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# Rethinking Amblyopia 2020

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## Abstract

Recent work has transformed our ideas about the neural mechanisms, behavioral consequences and effective therapies for amblyopia. Since the 1700's, the clinical treatment for amblyopia has consisted of patching or penalizing the strong eye, to force the "lazy" amblyopic eye, to work. This treatment has generally been limited to infants and young children during a sensitive period of development. Over the last 20 years, we have learned much about the nature and neural mechanisms underlying the loss of spatial and binocular vision in amblyopia, and that a degree of neural plasticity persists well beyond the sensitive period. Importantly, the last decade has seen a resurgence of research into new approaches to the treatment of amblyopia both in children and adults, which emphasize that monocular therapies may not be the most effective for the fundamentally binocular disorder that is amblyopia. These approaches include perceptual learning, video game play and binocular methods aimed at reducing inhibition of the amblyopic eye by the strong fellow eye, and enhancing binocular fusion and stereopsis. This review focuses on the what we've learned over the past 20 years or so, and will highlight both the successes of these new treatment approaches in labs around the world, and their failures in clinical trials. Reconciling these results raises important new questions that may help to focus future directions.

## INTRODUCTION

Amblyopia is a common neurodevelopmental abnormality that results in physiological alterations in the visual pathways and impaired vision in one eye, less commonly in both. It reflects a broad range of neural, perceptual, oculomotor and clinical abnormalities that can occur when normal visual development is disrupted early in life. This review focusses on unilateral amblyopia.

Aside from refractive error, amblyopia is the most common cause of vision loss in infants and young children. It causes a constellation of perceptual deficits in the vision of the amblyopic eye, including a loss of visual acuity, position acuity and contrast sensitivity, particularly at high spatial frequencies, as well as increased internal noise and prolonged manual and saccadic reaction times. There are also perceptual deficits in the strong eye, such

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as certain types of motion perception, reflecting altered neural responses and functional connectivity in visual cortex (Ho et al., 2005). Beyond the perceptual deficits are a range of visuo-motor deficits and potential psychological sequelae. Conventional clinical treatment in young children consists of correction of any refractive error and patching of the strong eye. Compliance with patching is challenging, and many amblyopic children fail to achieve normal acuity or stereopsis even after extended periods of treatment.

The broad goal of this review is to provide an update on the substantial progress made over the last 25 years or so in understanding the neural basis of amblyopia, the explosion of both randomized clinical trials and new experimental approaches to treatment that may improve compliance and outcomes, and evidence that amblyopic adults may still show some benefit of treatment. Why now? Although there have been a number of reviews on selected aspects of amblyopia, including a Special Issue of *Visual Neuroscience* (2018; referenced throughout this review), the year 2020 seems to be an appropriate time to take a close look at some of these new findings, approaches and possible future directions for recovering 20/20 (or at least improved) vision in amblyopia.

Amblyopia, and its association with strabismus (misalignment of the two eyes) was first described by Le Cat in the eighteenth century (as cited by Revel, 1971), and Cont Du Buffon in 1743 described what is still today the most widely prescribed treatment for amblyopia – occlusion of the strong eye. He also suggested “equalizing” vision in the two eyes with lenses by blurring the strong eye (cited by Revel, 1971).

Amblyopia has a prevalence of about 2–4 % in children (Ciuffreda, Levi & Selenow, 1991). Aside from refractive error, amblyopia is the most frequent cause of vision loss in infants and young children. Amblyopia reflects the damage that results when normal visual development is disrupted. In the clinical setting, this damage is generally expressed as a loss of visual acuity in an apparently healthy eye, despite appropriate refractive correction. However, there is a great deal of evidence showing that amblyopia results in a broad range of neural, perceptual, oculomotor and clinical abnormalities (for reviews see Kiorpes, 2006; Levi, 2006).

Amblyopia is almost always associated with a history of abnormal binocular visual development early in life. Specifically the main risk factors for amblyopia are three: a constant unilateral strabismus (one eye turned all or most of the time), usually in the form of esotropia (eye turn inward), anisometropia (unequal refractive error in the two eyes) or, much less common in developed countries, cataract (either in one or both eyes). A fourth, related risk factor is persistent high hyperopia (far-sightedness – Anker et. Al., 2003; Atkinson et al., 1996; Sjoestrand & Abrahamsson, 1996). It is important to note that these risk factors frequently co-occur (e.g., strabismus and hyperopic anisometropia; esotropia and high hyperopia) (Hunter & Cotter, 2018). If these risk factors occur late in life, though, amblyopia does not develop. The severity of the amblyopia is related to the degree of imbalance between the two eyes and the age at which the amblyogenic factor occurred. It is unclear how these factors interact, but it is clear that different early visual experiences result in different functional losses in amblyopia (McKee, Levi & Movshon, 2003 – Fig. 1), and an

important aspect is the presence or absence of binocular function (see Maurer & McKee, 2018 for a recent review).

## Sensitive Period for the development of amblyopia:

Amblyopia generally does not develop after age 6 to 8 years of age (Worth, 1903; von Noorden, 1981), leading to the suggestion that there is a "sensitive period" for the development of amblyopia. However, in humans the age of onset is difficult to determine, and the effects of treatment make it hard to obtain a clear picture of the "natural history" of the development of amblyopia. Consequently, much of our current understanding of the development of amblyopia derives from animal studies (see Boothe et al., 1985 for a review) and from retrospective reviews of clinical records (e.g., von Noorden, 1981). Advances in infant testing have provided more direct data on the development of naturally occurring amblyopia in humans (Mohindra et al., 1979; Maurer et al., 1983; Jacobson et al., 1981; Birch, 1983; Maurer et al., 1999; Norcia et al., 2015) and monkeys (Kiorpes and Boothe, 1981; Kiorpes et al., 1984, 1989) and provide strong evidence that amblyopia is induced by early deprivation.

Anatomical structures and behavioral and physiological functions that develop early may be less susceptible to the effects of abnormal visual input, than those that develop more slowly (Levi & Carkeet, 1993). This hypothesis can account for why different structures and functions may be vulnerable to visual deprivation at different times during development. For example, the sensitive period in layer IVc (the input layer) of the cortex of monkeys is shorter than that of other layers (LeVay et al., 1980), and there is evidence that different visual functions are affected when one eye lid is sutured shut is at different times. Visual functions that develop early are more immune to pattern deprivation, while those that develop late are at greater risk and remain susceptible for the longest time (Levi & Carkeet, 1993)

The upper limit for susceptibility of excitatory binocular interactions appears to be later than that for acuity or contrast sensitivity in monkeys and may extend to at least 7 or 8 years in humans. Interocular transfer studies provide an indirect estimate of the period of susceptibility of binocular connections in humans with strabismus (Banks et al., 1975; Hohmann and Creutzfeldt, 1975), and suggest that they are highly vulnerable during the first year and a half of life and remain at risk until at least age 7 years.

Amblyopia is classified by the accompanying amblyogenic factor (which is generally considered to be the cause), most commonly as strabismic amblyopia, anisometropic amblyopia, mixed amblyopia (i.e., both strabismus and anisometropia are present at the time of diagnosis), or less commonly form deprivation amblyopia (due to cataract, ptosis or corneal opacity) or meridianal amblyopia (due to high uncorrected astigmatism, in which the shape of the cornea results in different refractive error in the two meridians, and as a result, reduced vision in the more out of focus meridian).

While this classification by condition is clinically useful for descriptive purposes, an important and long-standing question is whether different causative factors (i.e., different early visual experiences) result in different functional losses. As shown in Fig. 1, rather than

classification by accompanying amblyogenic factor, classification by visual function shows a map of visual deficits, in which the strabismic group, shown in red, has a different pattern of visual loss than the anisometropic group, shown in green (McKee et al., 2003). This study used a limited range of functional vision tests, and a different or more extensive set of tests may result in a different map. Ideally, the most useful classification scheme would also provide important prognostic information that could help guide treatment (Maurer & McKee, 2018).

## BEHAVIORAL, OCULO-MOTOR & NEURAL CONSEQUENCES

### Behavioral deficits:

Amblyopia results in a constellation of behavioral deficits when viewing is with the amblyopic eye. These include a loss of visual acuity, position acuity and contrast sensitivity, particularly at high spatial frequencies, as well as increased internal noise and prolonged manual and saccadic reaction times to visual stimuli (McKee et al. 2016). These deficits are usually greatest in central vision. There is both behavioral and physiological evidence that the amblyopic deficit may be amplified downstream in the brain (see Levi, 2006; 2013; Kiorpes, 2006, 2019 for reviews). Thus amblyopes suffer not only from ‘low-level’ deficits in acuity and contrast, but also more impairments in more complex visual processing (Sharma, Levi & Klein, 2000; Kiorpes, 2006; Levi, 2006; Farzin & Norcia, 2011; Wong-Kee-You, Wei & Hou, 2020). These include processing stimuli defined by contrast or motion (sometimes referred to as “second-order” because they are not defined by changes in luminance), contour integration, temporal and spatial problems, and reduced attentional capacity (Popple & Levi, 2008). Amblyopic vision also appears to have increased random noise (Levi & Klein, 2003; Levi Klein & Chen, 2008; Li et al., 2008). This is true even when viewing with the preferred eye (Levi, Klein & Chen, 2008), suggesting that this elevation of random noise, as well as other deficits when viewing with the preferred eye (e.g., Ho et al, 2005), is of central origin, likely related to the absence of correlated binocular visual experience early in life (Kind, Mitchell, Ahmed, Blakemore, Bonhoeffer & Sengpiel, 2002; McKee, Levi & Movshon, 2003).

The lack of correlated binocular visual experience early in life may lead to suppression of the amblyopic eye by the fellow eye. For more than a century, suppression has been implicated as an important characteristic and possibly a cause of amblyopia (Worth, 1903) and loss of stereopsis. This notion is based on clinical (von Noorden, 1990), psychophysical (Levi, Harwerth & Smith, 1979; 1980; Smith, Levi, Manny, Harwerth & White, 1985; Hess, 1991; Harrad & Hess, 1992; Baker, Meese & Hess, 2008; Maehara, Thompson, Mansouri, Farivar & Hess, 2011; Mansouri, Thompson & Hess, 2008; Ding, Klein & Levi, 2013; Ding & Levi, 2014; Hess, Thompson & Baker, 2014; Hess & Thompson, 2015) and physiological (Harrad, Sengpiel & Blakemore, 1996; Sengpiel & Blakemore, 1996; Bi et al., 2011) evidence. Indeed, as discussed below, binocular suppression in area V2 is proportional to the depth of amblyopia (Bi et al., 2011). It is important to note that there remain many questions about the role, occurrence and nature of suppression in amblyopia (Barrett, Panesar, Scally and Pacey, 2012; Holopigian, Blake & Greenwald, 1986; Vedamurthy et al., 2015), and whether suppression is different in anisometropia and strabismus – passive in anisometropia,

where the amblyopic eye's image is blurred, but active in strabismus, in order to avoid diplopia.

Under normal everyday viewing conditions *with both eyes open*, the most common deficit in amblyopia is reduced stereoscopic depth perception. Reducing the vision of one eye (in neurotypical persons) by blurring, filtering or reducing contrast degrades stereoacuity (Westheimer & McKee, 1980; Donzis, Rappazzo, Burde, Gordon, 1983; Legge & Gu, 1989; Menon, Bansal & Prakash, 1997), and degrading vision in one eye has a more deleterious effect on stereopsis than by degrading both eyes (Westheimer & McKee, 1980; Legge & Gu, 1989).

Persons with amblyopia frequently manifest deficits in visually-guided hand movements (similar to occluding vision of one eye neurotypical persons (see Levi, Knill & Bavelier, 2015 for a review), resulting from impaired stereopsis, rather than to reduced visual acuity (Suttle, Melmoth, Finlay, Sloper and Grant, 2011; Melmoth, Finlay, Morgan and Grant, 2009; Niechwiej-Szwedo et al, 2012a & b; Grant, Melmoth, Morgan and Finlay, 2007), fixation instability (Subramanian, Jost and Birch, 2013), or poor vergence control (Melmoth, Storoni, Todd, Finlay, & Grant, 2007). A recent study suggests that impaired stereopsis may also affect the gaze strategies used during walking across complex terrains, suggesting that stereopsis is important for the visuomotor control of locomotion (Bonnen et al., 2019).

### Oculo-motor deficits:

Many amblyopes also show poor fixation stability when viewing with the amblyopic eye (Chung et al., 2015). Specifically, when attempting steady fixation, the amblyopic eye (particularly in strabismic amblyopes) drifts constantly, producing retinal image motion, and makes frequent microsaccades. Importantly, there has been a recent see-change in our understanding of the role of fixational eye-movements in vision [Martinez-Conde, Otero-Milan & Macknik, 2013; Rucci & Victor, 2015). As noted by Rucci & Victor (2015), "Fixational eye-movements are not a 'bug' but a feature: an integral and crucial stage of information processing, which enables the retina to represent space in a temporal fashion and to begin the process of feature extraction." Moreover, recent work suggests a tight coupling between visual sensitivity and fixational eye movements in normal vision (Scholes et al., 2015). Fixation stability is abnormal in amblyopic eyes: compared to the fellow eye, the amblyopic eye shows large slow drifts and microsaccades as large as 1 degree (Schor & Hallmark, 1978; Ciuffreda, Kenyon & Stark, 1979; Subramanian, Jost & Birch, 2008; González et al., 2012), and recent work has shown that the fixational eye movements of the amblyopic eye may account for more than half of the variance in the amblyopic observers' visual acuity(Chung et al., 2015).

Persons with strabismic amblyopia also have long latencies when making a saccade to a peripheral target with their amblyopic eyes. In a large sample (n = 145), McKee et al., (2016) found that strabismic amblyopes have a latency about 40 – 80 msec longer when viewing with the amblyopic eye than with the fellow eye. Persons with anisometropic amblyopia also have longer latencies when viewing with their amblyopic eyes, but the difference is significantly smaller than that of the strabismic amblyopes. What accounts for the sluggishness of saccadic eye movements? We hypothesize that for anisometropic

amblyopes the increased response time simply reflects the reduced contrast sensitivity that is characteristic of amblyopic vision. However, our recent work suggests that this is not sufficient to explain the results of strabismics. For strabismic amblyopes saccadic reaction time is substantially delayed with the amblyopic eye relative to the fellow eye, even with perceptually matched contrast (Gambacorta, et al., 2018). An intriguing recent hypothesis is that poor fixation stability with its increased frequency of microsaccades may affect the dynamics and the spatial allocation of selective attention in individuals with amblyopia (Verghese, McKee & Levi, 2019).

## Neural deficits:

The neural deficits in amblyopia are complex. They depend on the timing and nature of early abnormal visual experience, which differs in anisometropes and strabismics (Fig 1; McKee, Levi & Movshon, 2003; Levi, McKee & Movshon, 2011). Much of what we know about these neural deficits comes from studies of animals such as cats and mice. However, because of the close homology between the visual systems of humans and non-human primates, we focus mainly on neural deficits in both naturally occurring and experimental amblyopia in non-human primates.

In non-human primate models of amblyopia, the deficits are first seen in striate (area V1) and other visual cortical areas rather than in the retina or the lateral geniculate nucleus. For example, there is a striking loss of neurons that can be excited by both eyes (binocular neurons), and to a lesser extent a reduction in the number of neurons that can be driven by the deprived/amblyopic eye in area V1 (Blakemore & Vital-Durand, 1986; for recent reviews see Kiorpes & Daw, 2018; Kiorpes, 2019). In addition, some V1 neurons show reduced contrast sensitivity and spatial resolution (Kiorpes et al., 1998; Bi et al., 2011). However, these physiological losses of sensitivity and resolution in V1 do not provide a simple explanation of the behavioral losses (Levi, 2013). Considerations of noise, noise correlations, pooling and the weighting of information also play important roles in making perceptual decisions (Shadlen, Britten, Newsome & Movshon, 1996; Cohen & Newsome, 2009). More recent work that takes these into account show both increased neural response variability (noise) in V1 (Acar, Kiorpes, Movshon, 2019) and V2 (Wang et al., 2017) and higher correlations between neurons driven by the amblyopic eye in V1 of amblyopic monkeys. Increased noise and increased noise correlations reduce the visual information that is passed to downstream visual areas through the amblyopic eye. Moreover, the excitatory-inhibitory balance is altered in early visual cortex of amblyopic non-human primates (Hallum et al., 2017). Importantly some of the most profound effects of monocular deprivation can be substantially mitigated by brief periods of unrestricted binocular vision (Zhang et al., 2011) – a finding that has important implications for treatment.

There is also evidence for additional abnormalities in higher visual areas. For example, neurons in area V2 of amblyopic primates integrate visual information over larger areas than those of normal primates (Tao et al., 2014). Substantial binocular suppression of the amblyopic eye by the fellow eye is seen not only in V1 but also in area V2 (Bi et al., 2011; Wang et al. al, 2017; Shooner et al., 2017). In addition neural populations in the Middle

Temporal area (area MT, or V5) have reduced sensitivity to motion, commensurate with the known behavioral deficits in motion perception.

Human imaging studies have shown both structural and functional changes. Structural abnormalities are present in the lateral geniculate nucleus (Barnes et al., 2010; Hess et al., 2009), which shows reduced activity and connectivity with V1 on functional imaging (Li et al., 2011). The striking physiological changes V1 cascade downstream (Imamura et al, 1997; Goodyear, Nicolle, Humphrey & Menon, 2000; Barnes et al., 2001; Muckli et al., 2006; Lerner et al., 2003; 2006; Bonhomme et al., 2006; Conner, Odom, Schwartz & Mendola, 2007; Li, Dumoulin, Mansouri, & Hess, 2007; Ho & Giaschi, 2009; Secen, Culham, Ho & Giaschi, 2011; Mendola et al., 2018), even reaching areas concerned with attention and decision making (Farzin & Norcia, 2011), where they may be amplified. Functional mapping of amblyopic cortex suggests that parafoveal regions of space activate cortical areas that normally represent the fovea (Muckli et al., 2006; Conner, Odom, Schwartz & Mendola, 2007a & b; Clavagnier et al., 2015), and functional connectivity of visual areas appears to be altered in an eccentricity dependent manner (Mendola et al., 2018).

### Genetics.

Amblyopia is a non-genetic condition, but amblyogenic factors may have a genetic basis. For example, strabismus is often clustered in families, and a meta-analysis of twin studies suggests that genetic factors are necessary to cause strabismus (Wilmer & Backus, 2009). There is also a genetic contribution to refractive error (Dirani et al., 2006; Hammond et al., 2001), which may be a risk factor for strabismus and amblyopia if not corrected.

## TREATMENT

For centuries the main approach to the treatment of amblyopia consisted of optical correction of any refractive error (to ensure a clearly focused retinal image in each eye) and occlusion or penalization of the “strong” eye, thus “forcing” the brain to use the input from the “weaker” amblyopic eye (Worth, 1903). However, it is only in the last twenty years or so that a number of large-scale clinical trials have provided detailed evidence for the efficacy of this approach.

### Sensitive periods for treatment of amblyopia.

Amblyopia does not develop after about 6 to 8 years of age (Worth, 1903; von Noorden, 1981) and currently is treated almost exclusively in young children. The idea that there is a critical or sensitive period for treatment can be traced back to Claude Worth, who hypothesized that the reduced vision of the amblyopic eye represented arrested sensory development. Worth suggested that the presence of a “sensory obstacle” (e.g., unilateral strabismus) halted the development of visual acuity (“amblyopia of arrest”), so the depth of amblyopia is a direct function of the age of onset of the “sensory obstacle”, and, if amblyopia of arrest persisted, a further loss of visual acuity could occur (“amblyopia of extinction”) due to inhibition of the weak eye by the fellow eye. In Worth’s view, delaying treatment meant that only the loss due to amblyopia of extinction could be recovered. Based on his observations in almost 1000 strabismic amblyopes, Worth concluded that both the age

of onset and the length of time the obstacle was in place influenced the outcome of treatment.

The notion of a critical or sensitive period was cemented by the work of Hubel & Wiesel (1970; Wiesel, 1982), and the many studies that followed (Berardi et al, 2000; Hensch & Quinlan, 2018). Early monocular deprivation (lid suture) in kittens and monkeys results in substantial neural alterations, in particular a change in ocular dominance in the visual cortex and a profound loss of vision. These effects only occur during a critical or sensitive period. In kittens this sensitive period begins at about 4 weeks and lasts for 3–4 months. The losses can be reversed by suturing the previously open eye, but only if the reverse suture is performed within the sensitive period (Movshon & Van Sluyters, 1981; Blakemore & Van Sluyters, 1974). The notion that amblyopia in humans cannot be treated beyond age 7 or 8 years seems to stem from the idea that treatment for amblyopia was only effective during the early critical period for visual development, when the neural system is plastic [Fig. 2 – blue curve].

More recent studies in humans and nonhuman primates suggest that rather than an abrupt and complete drop in plasticity, there may be some residual plasticity that extends into adulthood (for a recent review see Hensch & Quinlan, 2018 - Fig. 2 – red curve). Moreover, there maybe multiple anatomical and physiological sensitive periods for development: visual functions that develop early (e.g. scotopic sensitivity) may be less susceptible to the effects of deprivation than late developing functions (e.g. stereopsis) (Harwerth et al., 1987; 1990]. Furthermore, the sensitive period for recovery may not be the same as the period of susceptibility. Studies in humans suggest that binocular connections may remain susceptible until at least the age of 7 years [Banks et al., 1975; Hohmann & Creutzfeldt, 1975]. In the following paragraphs we will explore the question of neural plasticity and whether there is a sensitive period for recovery of function. Additionally, there is evidence from studies in mice that it is possible to remove the “brakes” that limit plasticity and restore a degree of neural plasticity in adults (Morishita & Hensch, 2008; Hensch & Quinlan, 2018 – Fig. 2 green curve)

The sensitive period(s) for the developing amblyopia has been considered to suggest that there is also a sensitive period for its treatment. Thus, clinical treatment was often limited to young children. However, this view has been widely refuted (Kupfer, 1957; Levi & Polat, 1996; Levi, Polat & Hu, 1997; Holmes & Levi, 2018 and see below). Large scale randomized clinical trials show that treatment may be effective in older (13 to 17 years) children who have not been previously treated (Pediatric Eye Disease Investigator Group, 2005), and a substantial number of studies have shown significant and long-lasting effects of experimental treatments in adults. For a recent evidenced-based review, see Piano & Simmers (2019).

Moreover, evidence suggests that the visual system retains a degree of neural plasticity well into adulthood (Bavelier et al., 2010). For example, adults who lose vision in the non-amblyopic eye may spontaneously recover vision in amblyopic eyes in (Vereecken & Brabant, 1984; Rahi, Logan, Borja, Timms, Russell-Eggitt, & Taylor, 2002). This can be seen most dramatically in older adults with long-standing amblyopia who have lost their

strong eye through injury or disease. El Mallah et al. (2000) showed that in amblyopic patients who develop macular degeneration in their strong eye, the visual acuity of the amblyopic eye spontaneously improves. There are other reports of recovery of vision in amblyopic eyes in adults who lose vision in the non-amblyopic eye (Vereecken & Brabant, 1984; Rahi, Logan, Borja, Timms, Russell-Eggitt, & Taylor, 2002). An important implication of these studies is that the connections from the amblyopic eye may be suppressed rather than destroyed. A reduction of input from the strong eye would unmask these existing connections as occurs in adult cats with retinal lesions (Chino et al., 1992; Heinen & Skavenski, 1999; but see Smirnakis et al., 2005). These findings strongly implicate suppression of the amblyopic eye by the fellow eye. However, removing the strong eye is not a viable option for treating patients; but, as discussed below (Future directions), temporary inactivation of the fellow eye promotes anatomical recovery in cats that were aged beyond the critical period peak, and without detriment to the inactivated eye (DiCostanzo et al., 2020).

Indeed, it seems likely that the sensitive periods for producing amblyopia and for recovery are supported by different mechanisms of plasticity. There is evidence that mechanisms supporting the production of amblyopia are from those that promote recovery from amblyopia (Kaneko et al., 2008; Cho et al., 2009; Ranson et al., 2012). The dissociation between impairment and recovery processes suggests that the mechanisms mediating the two forms of plasticity are different, despite the fact that in animal models the critical period profile of impairment and recovery is largely overlapping, as has been revealed in cats (Olson and Freeman, 1980; Blakemore and Van Sluyters, 1974) and non-human primates (von Noorden, 1979; Blakemore, Garey & Vital Durand, 1978). Thus, while recovery from amblyopia is possible at older ages, development of amblyopia seems not to be.

### Optical (refractive) treatment.

As implied by the clinical definition of amblyopia, correcting refractive error alone does not initially result in normal visual acuity in the amblyopic eye. However, a number of clinical trials have shown that over a period of 10 to as much as 30 weeks, optical treatment *by itself* significantly improves visual acuity in both anisometropic and strabismic amblyopes, with about one third of the cases resolving just with this optical correction (Stewart et al., 2004a & b; Cotter et al., 2006, 2007, 2012; Asper et al., 2018). While the effects were strongest in younger children, older children (up to 17) also showed improvements with optical correction alone (Asper et al., 2018; Gao et al., 2018a). Moreover, more than a third of the children who received optical treatment improved their 3-D stereovision by a factor of two or more.

### Occlusion and penalization of the strong eye:

This has been the ‘gold standard’ treatment for the treatment of unilateral amblyopia since the French naturalist and botanist George-Louis Leclerc, Comte de Buffon in 1743 wrote that the weak eye could regain its strength by occluding the strong eye [For a detailed history of the treatment of amblyopia, see Louden & Simonsz, (2005)]. Occlusion generally refers to patching the strong fellow eye, typically with an opaque patch. Penalization of the strong eye can be achieved in a number of ways. One could place a lens or filter to blur its

vision. Alternatively, one can use atropine drops to eliminate accommodation in the strong eye, forcing the patient to use their amblyopic eye for near activities such as reading and writing, while still allowing the strong eye to be in focus at far distances.

Clinical trials have established that this approach is often quite successful, leading to improved visual acuity in the amblyopic eye. However, there is considerable individual variability in the response to patching (Holmes & Levi, 2018). Figure 4 summarizes data from 3 large Randomized Clinical Trials (randomized clinical trials) by the PEDIG group in children between about 3 and 7 years of age. Several points emerge. First, most of the almost 800 patients acuity improved. Second, even in this group with a narrow range of ages, a range typical of the time when many amblyopic patients are treated, there is a huge range of outcomes for any age. Although current data indicate that patients actually wear the patch about 50% of the prescribed time, this variability in outcome was not simply a matter of compliance, as studies using monitored occlusion show a similar variability in outcome (Stewart et al., 2004a & b). At this stage there is no way of predicting which patients will improve and which will not.

While patching and penalization can be effective, they have significant limitations. Their gains accrue very slowly. Patching requires about 170 hours for two lines of improvement in visual acuity for 4-year-olds, and more than 200 hours for a similar improvement for 6-year-olds (Stewart, 2007 – thick black line in Fig. 4). For children older than 7 it may require over 400 hours (Fronius, Cirina, Ackermann, Kohnen & Diehl, 2014). Patching itself may lead to reduced binocular vision and stereopsis, and to psycho-social problems such as a loss of self-esteem (Webber, Wood, Gole & Brown, 2008). The latter can make compliance a challenge. Any treatments (including optical treatment) that reduce the amount or duration of patching may improve compliance, as discussed further below. Even long periods of treatment may not result in normal acuity or stereopsis in a substantial proportion of amblyopic children (Birch and Stager, 2006; Birch et al., 2004; Repka et al., 2003; Repka et al., 2004; Repka et al., 2005; Rutstein et al., 2010; Stewart et al., 2004b; Wallace et al., 2006; Woodruff et al., 1994a). Morever, when vision is successfully restored to normal, visual acuity regresses within the first year of treatment in about 25% of patients (Holmes et al., 2004). Consequently, there have been a number of attempts over the last two decades to develop more effective and efficient approaches for treating amblyopia, using perceptual learning and videogame techniques (see Levi & Li, 2009; Levi, 2012; Birch, 2013; Tsirlin et al., 2015; Hess & Thompson, 2015; Levi, Knill & Bavelier, 2015 for reviews).

There is an effect of age over the range shown in Fig. 3, however the average data (large filled symbols) do not capture the huge range of individual outcomes (small dots), and we do not have a good predictor for prognosis in single subjects. An important factor is previous treatment. In the 13 to 17 year olds, those patients who had not been previously treated benefited much more than those who had been. Finally, while these results suggest the limits of conventional treatment, a review of the literature makes it clear that improvement in adults can exceed the predictions of the function shown in Figure 3. The open diamonds replot the remarkable results reported by Carl Kupfer (1957) from seven young adults with strabismic amblyopia, with initial acuity ranging from 20/70 to hand motion only, following 6 weeks of hospitalization during which they underwent complete, constant occlusion of the

strong eye combined with intensive fixation training. [Note that the Kupfer study was not a randomized clinical trial, and therefore may have been subject to experimenter bias, placebo effects, etc.]

## EXPERIMENTAL TREATMENTS: TARGETS, MECHANISMS AND FUTURE DIRECTIONS

### Optimizing Occlusion and Penalization.

There have been many attempts to increase the effectiveness of treatment for amblyopia, as adjuncts to patching and penalization. They include subcutaneous injection of strychnine, electrical stimulation of the retina and optic nerve, flashing lights, red filters and rotating gratings (reviewed by Revell, 1971), administration of Levodopa (Leguire et al., 1993; Levi, 1994 and Wang, Li & Li, 2020 for a recent meta-analysis) and Transcranial Magnetic Stimulation (TMS – Thompson, Mansouri, Koski & Hess, 2008).

Some of the recent attempts have stemmed from the successful recovery from visual deprivation in rodents. One example is the study by Legas et al., (2019) that showed no benefit from use of Citalopram, a serotonin reuptake inhibitor that promoted recovery in rodents (Vetencourt et al., 2008). Similarly, while the administration of physostigmine promoted recovery from visual deprivation in rodents (Morishita et al., 2010), it failed to translate to humans (Chung et al., 2017). Other experimental treatments that seemed to succeed in rodents, such as exercise and dark exposure, also appear to be limited in their ability to promote recovery in human adults or higher order mammals (Holman et al., 2018; Campana, Fongoni, Astle & McGraw, 2020).

As noted in the Lasker report on amblyopia (Mitchell and Sengpiel, 2018), cross-species studies are needed to mitigate translation failures, and to avoid elevating frustration among frontline caregivers. Importantly, these failures highlight the importance of appropriate animal models, ideally non-human primates, to avoid costly failures.

A full discussion of the many attempts to increase the effectiveness of treatment for amblyopia is beyond this review; however, few have been subjected to rigorous scrutiny, and those that were often failed to stand up to it (e.g. Tytla & LaBow-Daily, 1981). Below we focus on three more promising recent approaches: Perceptual Learning, Videogame play and binocular/dichoptic training. Unlike treatments such as dark exposure and pharmacological interventions, which aim to enhance the level of developmental plasticity at a particular age in order to set the stage for recovery (green line in Figure 2), these treatments are aimed at using available plasticity mechanisms (red line in Figure 2). In this way the therapies may logically combine for synergistic benefit.

### Perceptual Learning (PL).

Performance on sensory tasks can be improved through repeated and extensive practice. This is called perceptual learning (for reviews see Dosher & Lu, 2017; Buonomano & Merzenech, 1998). Perceptual Learning was originally defined as “Any relatively permanent and consistent change in the perception of a stimulus array following practice or experience

with this array…" (Gibson, 1967). The key idea is that practicing challenging, near-threshold visual tasks results in long-term improvements in performing those tasks. This has been shown for a large variety of visual tasks in neurotypical adults [Dosher & Lu, 2017]. Over the last 25 years, there have been dozens of small-scale studies of PL in amblyopia, involving hundreds of patients. The extant studies (see Levi & Li, 2009; Levi, 2012; Tsirlin et al., 2015 for recent reviews and a meta analysis) show improvements through PL on a broad range of tasks, including Vernier acuity, contrast detection, letter identification, position discrimination, spatial frequency discrimination, grating acuity, letter acuity and motion coherence, among others (small blue solid symbols in Fig. 4, replotted from Gambacorta et al., 2018). Most of these studies have reported that amblyopic patients improve in the trained task, although the amount of improvement varies substantially both between tasks and between individuals. Importantly, most studies also found that the improvement transferred, at least partially, to improved visual acuity by a mean of 1 to 2 lines. This improvement occurred regardless of the training task, whether training was monocular or binocular, the patient's age (over a fairly limited range) or the type of amblyopia (Levi & Li, 2009; Levi, 2012; Tsirlin et al., 2015).

During PL, amblyopic patients must attend and make fine discriminations with their amblyopic eyes, under challenging conditions. They are exposed to the same stimuli repeatedly and receive feedback. Thus, PL likely involves learning to attend to and use the most salient or reliable information for the task when viewing with the amblyopic eye. Indeed, when the strong eye is patched, normal everyday life may require attention and fine visual discriminations using the amblyopic eye, and this may account, at least in part, for the success of patching. However, PL provides intensive, active, supervised visual experience with feedback, requiring attention and action using the amblyopic eye, and thus may be more efficient.

As shown by the black line in Fig. 4, improvement during occlusion is slow. Visual acuity in 6–8 year old children improves by a factor of about 1.6 after about 240 hours of patching (Stewart et al., 2007). Perceptual learning may be faster and more efficient than patching, by as much as a factor of 8. It results in improvements of 1 –2 lines of acuity in a much shorter time. Combining occlusion with PL may reduce the duration of patching, thus reducing the emotional consequences of patching (Kvarnstrom, Jakobsson & Lennerstrand, 2001).

There are two important limitations of perceptual learning: specificity and boredom. Specificity refers to the training effects being confined to the trained stimulus and task. If improvements are limited to the trained stimulus, condition and/or task, then PL would have very little value for amblyopia. Fortunately, perceptual learning has a broader 'bandwidth' in amblyopia than in normal vision (Huang et al., 2008). Many different tasks transfer to improved visual acuity (Levi, 2012; Tsirlin et al., 2015) and other functions including stereoacuity and counting the number of briefly presented stimuli (Sharma et al., 2000). However, this transfer to acuity is often only partial. In some cases this may be due to the fact that the training improved performance for a specific orientation or tilt and not others, and that this limits improvements with stimuli such as letters that have multiple orientations.

The second limitation is that PL (as performed in laboratories) is, by its nature, highly repetitious, and may lead to boredom, making it less than ideal for clinical implementation. It is also important to note that this approach to the treatment of amblyopia has not yet been subjected to the scrutiny of a randomized clinical trial, which presumably will have to precede its broad deployment as a treatment. For these reasons, PL has not translated to clinical practice

### Playing Video Games.

An alternative approach is video game play. In neurotypical observers playing action video games causes the brain to develop an optimal perceptual template for the task at hand (see Bavelier et al., 2012 for a review). However, unlike PL, action video games have varied demands and visual experiences, training the brain to learn to make optimal use of the stimulus information, and promoting a broad transfer of learning. This raises the possibility that playing such games could result in improved visual performance in amblyopia.

About ten years ago, we (Li et al., 2011) asked amblyopic adults to play a commercial first-person shooter videogame (Medal of Honor: Pacific Assault) with their fellow eye patched. All showed improvements in visual acuity, from about 13 to 44%. Two subjects with mild amblyopia improved to 20/20! Unlike normal subjects, whose vision does not improve after playing a non-action game (Tetris), amblyopic observers also improved when playing a non-action game (SimCity) (Li et al., 2011; 2015). Interestingly, video game play and for perceptual learning lead to similar improvements in visual acuity with (Fig. 4).

Other visual functions, including counting briefly presented dots, Vernier acuity and attentional blink also improve following videogame play [Li et al., 2011; 2015]. Some amblyopic subjects show improved stereoacuity after perceptual learning of a stereo task (Ding & Levi, 2011), action video game play (Li et al., 2011), or viewing 3-D movies (Li et al., 2018) similar to the improvements in stereopsis with monocular perceptual learning (Levi, Knill & Bavelier, 2015). Note, that these unmasked cohort studies have not been subjected to rigorous, large randomized clinical trials, and therefore we do not know whether not they lead to larger improvements than dichoptic treatment or clinical patching regimens.

Commercial videogames (like the ones used by Levi & Li, 2011, 2015) provide a very rich, engaging and dynamic environment and both challenge and reward the player, enabling them to succed. Furthermore, action game play has also been shown to enhance visuo-spatial selective attention, aspects of visual short-term memory, and the ability to select a target in an ever-changing stream of stimuli in neurotypical subjects (Bavelier et. Al., 2012), and may therefore benefit persons with amblyopia, who have both low-level and high level deficits (Sharma et al., 2000; Wong-Kee-You, Wei & Hou, 2020). It has been suggested that playing action videogame may promote neural plasticity (Morishita & Hensch, 2008; Bavelier et al., 2010) because they release neuromodulators associated with arousal and reward (Koepp et al., 1998; Baroncelli, Maffei & Sale, 2011). The importance of action to amblyopic learning is not clear, though, since non-action video games can also confer some benefit (Li et al., 2011; 2015). Importantly, patients are more likely to comply with playing an immersive videogame than with patching or perceptual learning.

### Dichoptic Treatment.

As noted earlier, suppression has been implicated as a feature and possibly a cause, of amblyopia and loss of stereopsis. Another approach to treat amblyopia is to reduce this suppression by training under binocular/dichoptic conditions. A key aspect of this binocular treatment is to provide different stimuli to the two eyes. The amblyopic eye receives a more intense stimulus than the fellow eye, by reducing the contrast, the luminance or both of the image presented to the strong eye.

Over the past decade there have been a large number of unmasked cohort studies using dichoptic perceptual learning and videogame play to train adults and children with amblyopia. These have generally documented improvements in visual acuity that are similar to those obtained with monocular training (Birch et al., 2015; Hess & Thompson, 2015; Knox et al., 2012; Gambacorta et al., 2018; Vedamurthy et al., 2015A & b; Herbison et al.,2013; 2016; Li et al. 2014 – small open red symbols in Fig. 4, replotted from Gambacorta et al., 2018) although there appears to be an additional benefit for improved stereopsis in strabismic (but not anisometropic) amblyopia (Vedamurthy et al., 2015; Levi, Knill & Bavelier, 2015).

The efficacy of perceptual learning and video game play (both monocular and binocular) have been replicated by a number of small-scale studies (small symbols in Fig. 4) and generally result in, on average, a 1 to 2-line improvement in visual acuity both in children (as shown in Fig. 4) and in adults (Levi & Li, 2009; Levi, 2012; Tsirlin et al., 2015). The reason(s) for this 1 to 2 line improvement remain unclear. One hypothesis that it reflects changes in the ability to attend to (or upweight) the relevant signals and ignore the noise when viewing with the amblyopic eye in order to improve decision making (see Verghese, McKee & Levi, 2019 for a discussion), rather than low level changes in early visual cortex.

Recently, the binocular approach has been subjected to randomized clinical trials (Holmes et al., 2016; Manh et al., 2018; Kelly et al., 2016; Gao et al., 2018b). The results from these trials are shown by the large red symbols in Fig. 4, for both the experimental and control groups, and the results have been mixed, and sometimes disappointing. Although each of the these studies showed some improvement, two had improvements of less than 1 line, and the effects were no better and possibly slightly worse than the control conditions of patching (large black symbols), continued spectacle wear (large gray triangle), or presenting identical images to the two eyes (square with X). A more recent RCT with 48 children aged 4 to 10 either patched or playing a contrast rebalanced dichoptic game (Dig Rush), showed a larger improvement after 2 weeks for the game group (1.5 lines – large open red inverse triangles) than for the patched group (0.7 lines – large filled red inverse triangles; Birch et al., 2020).

There may be a number of reasons for the mixed outcomes of these clinical trials. On the one hand, many of the prior small-scale studies did not include appropriate or even any control groups, raising the possibility of placebo effects, Hawthorne effects and regression toward the mean. Small-scale studies often carefully select patients most likely to succeed, for example excluding patients with strabismus (or with large angle strabismus), and including subjects strongly motivated to volunteer. Not all small-scale studies included prolonged refractive adaptation, which as seen from the Holmes (2018) study had as much

effect as the treatment. The larger clinical trials generally used the same fixed settings for the interocular contrast ratio for all participants, whereas the small-scale studies used individualized settings to determine the interocular contrast ratio. Many small-scale studies used stereoscopes or prisms to carefully align the images to the two eyes, which is critical for binocular combination with strabismus, but some of the clinical trials did not. Finally, it is not clear whether the stimuli used in the clinical trials and small-scale studies were equally engaging. Nevertheless, even "DigRush" had rather poor compliance, even though it was purportedly the most "engaging" of the games used in the clinical trials (Holmes, 2018): only 56% completed more than 75% of the prescribed game play.

### Training stereopsis directly:

A number of recent laboratory studies have focused on training stereopsis directly in individuals with amblyopia as well as in non-amblyopic strabismics, with some success via perceptual learning (Ding & Levi, 2011; Astle, McGraw & Webb, 2011; Xi et al., 2014) videogame play (Vedamurthy et al., 2016) and viewing 3D movies (Li et al., 2018). For a review see Levi, Knill & Bavelier (2016), and a recent small RCT using perceptual learning embedded in a video-game format suggests that this may be a useful method for improving stereopsis in patients with amblyopia (Portela-Camino et al., 2018).

### Homeostatic Plasticity.

A counterintuitive approach, based on the notion of homeostatic plasticity (the mechanism that seeks to balance neural excitation and inhibition), is to patch the amblyopic eye – i.e., inverse occlusion. Patching the amblyopic eye was employed to treat amblyopia with eccentric fixation in Europe in the 1960s and subsequently abandoned, because it was found to be less effective than direct occlusion. For example, von Noorden (1965) reported that ≈ 49% of patients improved 20 20/30 or better with occlusion of the sound eye, compared with 24% who improved with inverse occlusion, and 10% got worse. However, there is strong evidence that brief periods of monocular pattern deprivation can increase the sensitivity of the deprived eye and reduce that of the non-deprived eye by temporarily modulating the ocular dominance balance (Zhou et al., 2013; 2019; Lunghi et al., 2019). This is considered a form of ocular dominance plasticity. Based on the assumption that multiple episodes of short-term patching of the amblyopic eye could result in long-term alterations in interocular balance in favor of the amblyopic eye (Zhou et al., 2013; 2019; Lunghi et al., 2019). The green inverted triangle shows the effect of 2 hours a day of inverse occlusion for 2 months (Zhou et al., 2019, triangle) in patients age 10 to 35. The green upright triangle shows the effects of just six 2-hour sessions of inverse occlusion while exercising for 6 (Lunghi et al., 2019). They suggest that the physical activity might have played a role in the improvement (Lunghi & Sale, 2015); however, the effect of exercise on ocular dominance plasticity in normal vision has been disputed (Zhou et al., 2017; Finn et al., 2018).

It seems clear from Fig. 4 that at least some of these new treatment modalities can provide a rapid but modest improvement in vision with the amblyopic eye of, on average, 1 to 2 lines. Note that like conventional treatment, there are very substantial differences in the amount of improvement, with some patients achieving as much as 4 lines (a factor of ≈ 2.5) or more. Is a 1 – 2-line improvement worth the effort? For patients with deep amblyopia a small

improvement in acuity is unlikely to make a noticeable difference to their vision and quality of life under everyday circumstances. However, for patients with mild amblyopia (20/40 – 20/60), the improvement may be sufficient to achieve some degree of binocular fusion and even stereopsis.

### Future directions:

It also seems critical to develop engaging methods that will result in better compliance. One possibility is the use of dichoptically presented movies or other video content (Li et al., 2014; Bossi et al., 2017). At this stage it is not clear whether active gaming is necessary, or if simply controlled visual input will provide the same "bang for the buck". It is also clear that we need better outcome measures, including better quantitative measures of stereopsis, hand-eye coordination, and quality of life to more fully assess the effects of treatment (Holmes & Levi, 2018). Importantly, it seems unlikely that any of these methods will completely replace patching or penalization; rather they may provide important adjuncts to conventional treatment that may speed the recovery of vision.

There is also ongoing research into other new treatments that can alter the balance between neural excitation and inhibition and restore plasticity beyond the sensitive period (See Bavelier et al., 2010; Baroncelli, Maffei & Sale, 2011; Hess & Thompson, 2015, for reviews). Acetylcholine plays important roles in visual cortical plasticity and perceptual learning (reviewed in Kang et al., 2014). One study found that donepezil a cholinesterase inhibitor that increases synaptic levels of acetylcholine, increased the magnitude and specificity of perceptual learning of motion direction discrimination in healthy humans (Rokem & Silver, 2010), and these effects were still evident 15 months later (Rokem & Silver, 2013). Unfortunately, recent studies show no such benefit of donepezil for perceptual learning of letter identification or crowding in patients with amblyopia (Chung et al., 2017), or of selective serotonin reuptake inhibitors such as citalopram (Legas et al., 2019). Another interesting pharmacologic observation is that intravitreal injections of tetrodotoxin results in faster recovery of amblyopia in cats (Fong et al., 2016), without detriment to the inactivated eye (DiCostanzo et al., 2020). Finally, rodent models also suggest a role for exercise, environmental enrichment and dark rearing; however, it is unclear how these relate to human amblyopia. Ultimately there may be a future role for combining new pharmacologic agents, behavioral techniques and other methods such as transcranial magnetic stimulation, and transcranial direct current stimulation (Thompson et al., 2008; Speigel et al., 2013) to improve the treatment of amblyopia in both children and adults.

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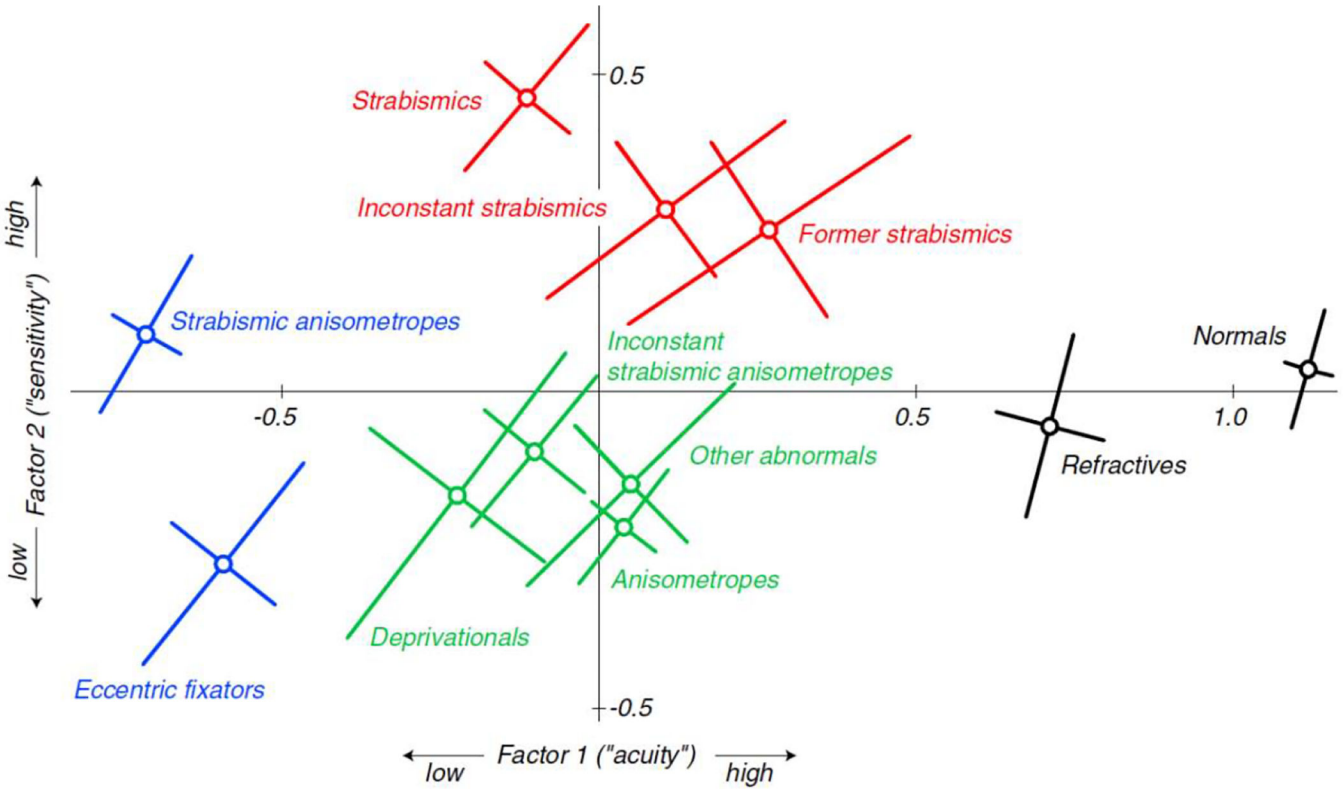


**Fig. 1. Amblyopia functional loss 'map'.**

Mean locations of 11 clinically defined categories in two-factor space for a large population of patients (427) with amblyopia or its risk factors. Factor 1 is closely related to three different acuity measures, and Factor 2 is closely related to the two contrast sensitivity measures. The diagonal bars show one standard error of the mean measured along the principal axes of the elliptical distributions. From McKee, Levi & Movshon, 2003.

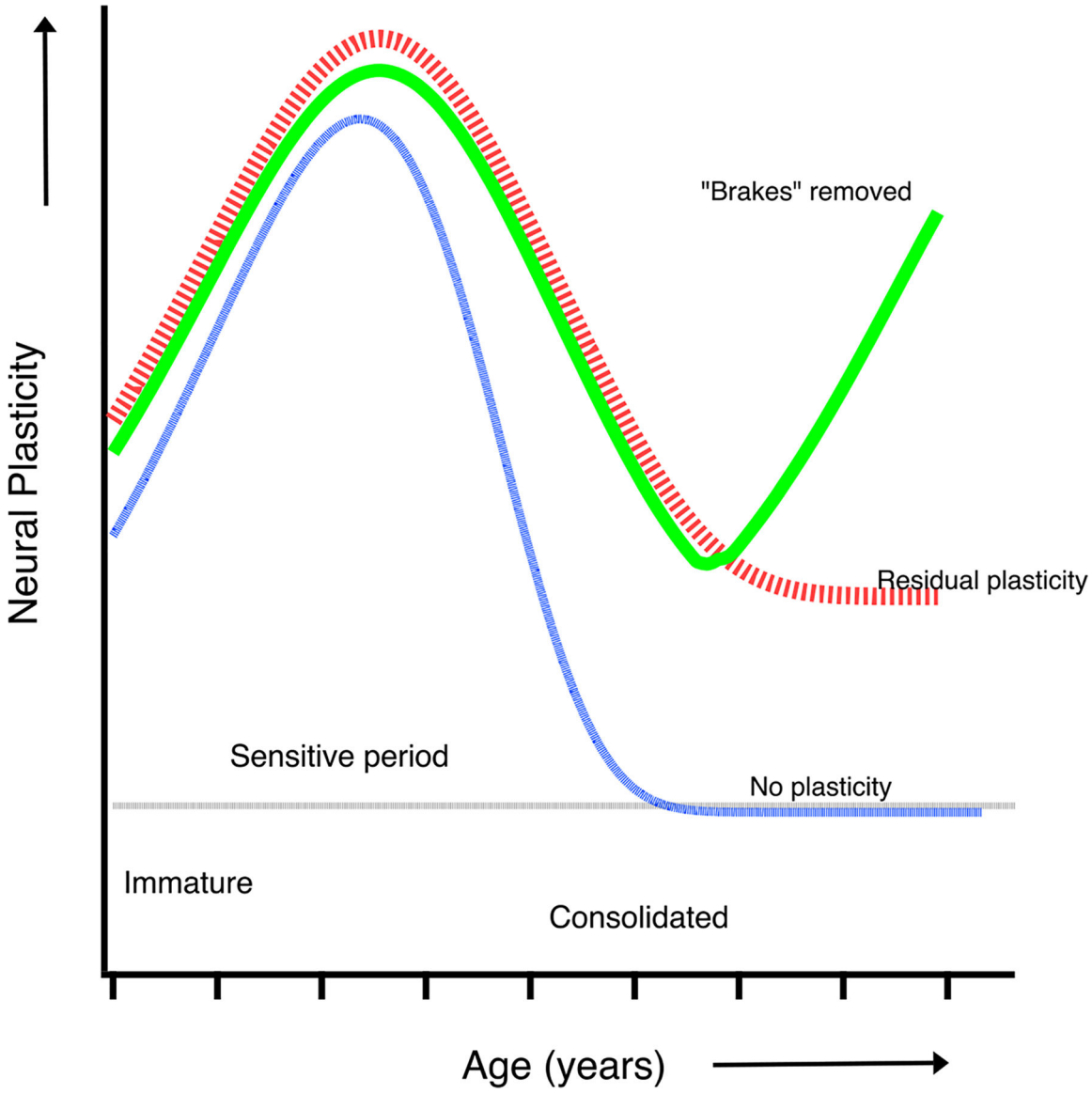


**Fig. 2. The sensitive period.**

This cartoon illustrates several hypotheses regarding neural plasticity during development. The blue curve shows plasticity increasing during early development when the neural system is immature, peaking and rapidly diminishing to zero when function is consolidated. The red curve is similar, but with residual plasticity extending into adulthood. The green curve illustrates removal of the factors (brakes) that limit plasticity and restore levels of neural plasticity in adults.

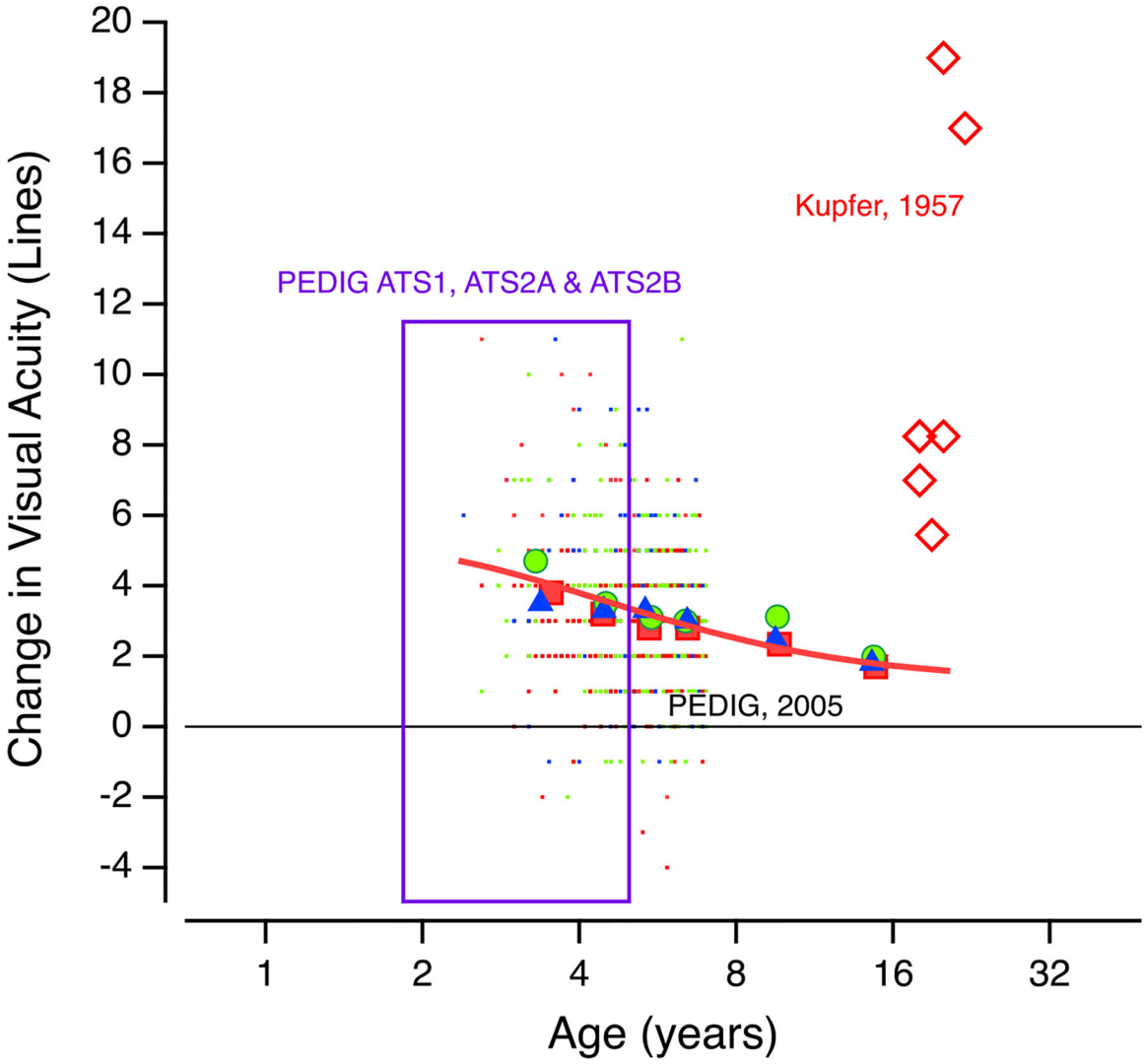


**Fig. 3. Change in visual acuity vs. Age of Treatment.**

Summary of 3 clinical trials: Trial ATS1 compared daily atropine to occlusion for at least 6 hours/day; trial ATS2A compared 6 hours/day versus full-time patching for severe amblyopia and trial ATS2B compared 6 hours versus 2 hours/day of patching in patients with moderate amblyopia. The tiny dots are the individual data from ≈ 800 patients; the large symbols show the mean idata in ≈ 1 year bins; included also are the mean data from an additional study (PEDIG 2005) that examined the effectiveness of treatment in children ages 7 to 17. A positive change in acuity is improvement. (after Holmes and Levi, 2018). Also shown here (red diamonds) are data from a small group of adult amblyopes who underwent intensive treatment (see text) from Kupfer, 1957. The red line is a fit to the mean PEDIG data.

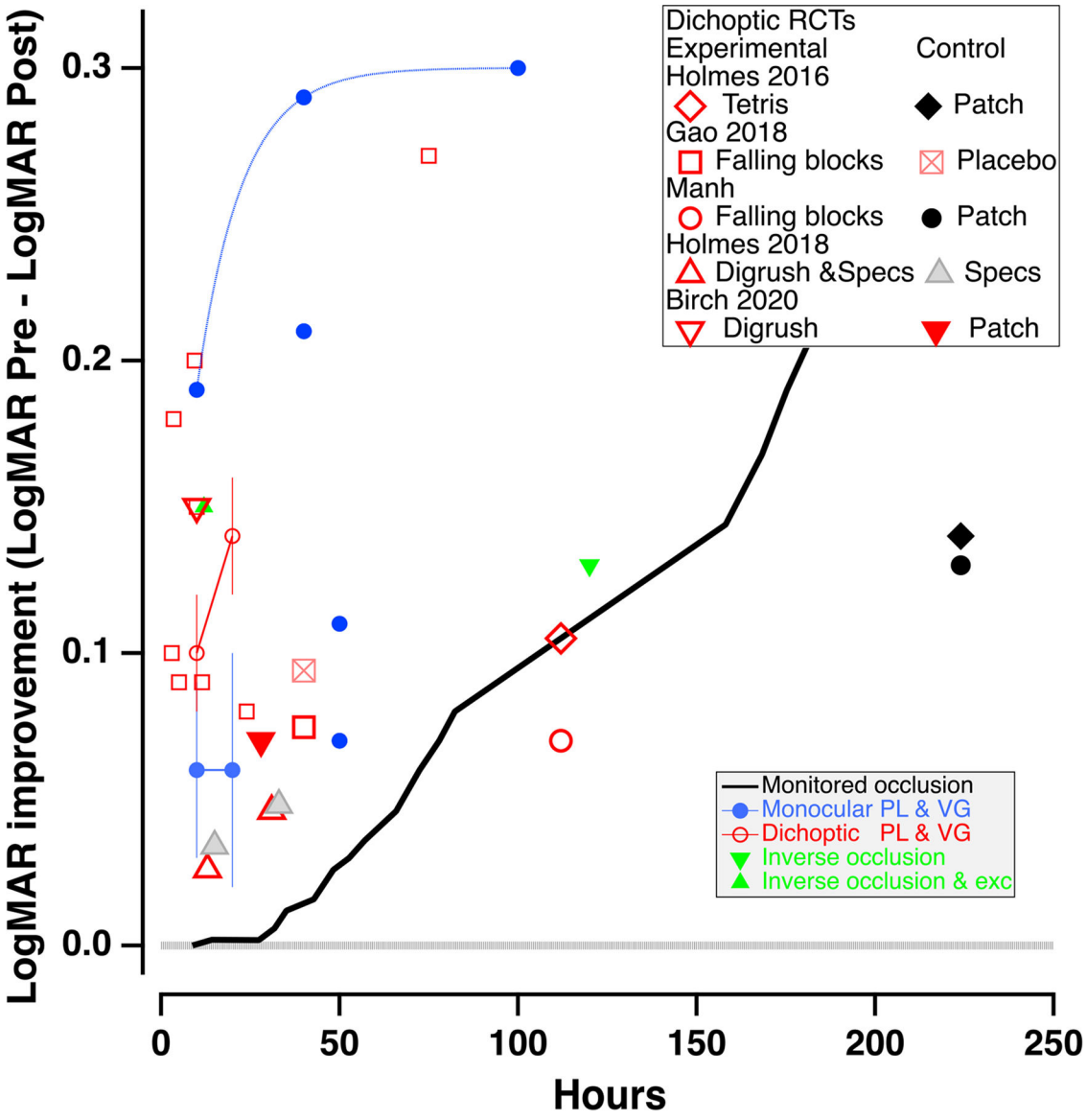


**Fig. 4. Improvement in visual acuity vs hours of training.**

VA improvement data (pre-post) from a broad range of experimental treatment studies in adults and children with amblyopia, as a function of hours of treatment. Small blue solid circles represent monocular perceptual learning or video game treatment, and the small red open circles indicate dichoptic/binocular treatment, replotted from Gambacorta et al., 2018 (fig. 6. Error bars are the SEMs). The black line shows the time course of monitored occlusion (solid line from Stewart et al., 2007). The solid green triangles are from studies using inverse occlusion (Zhou et al., 2019, inverted triangle) and inverse occlusion plus exercise (upright triangle, Lunghi et al., 2018). The large symbols show the results of recent large scale RCTs of dichoptic/binocular treatment, for both the experimental and control groups. The dotted horizontal line extending from 0.0 on the Y axis indicates no improvement in visual acuity.