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# Recovery from amblyopia in adults via decreased visual cortical inhibition caused by experience in an enriched environment

The mammalian primary visual cortex (V1) became a prime model for the study of neural substrates underlying the development of cortical circuits. A series of pioneering experiments carried out by Hubel and Wiesel (1969, 1972) demonstrated the existence of ocular dominance (OD) columns in the cortex. Thalamic projections that target V1, as well as V1's intrinsic connectivity, are arranged in alternating columns of neurons that are driven to different degrees by visual stimuli presented to either eye (Hubel and Wiesel 1969, 1972; Hubel *et al* 1977). Importantly, it was found that anomalous visual experience during a "critical period" of post-natal development had a marked impact on the functional organization these OD columns: V1 neurons of animals that had been monocularly deprived underwent "shifts" in OD; with time after sensory deprivation, the large majority of the V1 neuronal population would modify their responsiveness towards the non-deprived eye (Hubel *et al* 1977; Blakemore *et al* 1978).

Subsequent studies provided clear evidence that the development of OD columns in V1, and their malleability within the critical period, depend both on innate and experiential factors (for review, *see* Katz and Crowley 2002). These findings shed significant light onto the mechanistic basis of numerous clinical conditions like amblyopia, which is characterized by poor performance, or acuity, of one or both eyes in the absence of physical abnormalities. Although amblyopia can be treated in children, the capacity for functional recovery significantly diminishes as a function of age; this condition is thought to be permanent in adults due to the decrease in visual cortical plasticity that follows the critical period.

A remarkable report by Sale and colleagues (2007), published in *Nature Neuroscience*, highlights potential interventions that may rescue mal-adaptive plasticity in adults, as in the case of amblyopia, where changes in visual performance are detrimental. Furthermore, in this article the authors have discovered and described a central role for intra-cortical inhibition in the regulation of plasticity states in the visual cortex. Authors exposed adult rats to an enriched environment (EE), a protocol that provides subjects with greater variability in sensory and motor experiences relative to standard home cages, and known to drive robust anatomical and functional plasticity in most sensory cortices (for reviews, *see* van Praag *et al* 2000; Pinaud 2004). Enhanced visual experience in the EE recovered amblyopia induced by monocular deprivation followed by reverse-suture. The recovery of visual acuity was evidenced both by electrophysiological recordings of visual evoked potentials and by a standard visual acuity behavioural test (visual water-box task). Interestingly, this EE-induced recuperation of visual acuity paralleled a recovery in binocularity and appeared to be long-lasting, persisting for a minimum of two weeks. Thus, compared to controls housed in standard conditions, adult rats exposed to environmental enrichment display significant functional plasticity of V1 circuitry that impacts visual acuity behaviour.

Sale and co-workers next investigated if the restoration of visual acuity by EE exposure was associated with alterations in inhibitory transmission. Intra-cortical inhibition had been shown previously to dynamically regulate receptive field (RF) properties such as area, direction and orientation selectivity and, importantly, plasticity associated with OD (Sillito 1977, 1979; Eysel *et al* 1998; Tremere and Pinaud 2005). Previous research has demonstrated that the maturation of the inhibitory network of the visual cortex correlates with the progression and closure of the critical period for plasticity of OD (Huang *et al* 1999; Tremere and Pinaud 2005). Using *in vivo* brain microdialysis, Sale and co-workers showed that exposure of adult amblyopic animals to the EE setting led to a 3-fold decrease in baseline GABA levels in the binocular portion of the visual cortex contralateral to the deprived eye, an effect that was not paralleled by a decrease in glutamate levels (Sale *et al* 2007). One of the hallmark electrophysiological findings of such maturation of inhibitory circuits is the disappearance of long-term potentiation (LTP) of supragranular layer (layers II/III) field potentials. This form of potentiation is prevalent in developing animals but absent in the adult V1. In their studies, Sale and colleagues found that exposure of animals to the EE promoted

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the restoration of LTP in layers II/III, suggesting that this behavioural manipulation reduces GABAergic inhibition, a finding that is consistent with previous studies and the authors' microdialysis findings (Kirkwood and Bear 1994; Huang *et al* 1999).

To establish direct links between the recovery of amblyopia and reduced GABAergic inhibition in V1 following EE exposure, Sale and his co-workers implanted a group of rats with micro-osmotic pumps that delivered the GABA agonist diazepam (a benzodiazepine), for the duration of the EE experiment. Interestingly, this manipulation completely blocked the recovery of binocularity and visual acuity in animals exposed to the EE. These findings suggest that experience in the EE setting recovers OD and visual acuity through mechanisms that decrease intra-cortical inhibition. They are consistent with previous studies demonstrating impaired plasticity of OD columns in knock-out mice with targeted disruption of the 65 kDa glutamic acid decarboxylase (GAD65) gene, which encodes one of the enzymes required for GABA synthesis. In these genetically manipulated animals, normal plasticity of OD was reinstated by local infusions of diazepam (Hensch *et al* 1998). Together, these studies suggest that normal development of GABAergic networks is required for controlling OD plasticity in V1, possibly by weakening unused connections. Importantly, as Sale and colleagues indicate in their study, their findings highlight the potential for recovery of normal vision in amblyopic adults through the use of EE as a prospective, injury-free, intervention strategy. Furthermore, these findings further substantiate a major role for GABAergic transmission in the control of windows of enhanced plasticity in sensory cortices.

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