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# Inhibitory Neuron Transplantation into Adult Visual Cortex Creates a New Critical Period that Rescues Impaired Vision

## Highlights

- Interneuron transplantation to adult cortex reactivates critical period plasticity
- Transplantation recovers visual cortical function in visually impaired mice
- Transplantation restores normal perception to visually impaired mice

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## In Brief

Davis et al. demonstrate the creation of a new critical period using inhibitory neuron transplantation into adult visual cortex. Transplantation in adulthood reverses visual impairment caused by deprivation during the juvenile critical period.

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# Inhibitory Neuron Transplantation into Adult Visual Cortex Creates a New Critical Period that Rescues Impaired Vision

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## SUMMARY

**The maturation of inhibitory circuits in juvenile visual cortex triggers a critical period in the development of the visual system. Although several manipulations of inhibition can alter the timing of the critical period, none have demonstrated the creation of a new critical period in adulthood. We developed a transplantation method to reactivate critical period plasticity in the adult visual cortex. Transplanted embryonic inhibitory neurons from the medial ganglionic eminence reinstate ocular dominance plasticity in adult recipients. Transplanted inhibitory cells develop cell-type-appropriate molecular characteristics and visually evoked responses. In adult mice impaired by deprivation during the juvenile critical period, transplantation also recovers both visual cortical responses and performance on a behavioral test of visual acuity. Plasticity and recovery are induced when the critical period would have occurred in the donor animal. These results reveal that the focal reactivation of visual cortical plasticity using inhibitory cell transplantation creates a new critical period that restores visual perception after childhood deprivation.**

## INTRODUCTION

During a juvenile critical period, binocular vision drives the refinement of visual acuity. Deprivation of normal binocular vision during this period results in a lifelong visual deficit. Creating a new critical period in adulthood might give the visual system a second chance to rewire and recover normal vision. The maturation of inhibitory circuits in visual cortex is known to establish the timing of the juvenile critical period (Fagiolini and Hensch, 2000; Hensch, 2005; Hensch et al., 1998; Huang et al., 1999) and presents an attractive target for the reactivation of critical period plasticity in adulthood (Southwell et al., 2014).

Several manipulations of inhibition have been shown to stimulate plasticity in mouse visual cortex up to postnatal day 70 (P70) (Beurdeley et al., 2012; Fagiolini and Hensch, 2000; Kuhlman et al., 2013; Southwell et al., 2010; Stephany et al., 2014; Sugiyama et al., 2008). However, from P35 to P90, after the peak of the critical period, a weaker, qualitatively distinct form of young adult plasticity exists in mouse visual cortex (Lehmann and Löwel, 2008; Sato and Stryker, 2008; Sawtell et al., 2003). This form of young adult plasticity can be amplified with extensive training and depends upon inhibition (Fu et al., 2015). Therefore, it is possible that manipulations of inhibition boost young adult plasticity but cannot reactivate critical period plasticity.

The transplantation of embryonic inhibitory neurons into neonatal visual cortex induces new plasticity shortly after the critical period (~P45) (Southwell et al., 2010; Tang et al., 2014). Here we develop a method to transplant inhibitory neurons into adult recipient mice up to P192, long after young adult plasticity has subsided. We find that transplantation into adult visual cortex creates new plasticity that exhibits key hallmarks of the critical period.

The reactivation of critical period plasticity in adult visual cortex has the potential to reverse impairments in visual perception. Several manipulations have been used to recover visual function in impaired rodents (Kaneko and Stryker, 2014; Maya Vetencourt et al., 2008; Montey et al., 2013; Stephany et al., 2014; Tognini et al., 2012), but none have been shown to restore visual perception using a focal manipulation of plasticity in visual cortex. Here we use a behavioral test to demonstrate that inhibitory neuron transplantation restores the visual perceptual thresholds of impaired mice to normal levels.

## RESULTS

### Transplanted MGE Cells Disperse in Adult Cortex and Develop Molecular and Cellular Properties of Inhibitory Neurons

Neocortical inhibitory neurons are generated in the medial and caudal ganglionic eminences (MGE and CGE, respectively) of the ventral forebrain (Wonders and Anderson, 2006). First, we transplanted embryonic day 13.5 (E13.5) inhibitory neuron precursors from the MGE into adult primary visual cortex (V1). Cell placement was guided using intrinsic signal imaging to map the cortical location of primary visual cortex (V1) (Figure 1A). Transplanted MGE cells dispersed broadly through adult V1 and expressed a markerspecific to GABAergic neurons (VGAT: Figure 1B).