An imbalance in the quality of visual input across the two eyes during development induces amblyopia, a disorder affecting up to 4% of the world’s population. In animal models, long duration monocular deprivation induces severe deprivation amblyopia, manifest as a loss of spatial acuity through the deprived eye. Amblyopia is highly resistant to reversal in adulthood, due in part to the decline in synaptic plasticity in the primary visual cortex with age. However, we have previously shown that visual deprivation (dark exposure) rejuvenates plasticity in the adult amblyopic cortex, which can be harnessed to promote the full recovery of vision. The reactivation of plasticity is triggered by light reintroduction (LRx) after dark exposure (DE) and mediated an increase in the activity of an extracellular protease (matrix metalloproteinase 9) at a specific class of synapses (thalamic synapses onto cortical neurons). Two photon live imaging of MMP activity in the mouse visual cortex demonstrates that DE lowers the threshold for MMP activation, enabling weak visual input through the amblyopic pathway to drive degradation of extracellular targets. Thus, homeostatic mechanisms engaged by visual deprivation promote the activation of synaptic plasticity mediated by perisynaptic proteolysis.