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Sensory modality-specific homeostatic plasticity in the developing optic tectum

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Abstract

We describe a novel form of homeostatic synaptic plasticity in multisensory neurons in the optic tectum of *Xenopus laevis* tadpoles. Individual tectal neurons are known to receive converging inputs from multiple sensory modalities. We show that long-term alterations in either visual or mechanosensory activity *in vivo* result in homeostatic changes specific to each sensory modality. In contrast to typical forms of homeostatic synaptic plasticity, such as synaptic scaling, we show that this type of plasticity occurs in a pathway-specific manner more reminiscent of Hebbian-type plasticity.

Homeostatic synaptic plasticity is a type of plasticity in which synaptic strength is uniformly adjusted throughout a neuron to compensate for long-term changes in neural activity. Typically, homeostatic plasticity is global and multiplicative, such that all synapses in a cell are either increased or decreased by the same fraction, preserving the relative weights between synapses and optimizing the neurons dynamic range[1]. Experimentally, homeostatic synaptic plasticity is typically studied by altering global levels of neural activity over several days. For example, experimentally decreasing neural activity for 48 hours in cultured hippocampal neurons can lead to strengthening of excitatory synapses while chronically increasing activity can result in scaling down[2]. Similarly, *in vivo* sensory manipulations that increase or decrease activity have been used to induce scaling.[3,4] However, it is not clear whether selective long-term changes to a select subset of synaptic inputs to a neuron could result in a local form of homeostatic plasticity specific to these inputs. Here we describe a novel, pathway-specific form of homeostatic synaptic plasticity in the optic tectum of *Xenopus laevis* tadpoles.

The *Xenopus* tadpole optic tectum is a multisensory area where multiple sensory modalities converge onto individual neurons throughout development[5,6]. Using an *in vitro* whole-brain preparation we can electrically stimulate separate pathways conveying visual and mechanosensory input[5]. In this study we perform a series of *in vivo* sensory manipulations

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KED and CDA worked on the experimental design, performed the experiments and wrote the manuscript.

over the course of 48 hours and then test whether they result in homeostatic plasticity specific to the manipulated pathway.

We performed whole-cell recordings from 83 optic tectal neurons using isolated whole brain preparations from stage 49 tadpoles, as described previously[7] (see Supplementary Methods). We first tested whether glutamatergic synapses in the optic tectum could express conventional forms of homeostatic plasticity[1] by exposing tadpoles for 48 hours to AMPA receptor antagonist NBQX (30 μM) or $GABA_A$ receptor blocker picrotoxin (PTX, 100 μM). Decreasing neural activity with NBQX resulted in a significant increase in spontaneous EPSC (sEPSC) amplitudes, while increasing activity with PTX resulted in a significant decrease in sEPSC amplitude (Supp. Fig. 1; control: 5.33±0.53 pA, n=7, NBQX: 7.24±0.37 pA, n=8, $p<0.01$, PTX: 3.9±0.22 pA, n=8; $p<0.01$, $p<0.05$). No manipulations resulted in significant changes in sEPSC frequency. These data are consistent with global homeostatic plasticity being present in this system.

To assess synaptic strength at both types of sensory inputs independently, we placed a stimulating electrode on the optic chiasm to activate visual inputs and another in the contralateral hindbrain to activate mechanosensory inputs[5] (Fig. 1A). We found that most tectal neurons receive converging monosynaptic input from both pathways[5]. To measure quantal amplitude of a given synaptic input, extracellular Ca^{2+} was replaced with Sr^{2+}, resulting in asynchronous release of synaptic vesicles following electrical stimulation of a pathway[8] (Fig 1B). These asynchronous EPSCs (aEPSC) were separately analyzed for each pathway. We also analyzed sEPSCs, which primarily arise from synaptic contacts made by intratectal recurrent axon collaterals[9]. In control tadpoles there was no significant difference between the aEPSC amplitude evoked by either the visual or the hindbrain input (Fig. 1C–E; visual: 7.5±0.7 pA, hindbrain: 8.1±1 pA; n=9, $p=0.359$). Furthermore the range of amplitudes from both inputs was indistinguishable from the amplitudes of sEPSCs (Fig 1E; spont: 8±0.9 pA), indicating that in control conditions, the quantal amplitudes of all synaptic inputs are roughly matched to each other. Across cells there was a strong and significant correlation between the amplitude of evoked aEPSCs from different modalities and between evoked aEPSCs and sEPSCs (V vs HB: $r=0.71$, $p=0.037$; V vs spont.: $r=0.82$, $p=0.011$; HB vs spont.: $r=0.78$, $p=0.017$, Spearman R-Correlation).

We next asked whether long-term alterations in activity of a specific sensory modality would result in either compensatory homeostatic plasticity specific to that pathway, or in global alterations affecting all synapses. First, tadpoles were placed in the dark for 48 hours to selectively decrease visual input. We found that after treatment aEPSCs evoked from the optic nerve were significantly larger than aEPSCs evoked by hindbrain stimulation (Fig. 2 A–C, left, Fig. 3A; visual: 10.74±0.76 pA, hindbrain: 7.57±0.7; n=10, $p=0.002$). We also found that visual aEPSCs were significantly larger than sEPSCs (Fig 2 D, left; spont: 7.58±0.42 pA, $p<0.001$); suggesting that visual deprivation resulted in a selective increase in retinotectal synapses. This change could be reversed by returning tadpoles to a normal rearing environment (12:12 hr light/dark cycle) for 48 hours (Supp. Fig. 2; visual: 6.04±0.44 pA, hindbrain: 6.09±0.45 pA; n=11, $p=0.831$). We also tested whether 48 hours of dark treatment resulted in changes in paired pulse facilitation (PPF), an index of presynaptic release probability. We found that visual synapses typically exhibit more PPF than hindbrain

inputs, but we did not find any effects of dark rearing on PPF (Supp. Fig 3A,C; hindbrain: control PPF, 111.2±28.4%, dark PPF, 90.37±11.7%, p=0.82; visual: control PPF, 216±54.2%, dark PPF, 279±53.6, p=0.34, n=8 and 7, Mann-Whitney), nor in the ratio between PPF in visual vs. hindbrain pathways (Supp. Fig. 3B; control: 2.41±0.52, dark: 2.61±0.45; p=0.82). These data are consistent with no pre-synaptic changes occurring following 48 hours of dark rearing.

Next, tadpoles were kept in normal light/dark conditions but were presented with a constant vibration stimuli for 48 hours to activate mechanosensory pathways. Vibration was delivered by gently bubbling air into their rearing tank. After treatment, aEPSCs evoked by hindbrain stimulation were significantly smaller than visual aEPSCs (Fig. 2 A–C, middle, Fig. 3A; visual: 8.24±0.64 pA, hindbrain: 6.41±0.63 pA; n=9, p=0.019), indicating a pathway-specific change. Because activating afferent hindbrain input will also drive activity in recurrent intratectal synapses (Supp. Fig. 4), we would expect that these would also be decreased after long-term mechanosensory stimulation. Consistently, sEPSCs were also significantly smaller than retinotectal aEPSCs (Fig. 2D, center; spont: 6.89±0.61 pA, p=0.02). Finally, we tested whether we could eliminate differences between hindbrain and visual inputs by evoking a more global type of homeostatic plasticity[1] by strongly driving the system while simultaneously presenting mechanosensory stimulation. Tadpoles were exposed to 48 hours of mechanosensory stimulation while in the presence of 100 μM PTX, a $GABA_A$ antagonist, in the rearing media.[9] This would be expected to strongly activate the tectal network without necessarily enhancing visual input. After this treatment we found no difference between visual and hindbrain-evoked aEPSCs (Fig. 2 A–C, right; visual: 6.71±1.8 pA, hindbrain: 6.86±1.6 pA; n=15, p>0.99) and no difference between aEPSCs and sEPSCs (Fig. 2D, right; spont: 6.66±1.8 pA). However sEPSCs in the Mechanosensory + PTX treated group were significantly smaller than control sEPSCs (Fig. 3B, p=0.005). This suggests that stronger activation of the tectal circuitry can lead to global compensatory changes in synaptic transmission which can override local differences in synaptic activity.

To our knowledge, this is the first example of homeostatic synaptic plasticity which is pathway specific and which can be induced by long-term *in vivo* manipulations of sensory activity. A synapse-specific form of homeostatic plasticity has been described in mossy fiber and recurrent collateral inputs to CA3 neurons in organotypic cultures[10]. However in that experiment it was not possible to manipulate different pathways independently and experiments were performed *in vitro*. Cross-modal homeostatic plasticity has been also described after visual deprivation, but there changes occurred in separate sensory cortices, and not in individual neurons receiving converging inputs[11].

Or data indicate that pathway-specific homeostatic synaptic plasticity can be overridden by stronger global activation. What are potential mechanisms for these types of plasticity? Inputs to individual tectal neurons from visual and mechanosensory pathways are anatomically segregated: visual inputs terminate primarily in the distal portion of the dendritic arbor, while mechanosensory inputs terminate more proximally[5,6]. The *in vivo* sensory manipulations presented here could use this segregation to restrict activity to a local portion of the dendrite, creating a local signal for homeostatic plasticity. In contrast, global manipulations, such as adding PTX + mechanosensory stimulation, may override local

signals to produce conventional forms of global homeostatic plasticity. The presence of dendritic spiking may mediate the transition between local and global forms of homeostatic plasticity. It is unclear whether local and global homeostatic plasticity require separate mechanisms or whether they share a common mechanism which is normally spatially restricted but can also be expressed globally. Known plasticity mechanisms such as BDNF release from dendrites[12,13] or local dendritic protein synthesis[14], are both activity dependent and could be harnessed to induce either global or local changes in synaptic strength.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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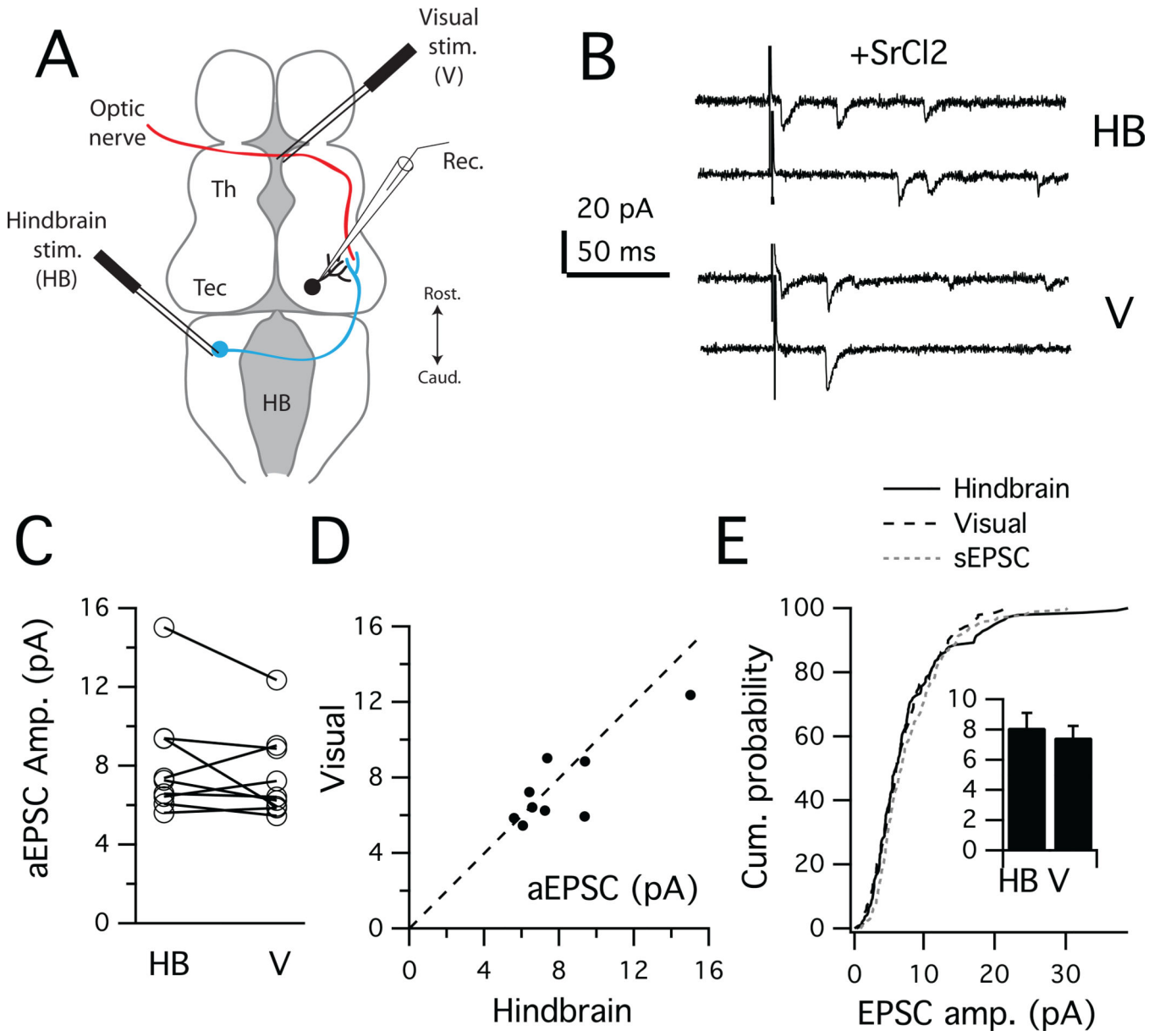

Figure 1. Multisensory convergence in optic tectal neurons

(A) Stimulation and recording configuration. Using a whole-brain preparation from Xenopus tadpoles, stimulating electrodes were placed in the optic chiasm and contralateral hindbrain to activate visual or mechanosensory inputs to the tectum. Whole-cell recordings were performed from optic tectal neurons. (B) Extracellular Ca++ was substituted with Sr++ to evoke asynchronous EPSCs (aEPSC). (C) aEPSCs evoked by HB or V stimulation were not significantly different. (D) Scatterplot of aEPSC amplitude evoked by each pathway. (E) Cumulative probability distribution of aEPSC amplitudes from both pathways superimposed with spontaneous EPSC (sEPSC) amplitudes show no differences in amplitude distributions.

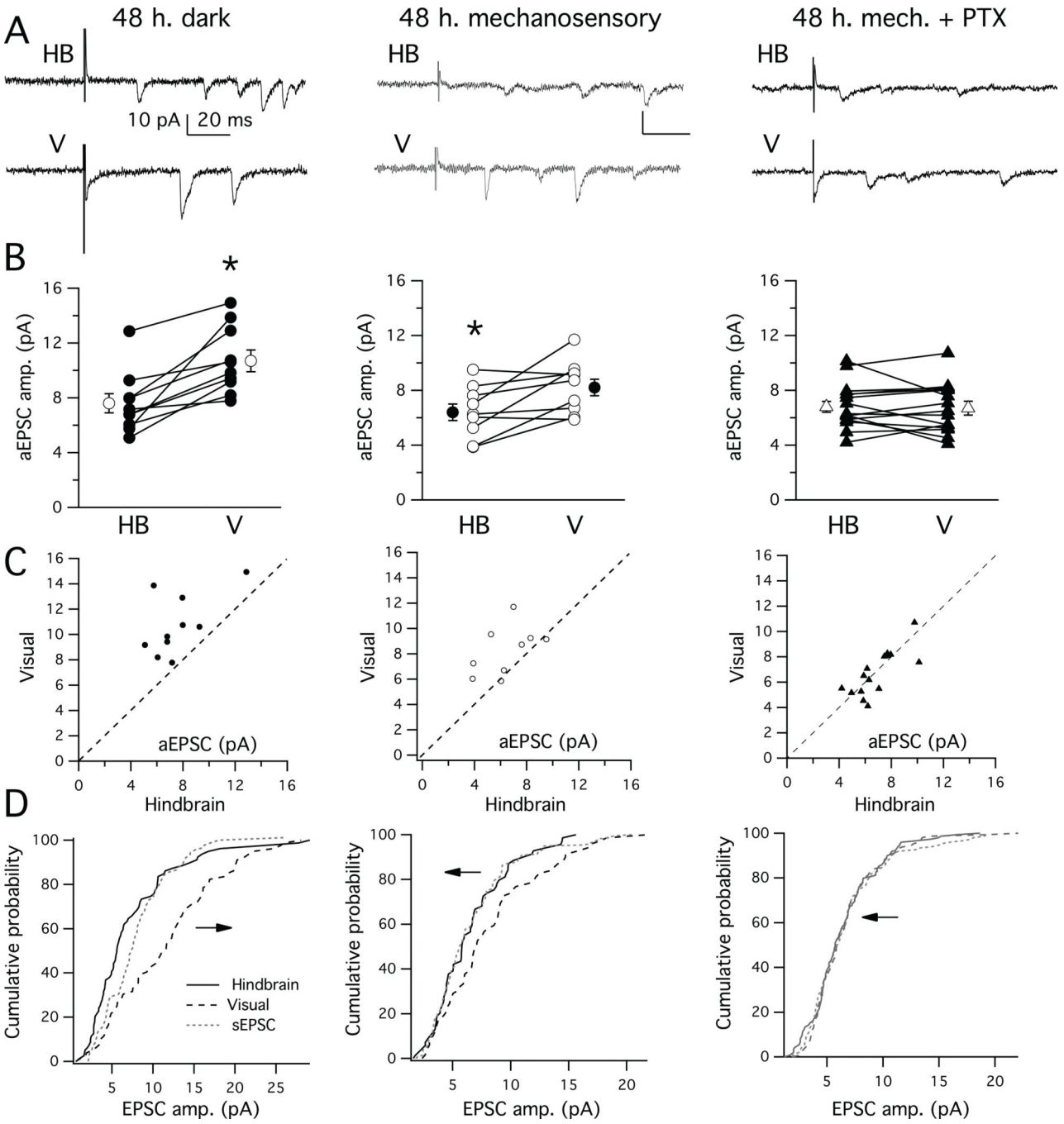

Figure 2. Modality-specific changes in aEPSC amplitude after various sensory manipulations

(A) aEPSCs evoked by visual or hindbrain stimulation after 48 hours of visual deprivation (left), enhanced mechanosensory stimulation (middle) or enhanced mechanosensory stimulation in the presence of inhibitory blockers (right). (B) Comparison of hindbrain and visual stimulation after various experimental conditions. Symbols next to paired data represent average values and error bars are SEM. (C) Scatterplot of aEPSC amplitude evoked by each pathway after various experimental conditions. (E) Cumulative probability

distribution of aEPSC amplitudes from both pathways superimposed with spontaneous EPSC (sEPSC) amplitudes after various experimental conditions. Stars indicate $p<0.05$.

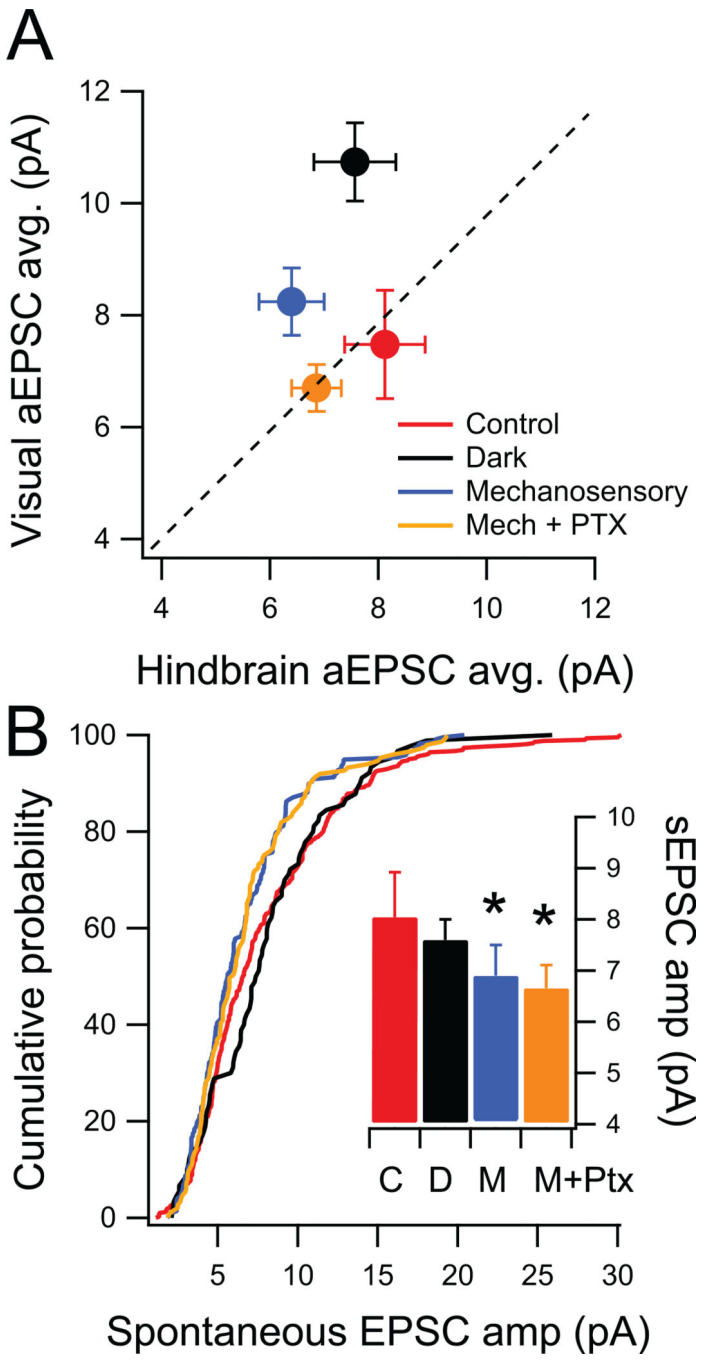

Figure 3. Summary of synaptic changes after *in vivo* sensory manipulations

(A) Averaged data comparing aEPSC amplitude evoked by visual and mechanosensory pathways under various conditions. Notice modality specific changes. (B) Cumulative probability plots of sEPSC amplitudes from different experimental groups. Inset shows average sEPSC amplitudes across conditions. Error bars are SEM, stars indicate $p<0.05$. For direct comparisons see Sup. Fig. 5.