivity of neural circuits during development. These changes are thought to utilize the Hebbian, correlation based mechanisms of long-term potentiation (LTP) and long-term depression (LTD). These Hebbian changes, however, are inherently unstable and can lead to the runaway excitation or depression of a subset of synapses when left unchecked. For example, if LTP is based on the ability of a presynaptic neuron to fire a postsynaptic neuron effectively, then the resulting potentiation will subsequently increase the capacity of that connection to induce firing again in the future, thereby resulting in even greater LTP. This ongoing cycle can eventually cause a destabilizing effect on the circuit (Turrigiano & Nelson, 2004). For this reason, Hebb-based models for experience-dependent development and plasticity of neural circuits typically require some type of homeostatic rules to constrain synaptic strength within certain physiological limits.

In the last decade, a number of studies have investigated homeostatic mechanisms that can permit selective changes at appropriate synapses without degrading the function of the entire neural circuit (Burrone & Murthy, 2003; Turrigiano & Nelson, 2004). In cortical and hippocampal cultures, for example, individual neurons dynamically adjust the strength of all their excitatory synapses during different levels of input activity in order to maintain a target firing rate. In response to a global reduction in afferent activity, excitatory synapses will increase their strength, whereas a global increase in activity will induce an overall reduction in synaptic strength (O'Brien *et al.* 1998; Turrigiano *et al.* 1998; Burrone *et al.* 2002).

One of the mechanisms that may mediate this type of homeostasis is termed 'synaptic scaling'. In synaptic scaling, the distribution of amplitudes of excitatory

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currents at all the synapses onto a neuron (the miniature excitatory postsynaptic current; mEPSC) increases in response to reduced activity, and decreases in response to increased activity (Turrigiano *et al.* 1998). These distributions are scaled up or down in a proportional manner, thereby preserving the relative differences in synaptic weights among all the synapses onto any given neuron (Turrigiano, 1999). Interestingly, synaptic scaling has been observed in the developing visual system in response to changes in sensory input. Depriving one eye of visual input for 2 days (monocular deprivation) results in an increase in the strength of individual synapses onto pyramidal neurons in the rodent visual cortex (Desai *et al.* 2002). These changes are consistent with the observations of synaptic scaling described in culture, and are reversed with subsequent visual experiences (Desai *et al.* 2002).

In addition to synaptic scaling, a number of other mechanisms exist that could constrain the output of individual neurons. For example, the threshold for Hebbian LTP and LTD could be changed in order to promote stability and maintain synaptic input around a set point. The same results could also be achieved via the reciprocal regulation of the number and strength of synaptic inputs. Finally, the firing rate of neurons could also be kept constant by adjusting the voltage-dependent active conductances that control intrinsic excitability.

Response homeostasis in the superior colliculus

To examine whether such mechanisms play a role during the refinement of sensory maps and the construction of receptive fields, we have used the mouse retinocollicular system as a model. In this pathway, retinal ganglion cell (RGC) projections to the superficial layers of the superior colliculus (SC) form a precise point-to-point map of visual space. The initial, coarse targeting of RGC axons to their targets is guided by molecular cues expressed in RGCs and the CNS (McLaughlin & O'Leary, 2005). The subsequent refinement of this crude map occurs via a process of activity-dependent competition that requires spontaneous retinal waves (Grubb *et al.* 2003; McLaughlin *et al.* 2003; Chandrasekaran *et al.* 2005). These waves consist of bursts of action potentials that sweep across the retina to produce highly correlated activity among neighbouring RGCs, and are therefore hypothesized to play an instructive role in map refinement by regulating Hebbian competition among retinocollicular synapses (Crair, 1999; Torborg & Feller, 2005; Shah & Crair, 2008).

Using various strains of mutant mice with specific mapping defects in the superior colliculus, we have used *in vivo* recording techniques to test the hypothesis that homeostatic mechanisms exist to preserve the response of individual SC neurons within a given range, a phenomenon we term 'response homeostasis' (Chandrasekaran *et al.* 2005, 2007). In mice that lack the $\beta 2$ subunit of the nicotinic acetylcholine receptor ($\beta 2^{-/-}$ mice), spontaneous retinal waves are disturbed during the first postnatal week (Bansal *et al.* 2000). As a result of disrupting this instructive signal, anatomical refinement of the retinotopic map in the superior colliculus (SC) is perturbed in $\beta 2^{-/-}$ animals (McLaughlin *et al.* 2003; Chandrasekaran *et al.* 2005). Consistent with the anatomical phenotype, RF areas are, on average, much larger in $\beta 2^{-/-}$ mice. Interestingly, the peak visual response to small stimuli is also much weaker, and the decrease in peak response compensates for the increase in RF area such that the total visual response (defined as the sum of responses across the entire RF) remained constant between genotypes (Chandrasekaran *et al.* 2007). Because the product of RF area and peak response is proportional to the total response, a plot of the logarithm of these measures should result in a linear relationship of slope -1 if the total response is constant across individual neurons. Figure 1*A* depicts such a plot, and indeed a line of slope -1 is a good fit for control as well as $\beta 2^{-/-}$ neurons (Control: $r^2 = 0.59$; $\beta 2^{-/-}$ $r^2 = 0.52$; combined $r^2 = 0.79$). The existence of this relationship on a cell-by-cell basis suggests that there is a cellular mechanism in place that regulates neuronal response regardless of receptive field size, both in WT and $\beta 2^{-/-}$ mice.

We also examined whether response homeostasis persists when the molecular mechanisms that mediated axon guidance and branching of retinal ganglion cell projections to the superior colliculus are disrupted (Chandrasekaran *et al.* submitted). Bone morphogenetic protein (BMP) has been shown to control the graded expression of molecules that are implicated in the guidance of RGC axons and pattern the dorsal–ventral (DV) retinal axis (Plas *et al.* 2008). In BMP receptor (BMPr) mutant mice, dorsal RGC axons project ectopically to locations in the SC that normally receive input from more ventral retinal regions. *In vivo*, we observe a mixture of physiological phenotypes in SC neurons from BMPr mutant mice. These include ectopic, split, enlarged and patchy/distorted receptive fields (Chandrasekaran *et al.* submitted). Regardless of this large variation in RF size, however, response homeostasis is maintained in BMPr mutant mice (Fig. 1*B*). A plot of RF peak response *versus* RF area in the log domain is well fitted by a line of slope -1 for BMPr mutant mice neurons (Fig. 1*B*, open circles, $r^2 = 0.7$) and for control neurons (Fig. 1*B*, filled circles, $r^2 = 0.67$), suggesting that the total integrated response of the cell is kept constant despite large differences in how receptive fields are constructed in individual neurons.

Cellular mechanisms for maintaining homeostasis

Postsynaptic Ca^{2+} dynamics have been implicated in the read-out of neuronal homeostasis, as increases and

decreases in Ca^{2+} are correlated with changes in firing properties (Turrigiano *et al.* 1994, 1995). Interestingly, the calcium–calmodulin stimulated enzyme CaMKII is implicated in this process, as over-expression of αCaMKII decreases mEPSC frequency while increasing mEPSC amplitude in cultured hippocampal neurons (Thiagarajan *et al.* 2002). The homeostatic action of CaMKII activity can also mediate competition in cortical neurons, as a decrease in synapse number has been attributed to uncorrelated inputs, while only inputs that are able to drive the post-synaptic neuron and activate CaMKII become functionally and structurally enhanced (Pratt *et al.* 2003). These results reveal a role for Ca^{2+} levels in regulating homeostasis, and implicate calcium–calmodulin stimulated enzymes in the same pathway. We have previously shown that in mice lacking the calcium–calmodulin stimulated enzyme adenylate cyclase 1 ($AC1^{-/-}$), retinotopic map formation in the SC is impaired (Plas *et al.* 2004). We have also shown that the loss of AC1 signalling leads to disrupted receptive fields and the retention of a greater number of retinal inputs onto SC neurons (Shah *et al.* submitted). Unlike $\beta2^{-/-}$ mice and BMPr mutant mice, however, we find that the total integrated response to visual stimuli is increased in $AC1^{-/-}$ mice and response homeostasis is not preserved (Shah *et al.* submitted). Our analysis shows that the linear relationship between RF peak response and RF area, apparent in littermate controls (Fig. 1*C*, Control $r^2 = 0.53$), did not hold in $AC1^{-/-}$ neurons (Fig. 1*C*, $AC1^{-/-}$ $r^2 = 0.21$). We conclude that AC1 signalling is required for the activity dependent regulation of total synaptic input. These results identify AC1 as a potential molecular mechanism for cellular homeostasis in SC neurons and implicate AC1 in activity-dependent competition as well as in the read-out of overall activity during developmental changes in functional connectivity.

Synaptic mechanisms for maintaining homeostasis: learning rules and metaplasticity

Another mechanism for preserving the stability of neuronal responses is based on the concept of 'metaplasticity'. In metaplasticity, the history of activity at any given synapse can regulate the capacity for further plasticity at that synapse (Bienenstock *et al.* 1982; Abraham & Bear, 1996). Synapses would have a variable modification threshold, and if their responses are previously strengthened, then their threshold for further LTP is increased, and vice versa. This process therefore could constrain synaptic weights within a narrow range. Over the last decade, this 'sliding threshold' model for synaptic plasticity has gained experimental support. In the hippocampus and visual cortex, for example, the sign and magnitude of plasticity correlates with initial synaptic strength, with weaker synapses showing LTP and stronger synapses showing LTD (Bi & Poo, 1998; Montgomery *et al.* 2001; Hardingham *et al.* 2007). Accordingly, neural

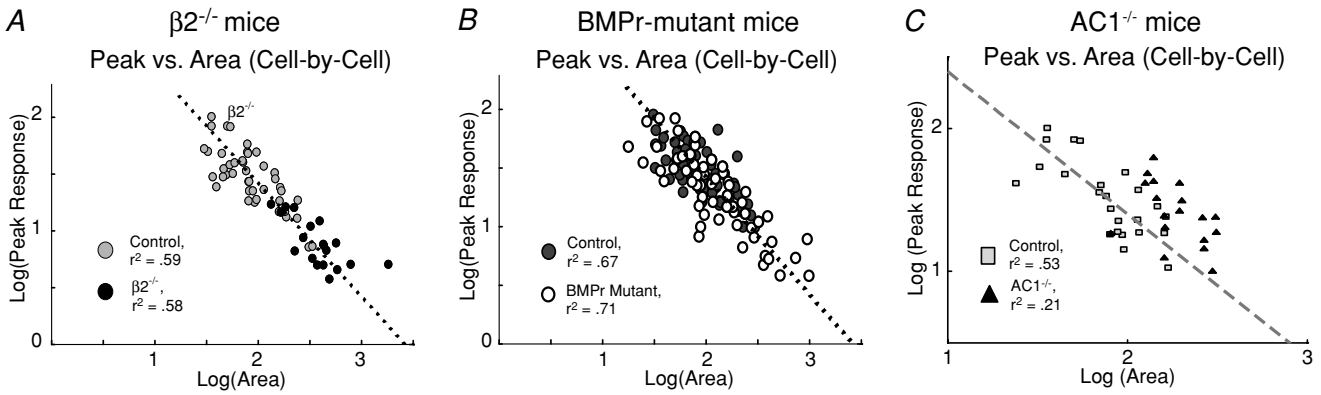

Figure 1. Response homeostasis is maintained on a cell-by-cell basis *in vivo* in $\beta2^{-/-}$ and BMPr-mutant mice but not $AC1^{-/-}$ mice

All graphs depict scatter plots of receptive field (RF) peak response *versus* RF area in the log domain on a cell-by-cell basis. *A*, response homeostasis in $\beta2^{-/-}$ SC neurons (from Chandrasekaran *et al.* 2007, reproduced with persmission from the Society for Neuroscience). Both control and $\beta2^{-/-}$ neuron responses are fitted well by a line of slope −1, demonstrating that, in each cell, RF area and response are precisely coordinated (control as grey circles; $r^2 = 0.59$; $\beta2^{-/-}$ as black circles; $r^2 = 0.58$). *B*, response homeostasis in BMPr mutants (from Chandrasekaran *et al.* submitted). Plot of RF peak response *versus* RF area from littermate control ($r^2 = 0.67$) and BMPr mutant cells ($r^2 = 0.7$) are well fitted by a line of slope −1, demonstrating that the changes in RF shape do not prevent neurons in the SC from maintaining response homeostasis. *C*, response homeostasis is disrupted in $AC1^{-/-}$ SC neurons (from Shah *et al.* submitted). Control neuron responses are fitted well by a line of slope −1, demonstrating that, in each cell, RF area and response are precisely coordinated (control as grey squares; $r^2 = 0.53$). In $AC1^{-/-}$ neurons, however, such a relationship does not hold, and responses are poorly fitted by a line of slope −1 ($AC1^{-/-}$ as black triangles, $r^2 = 0.21$).

activity during development can dynamically gate the threshold for plasticity by regulating synaptic maturation. For example, sensory deprivation experiments that result in a delayed maturation of cortical synapses also result in a greater potential for LTP at these immature synapses (Kirkwood *et al.* 1995, 1996; Franks & Isaacson, 2005). Our work at the retinocollicular synapse has revealed that young synaptic populations that are immature and weak on average also show LTP on average, while more mature populations that have strengthened over development do not (Shah & Crair, 2008). Furthermore, the lack of patterned retinal waves in $\beta2^{-/-}$ mice prevents the normal developmental strengthening of retinocollicular synapses. Interestingly, the capacity for LTP is preserved in these immature and weak synapses (Shah & Crair, 2008). These results reveal that dynamic, activity-dependent regulation of the capacity for synaptic plasticity may also play a part in keeping SC neuron output within an effective range.

Response homeostasis through regulation of synapse number and strength

Neurons can also restrict their output by regulating the number and strength of their synaptic inputs. Experiments at the neuromuscular junction (NMJ) have revealed numerous cell-autonomous mechanisms that serve to keep NMJ transmission constant in the face of altered activity (Davis & Goodman, 1998*b*). When the number of synapses is decreased genetically, there is a compensatory increase in strength of individual motoneuron synapses (Schuster *et al.* 1996; Davis & Goodman, 1998*a*). Conversely, when synaptic strength is genetically reduced postsynaptically, there is a compensatory increase in presynaptic transmitter release to preserve the level of transmission (Davis *et al.* 1998; Paradis *et al.* 2001). These results suggest that homeostatic mechanisms adjust NMJ transmission over development as synaptic competition and plasticity drive changes in the number and strength of inputs.

Developmental regulation of the number and strength of inputs has also been observed in the visual system of a number of species (Katz & Shatz, 1996). Over the first 3 postnatal weeks in the mouse LGN, retinal inputs are pruned and the AMPA/NMDA ratios and AMPA miniature amplitudes of the remaining retinal inputs are concurrently increased (Chen & Regehr, 2000). In the developing frog retinotectal system, excitatory visual receptive fields are initially large and single fibre retinal inputs are small. Over the course of development, RF areas decrease and the remaining retinal inputs are strengthened (Tao & Poo, 2005).

Our observations at the mouse retinocollicular synapse support a similar model of activity-dependent development. Using *in vitro* techniques, we have shown that response homeostasis in $\beta2^{-/-}$ animals is associated with modulation of the number and strength of retinal inputs (Chandrasekaran *et al.* 2007). In young adults aged P21–25, $\beta2^{-/-}$ SC neurons sample a similar number of equal strength retinal inputs relative to controls. Interestingly, homeostasis is also maintained earlier in development at P6–7 in $\beta2^{-/-}$ SC neurons, but via a different mechanism. At this age, $\beta2^{-/-}$ SC neurons sample a larger number of weaker strength retinal inputs than controls (Chandrasekaran *et al.* 2007). Combined, these studies suggest that homeostatic mechanisms act in concert with activity-dependent learning rules in a diverse range of neural systems to permit the fine-scale refinement of functional connectivity during development while preserving output response within an effective range.

Homeostatic regulation of intrinsic excitability

As described above, we find that the regulation of retinocollicular synapse number and strength is sufficient to explain the response homeostasis we observe *in vivo*. However, it is possible that changes in intrinsic excitability also contribute to the maintenance of response homeostasis. Many elegant studies have shown that neurons are capable of maintaining a constant firing rate despite changes in activity by regulating the rich array of voltage-gated conductances that they express (Zhang & Linden, 2003). This regulation can influence postsynaptic responsiveness (intrinsic excitability) by changing the threshold for spike generation and variability in interspike intervals. In cultured cortical neurons, for example, 48 h of activity blockade lowered the spike threshold and increased firing rate by selectively increasing voltage-gated sodium currents and decreasing persistent potassium currents. Interestingly, these conductance changes occurred on a similar time scale to the overall homeostatic changes in firing rate, suggesting a mechanistic link (Desai *et al.* 1999).

Studies in the retinotectal system of frogs have shown that intrinsic excitability is developmentally regulated (Aizenman *et al.* 2003; Pratt & Aizenman, 2007). A transient increase in tectal cell excitability occurs via the regulation of voltage-gated sodium currents, and as total synaptic drive increases, excitability decreases (Pratt & Aizenman, 2007). This allows tectal neurons to maintain a constant input–output function regardless of changes in the magnitude and pattern of retinal inputs. Furthermore, this increase in excitability occurs during a period where tectal cell morphology is highly dynamic and the refinement of retinotectal receptive fields is occurring (Wu & Cline, 2003; Tao & Poo, 2005). As changes in intrinsic excitability can regulate the ability of Hebbian learning rules to modify synaptic weights (Debanne *et al.* 2003; Zhang & Linden, 2003), these results suggest

that homeostatic changes in intrinsic excitability play an important role in the activity-dependent development of retinotopic maps. We have shown that at P6–7, $\beta2^{-/-}$ SC neurons sample a greater number of weaker retinal inputs than control SC neurons, and we proposed that this regulation is sufficient to mediate response homeostasis *in vivo* (Chandrasekaran *et al.* 2007). It remains unknown, however, to what extent changes in intrinsic excitability also contribute to response homeostasis and map formation in this circuit. To address this, we used an *in vitro* preparation to perform current clamp recording in control and $\beta2^{-/-}$ SC neurons in the superficial layers of the SC at P6–8 (see Methods). We held the membrane potential at around −60 mV and delivered a series of 200 ms long square-wave depolarizing current injections and measured the number of action potentials fired at each current amplitude. Figure 2*A* shows example spiking responses from a P7 control and a P7 $\beta2^{-/-}$ SC neuron at three different current steps. A summary of the averaged input–output curves for each genotype in shown in Fig. 2*B*. We did not observe any changes in intrinsic excitability (Fig. 2*B*), spike threshold (Fig. 2*C*), or input resistance (Fig. 2*D*) between control and $\beta2^{-/-}$ SC neurons, suggesting that such regulation does not contribute to maintaining response homeostasis in $\beta2^{-/-}$ SC neurons. One reason why we may not observe such differences is that the overall activity levels may not be sufficiently different between control and $\beta2^{-/-}$ retinocollicular networks to trigger changes in excitability. Changes in the pattern of activity, however, can initiate regulation of the number and strength of inputs (Chandrasekaran *et al.* 2007). It is worth noting, however, that changes in intrinsic excitability may play a role in regulating homeostasis at earlier ages than those examined here. Furthermore, subtle differences in the number and distribution of voltage-activated ion channels in SC neurons, like those responsible for I_A or I_h, may not be apparent in our input–output curves *in vitro*, but may still be involved in regulating response homeostasis *in vivo*. Moreover, as we are randomly sampling from a heterogeneous population of neurons in the SC, it is possible that differences in spike firing in different cell types are averaged out.

Conclusions

The mechanisms of homeostatic plasticity are ubiquitous in developing neural circuits, owing to their essential role in maintaining network stability in the face of changing activity patterns and positive-feedback cycles of synaptic strengthening and weakening. Many elegant studies across numerous species and brain regions have revealed multiple forms of neuronal homeostasis, including synaptic scaling, metaplasticity, changes in synapse number and strength, and regulation of intrinsic excitability. Work from our laboratory has revealed the phenomenon of response homeostasis, which maintains the output of individual superior collicular neurons *in vivo* despite changes in activity patterns or large differences in functional

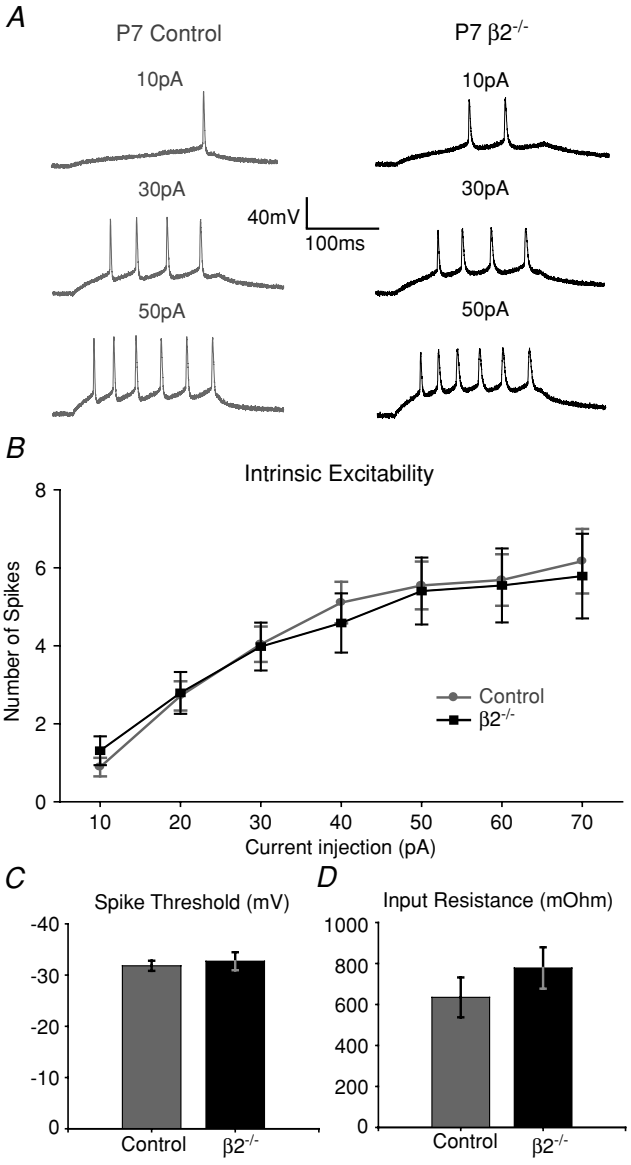

Figure 2. Intrinsic excitability of control and $\beta2^{-/-}$ SC neurons is similar at P6–8
A, example current clamp recordings showing spiking responses at different current injection intensities in a P7 control (left) and P7 $\beta2^{-/-}$ (right) SC neuron. *B*, averaged input–output curves plotting the number of action potentials elicited in response to 200 ms long square current pulses at various amplitudes. Control curve ($n = 13$) is shown in grey, $\beta2^{-/-}$ curve ($n = 10$) in black. No differences in the excitability of SC neurons were observed between genotypes ($P > 0.4$ for every current amplitude, Student's *t* test). *C*, no difference in the spike threshold was observed between genotypes ($P = 0.6$). *D*, input resistance measurements were also similar across control and $\beta2^{-/-}$ cells ($P = 0.3$).

connectivity during the construction of visual receptive fields. Further *in vitro* studies have supported a metaplastic model of retinocollicular map development and the dynamic regulation of retinocollicular synapse number and strength, suggesting that homeostatic mechanisms and synaptic learning rules are concurrently active during the refinement of sensory maps. We also identify adenylate cyclase 1 as a potential molecular mechanism for the readout of total synaptic activity. Combined, our observations provide exciting clues for further investigation into the role of calcium signalling in mediating response homeostasis, as well as a framework for probing the functional differences between Hebbian synaptic competition and neuronal homeostasis during sensory map development.

Methods

Mice lacking the $\beta 2$ subunit of nicotinic acetylcholine receptors ($\beta 2^{-/-}$ mice) were generated in the Beaudet laboratory at Baylor College of Medicine and back-crossed at least six generations onto the C57BL/6 background. Genotypes were determined by genomic PCR using primer sequences and amplification parameters described in Xu *et al.* (1999). All experiments were performed blind to genotype; control mice were wild-type and heterozygous littermates of $\beta 2^{-/-}$ mice. Animals were treated in accordance with IACUC and Yale University School of Medicine guidelines.

In vitro measurement of intrinsic excitability

Mice were first anaesthetized with isoflurane (2–4%, AErrane from Baxter Healthcare, Deerfield, IL, USA) and then decapitated. Parasagittal slices were prepared at P6–8 and patch clamp recordings were obtained from neurons in the superficial layers of the superior colliculus (SGS) as previously described (Shah & Crair, 2008). Whole cell recording electrodes contained (in mM): 100 potassium gluconate, 20 KCl, 5 NaCl, 10 Hepes, 0.5 EGTA, 4 MgATP, 0.3 GTP, 7 phosphocreatine, pH 7.2–7.5, 290–310 mosmol. After obtaining a stable voltage-clamp recording to monitor input and series resistance, the recording was switched to current clamp. Resting membrane potential was adjusted to between −60 and −65 mV. A 200 ms long, square-wave current injection was delivered via the amplifier in order to depolarize the membrane. Current injections were given at 10 pA amplitude intervals from 10 to 70 pA, and 8–10 sweeps were collected for each amplitude. To analyse the number of spikes, we took the first derivative of each sweep and used a threshold of 30 mV ms^{-1} to define an action potential. The number of spikes elicited for each current injection amplitude was averaged for each cell, and the values were then averaged across experiments (Fig. 2). For the spike threshold analysis, we analysed the first spike elicited at various current injection amplitudes for each cell. Spike threshold was defined as the voltage at which dV/dt crossed 30 mV ms^{-1}.

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