Brief Communication

Optimization of visual training for full recovery from severe amblyopia in adults

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The severe amblyopia induced by chronic monocular deprivation is highly resistant to reversal in adulthood. Here we use a rodent model to show that recovery from deprivation amblyopia can be achieved in adults by a two-step sequence, involving enhancement of synaptic plasticity in the visual cortex by dark exposure followed immediately by visual training. The perceptual learning induced by visual training contributes to the recovery of vision and can be optimized to drive full recovery of visual acuity in severely amblyopic adults.

An asymmetry in visual input across the two eyes caused by strabismus, anisometropia, or cataract causes amblyopia, the most common basis for monocular blindness. Interventions to treat amblyopia include blocking input to the fellow eye to reduce suppression and/or active visual training of the amblyopic eye. However, these interventions are typically more successful in children than in adults (Epelbaum et al. 1993). The particularly severe deprivation amblyopia induced by the presence of a unilateral congenital cataract at birth is especially resistant to treatment (Vaegan and Taylor 1979; Mitchell and MacKinnon 2002; Lewis and Maurer 2009).

In animal models, monocular lid suture is used to occlude patterned visual input to one eye and induce deprivation amblyopia. Long-term monocular deprivation initiated early in postnatal life has been shown to weaken the strength and selectivity of visually evoked responses in primary visual cortex and reduce visual acuity in many species (Wiesel and Hubel 1963; Kim and Bonhoeffer 1994; Liao et al. 2004; Montey et al. 2013). The anatomical and functional deficits induced by early chronic monocular deprivation are particularly difficult to reverse (Liao et al. 2004; Pizzorusso et al. 2006; Iny et al. 2006; He et al. 2007). The obstacles to recovery include the significant depression of excitatory synapses serving the deprived eye (Yoon et al. 2009; Montey and Quinlan 2011; Cooke and Bear 2013) and developmental accumulation of molecular constraints on synaptic plasticity in the visual cortex (Bavelier et al. 2010; Takesian and Hensch 2013; Sengpiel 2014). However, here we test the hypothesis that vision can be recovered in adult amblyopes that receive dark exposure followed promptly by visual training. In addition, we ask whether perceptual learning induced by visual training contributes to the recovery of vision, and can be optimized to drive full recovery from severe amblyopia in adulthood.

Long-Evans rats received monocular lid suture (under 50 mg/10 mg/kg, i.p. ketamine/xylazine) from post-natal day 14 (early onset) or post-natal day 28 (late onset) until adulthood (~post-natal day 185) to induce severe amblyopia (He et al. 2007; Montey et al. 2013). A two alternative, forced choice, water-based spatial frequency detection task (modified from Prusky et al. 2000) was used to first assess visual detection thresholds of the nondeprived eye. Naïve, chronically deprived adults were trained to use their nondeprived eye to associate a hidden escape platform with a high contrast (100%), low spatial frequency (0.208 cycles/degree), 0° sinusoidal grating (positive stimulus), and the absence

of the escape platform (negative stimulus) with a gray LCD monitor of equal luminance (75 cd/m²), white balance (5000K), gamma value (1.8), and contrast (100%). Once the association is learned (~7 d with 2 × 10 trials/d), lane dividers are introduced (first 17.8 cm, then 53.4 cm) to define a choice point allowing calculation of the spatial frequency of the visual stimulus. The positive visual stimulus is presented to the left and right monitors in pseudorandom order. Trials to detect 0.208 cycle per degree sinusoidal gratings continue until the subjects demonstrate task learning (>90% correct choices for 6 × 10 trials). Although the number of trials required to demonstrate task learning was variable (average ± SEM: 141 ± 28.9 total trials), all subjects learned to perform the task monocularly.

To estimate visual detection thresholds, the spatial frequency of the positive visual stimulus is increased 0.05 cycles per degree following performance of ≥60% correct choices in a block of trials. Individual frequency of seeing curves reveal that all subjects made 100% correct choices at low spatial frequencies (3 trials per frequency), and performance decreased at higher spatial frequencies (5–10 trials per frequency; Fig. 1A). The highest spatial frequency with performance of ≥60% correct choices on two consecutive blocks of trials is reported as daily detection threshold. Trials begin the next testing day with a visual stimulus 0.05 cycles per degree lower than the previous detection threshold. There is a weak negative correlation between the final plateau acuity of the nondeprived eye and the number of trials required to demonstrate task learning ($R^2 = -0.377$; Fig. 1B). Nonetheless, population averages demonstrate that performance improved over testing days 1–3, reaching a final plateau acuity of 0.808 ± 0.042 cycles per degree on day 3 (Fig. 1C, $n = 10$).

It is increasingly apparent that repetitive performance of many visual tasks (i.e., visual training) enhances visual perception and decreases visual detection thresholds (Sagi 2011; Kawato et al. 2014). Importantly, this type of visual perceptual learning is typically limited to familiar aspects of the stimulus. To ask whether the many repetitions of the task necessary to assess acuity of the nondeprived eye (average trials ± SEM: 110.10 ± 27.52) induced stimulus-selective perceptual learning, the task was repeated with a novel visual stimulus (45° sinusoidal grating). The detection threshold with the novel stimulus dropped significantly

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Figure 1. Visual task repetition improves detection thresholds of the nondeprived eye. (A) *Inset*: Experimental design. Monocular deprivation was initiated at eye opening (~post-natal day 14; P14) and maintained until adulthood (~P185). Subjects learned to perform the visual detection task with the nondeprived eye; the spatial frequency of positive stimulus is increased incrementally to estimate visual detection thresholds. Individual frequency of seeing curves for visual task performance with the nondeprived eye. Data for all trials with 0° sinusoidal gratings. (B) Weak negative correlation between the number of trials required to demonstrate task learning and plateau acuity for 0° sinusoidal gratings ($n = 10$). (C) Visual detection thresholds estimated by task performance. Detection of 0° sinusoidal gratings improves over repetitions to plateau on the third day (blue symbols). Presentation of novel visual stimuli (45° sinusoidal gratings, red symbols; 0° square wave gratings, green symbols and 45° square wave grating; black symbol) significantly reduced task performance, which improved again with task repetition. Baseline acuity (dashed line) is the highest spatial frequency that transferred to novel visual stimuli (0.693 ± 0.070 cycles per degree; $n = 10$; (*) $P = 0.05$ paired t -test, first day of novel stimulus versus last day of familiar stimulus).

(to 0.693 ± 0.070 cycles/degree; $*P < 0.05$; paired t -test), but improved over repeated performance to plateau (0.890 ± 0.050 cycles/degree; Fig. 1C). Introduction of additional novel stimuli (0° and 45° square-wave gratings) also reduced detection thresholds, followed by improvement to plateau. This indicates that the maximum detection threshold (plateau acuity) revealed by task performance with a familiar stimulus contains a “baseline” component that generalizes to novel stimuli (0.693 ± 0.070 cycles/degree = transfer acuity) and a stimulus-selective component that reflects perceptual learning (plateau acuity – transfer acuity = learned 0.20 cycles/degree).

The age at the onset of an asymmetry in visual input across the two eyes impacts the severity of the subsequent amblyopia, as well as the potential for recovery. To ask how the age of monocular deprivation impacts the severity of the visual deficit and subsequent recovery in our rodent model, we compared the amblyopia induced by early (P14) versus late (P28) onset chronic monocular deprivation. Estimation of nondeprived eye acuity was followed by reverse suture (open the deprived eye, close the deprived eye) to limit subsequent task performance to the chronically deprived eye. Early onset (P14) chronic monocular deprivation induced a severe visual deficit, as task performance with the chronically deprived eye revealed no residual acuity. Repeated

performance of the task (~320 trials with 2×10 trials/d; 3 d/wk) did not promote improvement of vision (white symbols; Fig. 2A). In contrast, deprived eye visual acuity emerged quickly if dark exposure preceded task performance. Detection thresholds improved with repeated performance of the task to plateau at 0.476 ± 0.068 cycles/degree (average $\pm$ SEM; 25.1 ± 5 trials/d, 3 d/wk; blue symbols, Fig. 2A), representing significant difference

Figure 2. Age at onset of chronic monocular deprivation impacts the severity of the amblyopia. (A) *Inset*: Experimental design. Chronic monocular deprivation was maintained from P14–P185. Estimation of nondeprived eye visual acuity (black symbols) preceded performance of visual task with chronically deprived eye. Early onset chronic monocular deprivation reduces visual acuity below detection thresholds and does not improve with repeated task performance (white symbols; $n = 6$). In contrast, dark exposure promotes significant improvement in visual detection thresholds with visual task repetition (blue symbols, $n = 6$). (B) *Inset*: Experimental design. Chronic monocular deprivation was maintained from P28–P185. Modest spatial acuity is retained in the deprived eye following late onset chronic monocular deprivation, and does not improve with repeated task performance (white symbols; $n = 6$). In contrast, dark exposure prior to task performance promotes significant improvement in visual detection thresholds with visual task repetition (white symbols, $n = 6$). (C) Age at onset of chronic MD impacts the visual acuity retained by the deprived eye (deprived eye, no dark exposure), and the visual acuity recovered by repetitive task performance (deprived eye + dark exposure; (*) $P = < 0.005$ t -test. The visual acuity of the nondeprived eye was not affected by age at onset of MD).

in acuity relative to subjects that were not dark-exposed (t -test $P < 0.001$) but significantly different from nondeprived eye acuity (0.757 ± 0.046 cycles/degree; black symbol Fig. 2A; $P < 0.001$ paired t -test deprived versus nondeprived eye). Dark exposure was administered in a light-tight room with animal care provided under infrared illumination.

In contrast, late onset (P28) monocular deprivation induced amblyopia that was less severe. Task performance with the chronically deprived eye revealed residual acuity of 0.208 cycles/degree (± 0.03 , average $\pm$ SEM; white symbols Fig. 2B). Again, repeated performance in the task (~ 320 trials) did not promote an improvement in vision. However, visual acuity improved significantly if dark exposure preceded visual training, to plateau at 0.658 ± 0.046 cycles/degree (average $\pm$ SEM, $n = 6$; 26.7 ± 8.5 trials/d; 3 d/wk; red symbols, Fig. 2B). Deprived eye plateau acuity was significantly higher than acuity in subjects that were not dark-exposed (t -test $P < 0.001$), but significantly different from nondeprived eye acuity (0.802 ± 0.029 cycles/degree; black symbol Fig. 2B; $P < 0.03$ paired t -test deprived versus nondeprived eye). Thus, the age at initiation of chronic monocular deprivation significantly impacted the residual acuity of the deprived eye, and the magnitude of recovery following visual training (Fig. 2C).

To explore the impact of visual training on the recovery of vision, we manipulated the time course of visual task performance. Late onset monocular deprivation was followed by dark exposure and visual training of the chronically deprived eye (Fig. 3A; blue symbols). In this case, after 4 d of normal visual training, performance in the task was suspended for 3 wk. Resumption of task performance revealed no change in detection thresholds over the hiatus (before: 0.25 ± 0.03 ; after: 0.32 ± 0.07 cycles per degree; $P > 0.05$ paired t -test). Nonetheless, repetitive performance improved visual detection thresholds to plateau of 0.646 ± 0.056 cycles per degree ($P < 0.02$ paired t -test versus nondeprived eye acuity of 0.785 ± 0.075 cycles/degree). The visual acuity of controls run in parallel with standard continuous visual training reached a similar plateau at 0.681 ± 0.037 cycles per degree (red symbols; Fig. 3A). Thus, the hiatus from visual training did not impact the magnitude of the visual recovery or the number of trials required to reach performance plateau (Fig. 3B). In contrast, delaying the initiation of visual training several weeks after dark exposure prevented the recovery of vision in the deprived eye (white symbols; Fig. 3A). Therefore, instructive visual experience during a transient window of enhanced cortical plasticity was necessary to promote recovery from deprivation amblyopia in adults.

Repetitive performance of the visual detection task appears to actively drive recovery of vision in dark-exposed amblyopes, with modest changes overnight. To ask whether the difficulty of

the discrimination task impacted daily performance plateaus, the visual detection task was modified to reduce difficulty. The spatial frequency of the initial visual stimulus presented to the deprived eye was lowered to 0.102 cycles per degree, and the increment for subsequent increases in spatial frequency was reduced to 0.04 cycles per degree. Again, deprived eye visual acuity emerged rapidly in amblyopes following dark exposure and visual training (Fig. 3C). However, performance of the modified visual task promoted greater improvement in detection thresholds, which plateaued at 0.959 ± 0.028 cycles/degree (blue symbols; $P > 0.05$ paired t -test versus nondeprived eye acuity of 0.841 ± 0.035 cycles/degree). Importantly, this acuity transferred to novel visual stimuli (cycles/degree average $\pm$ SEM: 45° sinusoidal grating, red symbols, 0.925 ± 0.070 ; 90° square wave gratings, green symbols, 0.935 ± 0.071 ; 135° square wave grating, black symbol, 0.936 ± 0.0162). Detection thresholds for novel stimuli further improved with repeated task performance. Although significantly fewer trials were completed (modified: 355.37 ± 18.98 , $n = 7$; standard: 402.44 ± 28.83 , $n = 9$; $P < 0.015$ t -test), performance of the modified task resulted in higher maximum

Figure 3. Visual task parameters impact the recovery of vision. (A) Inset: Experimental design. Monocular deprivation was maintained from P28–P185. Performance of the visual task with the chronically deprived eye proceeded on a discontinuous schedule (insertion of a 3 wk hiatus), a delayed schedule (initiated 6 wk after eye opening), or a standard continuous schedule. Visual detection thresholds did not improve over the hiatus but improved significantly upon resumption of repetitive task performance (blue symbols; $n = 3$). Final detection thresholds were similar following discontinuous and continuous training (red symbols; $n = 3$). No recovery of vision occurred when initiation of the visual task was delayed after dark exposure (white symbols; $n = 6$). (B) Continuous versus discontinuous task performance resulted in a significant difference in detection thresholds at 41 d after eye opening, but not in final plateau acuity. (*) $P < 0.05$ paired t -test. (C) Inset: Experimental design. Monocular deprivation was maintained from P14–P185. Performance in a modified visual detection task following dark exposure and eye opening enhanced visual detection thresholds (0° sinusoidal gratings; blue symbols) and increased transfer to novel visual stimuli (45° sinusoidal gratings, red; 0° square wave gratings, green; and 45° square wave grating, black). Additional task repetition further increased detection thresholds above baseline (dashed line). (*) $P = 0.05$ paired t -test, first day of novel stimulus versus last day of familiar stimulus; $n = 10$. (D) Reduced variability, accelerated time to plateau, and increased recovery of deprived eye acuity following performance of the modified visual detection task (red circles) versus standard task (blue diamonds).

detection thresholds (modified task 0.959 ± 0.028 ; standard task 0.476 ± 0.068 ; $P < 0.05$, t -test; Fig. 3D).

Together this demonstrates that chronic monocular deprivation induces severe amblyopia that is not reversed by visual training alone. Nonetheless, binocular visual deprivation through dark exposure, which transiently enhances synaptic plasticity, promotes the recovery from severe amblyopia if quickly followed by instructive visual experience. Importantly, the timing and difficulty of the visual task significantly impacted visual recovery. This demonstrates, that the two-step sequence of reactivation of synaptic plasticity by dark exposure followed by instructive visual experience can be customized to promote full recovery from the most severe amblyopia in adulthood.

Repetitions of a visual task have been shown to lower detection thresholds and improve spatial acuity in species ranging from rodents to humans (Sagi 2011; Bonaccorsi et al. 2014; Kawato et al. 2014). Indeed, repetitive task performance improved the visual detection thresholds for both the nondeprived and deprived eye of amblyopic rats. Examination of the maximal detection thresholds achieved by repeated performance in the task revealed a “baseline” component that generalized to novel stimuli and “learned” component that was stimulus-selective. Ultimately, the tradeoff between the specificity and generalizability of visual perceptual learning is determined by the strength of stimulus selectivity of neurons in primary visual cortex. The significant reduction of visual response strength and selectivity induced by chronic monocular deprivation (Montey and Quinlan 2011) predicted that perceptual learning through the amblyopic eye would be less stimulus-specific, as has been demonstrated in humans (Huang et al. 2008). The stimulus selectivity of visual perceptual learning likely reflects the input specificity of learning-induced synaptic modifications. Interestingly, visual perceptual learning has been reported to potentiate the strength of intracortical synapses, and raise the ceiling for further potentiation of thalamo-cortical synapses in primary visual cortex of binocular rodents (Hager and Dringenberg 2010; Sale et al. 2011; Hager et al. 2015). Similar stimulus selectivity is observed in the enhancement of VEP amplitudes and single neuron responses following passive visual stimulation in rodents and humans (Frenkel et al. 2006; Cooke and Bear 2010; Clapp et al. 2012; Montey et al. 2013; Kaneko and Stryker 2014).

The reactivation of plasticity in primary visual cortex by dark exposure and other experimental manipulations has revised the idea that critical periods are limited to early post-natal development (Bavelier et al. 2010; Takesian and Hensch 2013; Sengpiel 2014). Importantly, the plasticity that is re-engaged by dark exposure is transient and must be quickly followed by instructive visual experience to promote the recovery of visual acuity. Dark-exposure engages several mechanisms predicted to lower the threshold for synaptic plasticity in principle neurons (Cooper and Bear 2012). For example, dark exposure returns the NMDA subtype of glutamate receptor to the “juvenile” form, enhances the temporal summation of NMDAR-mediated synaptic currents and promotes re-expression of forms of synaptic plasticity typically limited to juveniles (Quinlan et al. 1999; Yashiro et al. 2005; Huang et al. 2010; Montey and Quinlan 2011). In addition, dark exposure scales up excitatory synapses on principle neurons, increases visual cortex excitability, and expands the integration window for spike-timing dependent plasticity (Goel and Lee 2007; He et al. 2007; Guo et al. 2012). The success of dark rearing, and other manipulations, such as environmental enrichment, to promote the recovery from amblyopia in rodents and felines (He et al. 2006; Sale et al. 2007; Maya Vetencourt et al., 2008; Duffy and Mitchell 2013; Stodieck et al., 2014) likely depends on the reactivation of these and other forms of activity-dependent plasticity (Kuo and Dringenberg 2009; Harauzov et al. 2010; Mainardi et al. 2010; Djuricic et al.

2013) that are engaged by visual perceptual learning (Baroncelli et al. 2012; Montey et al. 2013).

In normal binocular rodents, the difficulty of a visual discrimination task has been shown to impact the rate of perceptual learning (Treviño et al. 2013), and depend on incremental increases in task difficulty (Sale et al. 2011). Our findings demonstrate that task difficulty impacts the rate and magnitude of the visual learning that underlies recovery of visual acuity in dark-exposed amblyopes. Visual training is increasingly used to enhance visual acuity and recover stereoscopy in amblyopic humans and experimental animals (Levi and Li 2009; Bonaccorsi et al. 2014; Kawato et al. 2014; Sengpiel 2014). Recent approaches to visual training include dichoptic visual stimulation (in humans and felines) and the use of action video games (Mitchell and Duffy 2014; Hess and Thompson 2015; Levi et al. 2015; Murphy et al. 2015). However, the improvements in visual acuity typically achieved with these methods have been relatively modest in humans (Tsirlin et al. 2015). We propose that the reactivation of synaptic plasticity by dark exposure may improve the response to visual training in human amblyopes.

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