Reasons why we might want to question the use of patching to treat amblyopia as well as the reliance on visual acuity as the primary outcome measure

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ABSTRACT
Recent evidence suggests that the primary deficit in amblyopia is loss of binocular vision and that the loss of monocular acuity is a secondary consequence. This new understanding derived from recent laboratory studies questions the present therapy and its primary acuity-based endpoint, which have been the gold standard in the treatment of this condition for the past 200 years.

WHY PATCHING?

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Historical perspective

The current treatment for amblyopia has its origins in the mid 18th century. There were two opposing schools of thought at the time, one championed by De Buffon that believed the loss of acuity was the primary factor in the condition and another championed by Darwin that supported the idea that the loss of binocular vision was the primary factor, the loss of acuity being its consequence. While there was no strong scientific support at the time to swing the argument one way or the other, the fact that acuity was relatively better understood than binocular function and able to be measured more easily, tilted the balance in terms of the monocular loss model. Patching therapy, in one form or another, ensued thereafter for over 200 years. It is only now that our understanding of binocular vision and its underlying neural circuits are more advanced, that we are in a position to re-examine this issue and question the course that was taken so long ago.

From the beginning, it was accepted that there were three main pieces to the amblyopia puzzle; loss of monocular function (eg, visual acuity and contrast sensitivity), interocular suppression (ie, reduced participation of the amblyopic eye under binocular viewing) and loss of binocular function (ie, fusion and stereopsis). The aetiological order was what was in doubt; did the loss of monocular vision lead to suppression and eventual loss of binocular function or was it the other way around?

Evidence for the primary role of the binocular deficit

The key to identifying whether amblyopia produces the binocular deficit or whether the binocular deficit results in amblyopia lies in the form of the relationship between suppression and amblyopia. If amblyopia, that is the loss of monocular foveal acuity, is primary, then its magnitude will be inversely related to the level of suppression; the greater the initial acuity loss, the less the suppression needed to eliminate diplopia. On the other hand, if the loss of binocular vision is the primary deficit,
then the resulting loss of monocular acuity is a consequence of suppression and one would expect there to be a direct relationship; the greater the suppression, the greater the acuity loss. The form of this relationship has now been measured in both amblyopic adults and amblyopic children using a variety of different techniques. There is a direct relationship between the magnitude of suppression and the acuity deficit in amblyopia strongly suggesting that the binocular deficit is primary. In support of this conclusion, it is noteworthy that amblyopia does not occur on its own without an associated binocular deficit and re-establishing binocular vision with a binocularly based approach results in improvements in acuity (monocular deficit). Suppression lies at the heart of the problem, which is thought to occur at an early cortical site, most likely area VI.

Knowing that the primary deficit is most likely the loss of binocular vision and that the secondary consequence is a loss of monocular acuity due to chronic suppression guides any therapeutic intervention. Restoration of binocular vision by strengthening fusion and consequently reducing suppression should form the foundation of any therapeutic intervention. Monocular acuity, being a secondary consequence, will be expected to improve as a simple consequence of this approach. This is consistent with the approach first recommended by Darwin, Javal, Worth and Maddox and detailed in a number of recent reviews.

The unphysiological nature of the opaque patching approach
Primates, because of their front facing eyes, which affords significant overlap between the left and right visual fields, are endowed with binocular vision. The foundations for binocularity are well established (though not stereopsis) at birth and is supported by a set of elaborate excitatory and inhibitory circuits in the early visual cortex. Most if not all cortical cells receive some influence from both eyes. At least in binocularly normal adults, wearing a patch over one eye, can fundamentally disrupt the excitatory/inhibitory balance and since the cortex, even in the adult, has a degree of plasticity, compensatory changes occur in the relative strengths of these circuits to restore the circuit balance during patching. One important concern in very young children is the loss of vision that can occur in the patched eye, so-called occlusion amblyopia. In a condition where there is one good eye, any loss of its function is of critical importance, even if it might only occur in a small percentage of cases. A retrospective review of patients under the age of 10 undergoing full-time patching revealed that 19.3% developed reverse amblyopia. For part time patching, the rate is about 6% and considered to be a less common side effect. In binocularly normal adults, the disruption to this binocular control circuit is not limited to affecting the patched eye, the unpatched eye can also be affected because of its reciprocal binocular connections. Recently, it has been shown that patching one eye of a binocularly normal individual causes a gradual loss of visual function in the fellow unpatched eye over about an hour. This can be shown by monitoring visual sensitivity psychophysically in humans or by monitoring the blood flow in ocular dominance columns in the primate primary visual cortex using the high-resolution imagery afforded by Functional Ultrasound imaging (FUS) imaging. Finally, it is obviously far from ideal to treat the visual system, especially one that is inherently binocular, using a purely monocular approach and hope that any effects so accrued will be sustained once the monocular treatment is concluded and visual system restored to its more natural binocular state. It is not surprising that there is a relatively high-regression rate (ie, 25%), 6 months after the conclusion of patching treatment.

Other forms of patching
The importance of maintaining binocular function during treatment has been acknowledged by the use of partially binocular patching approaches such as the use of a blur lens, atropine or Bangerter filters. While these approaches go some way to maintaining binocular stimulation, they would not be expected to be as effective as the new binocular therapies at reducing the suppression experienced by the amblyopic eye. This is because, while they do reduce the contrast in the fellow eye, they do so only for high spatial frequencies (fine detail). Low spatial frequencies (coarse detail) which are strongly suppressed in the amblyopic eye, reduce the extent of binocular vision in this important range and limit the effectiveness of these approaches.

The burden on the patient and their family
Wearing an eye patch is seen as a social stigma, and many patients who wear a patch reported lower self-esteem, feelings of poor social acceptance, depression, frustration, feelings of isolation, clumsiness, body image issues and bullying from their peers. Most quality of life reports from amblyopic patients are targeted at issues with the treatment rather than the actual disease. The relationship between the parents who are keen on improving compliance and the child who suffers from the social stigma associated with patching is put at a great strain at a critical time in the child’s development. Children undertaking the therapy can have difficulties understanding daily activities that negatively impact career choices and educational attainment. Patching therapy is convenient for the practitioner, easy to instigate and well suited to being administered away from the clinic because of its simplicity but very difficult for the child and quite problematic for the parents and not without compliance problems. There are pros and cons associated with patching therapy that have to be taken into account in evaluating this current approach relative to other alternatives.

Binocular therapy
The modern instigation of this well-established approach (see above) involves the use of dichoptic presentation
of visual information, so that the contrast of elements shown to the fellow good eye can be reduced to the point where the amblyopic eye contributed to binocular vision (see Hess et al for review\textsuperscript{17}). It is based on the finding that the reduction of this suppressive drive from the good eye by a contrast reduction results in normal binocular combination in amblyopic observers.\textsuperscript{29} To increase attentional compliance, this procedure is usually implemented on a videogame platform\textsuperscript{30} or movie platform.\textsuperscript{31} The contrast imbalance is gradually reduced as long as the patient continues to perform well in their gameplay, this ensures that the game is played binocularly. One hour a day of game play for 2–8 weeks helps re-establish binocular vision and stereopsis and also improves visual acuity of the amblyopic eye.\textsuperscript{32,33} These results are sustainable.\textsuperscript{34} The pros are that the treatment is carried out under binocular conditions that are consistent with everyday viewing, which is probably why there is not the 25% regression rate associated with patching.\textsuperscript{25} This approach can be carried out at home.\textsuperscript{33,35–37} There are no associated psychosocial side effects, it is much faster in achieving the same acuity improvement (weeks vs months) and is enjoyable. It also has to knock on advantages for improved fine motor control\textsuperscript{38} because of its binocular emphasis. The cons are that it is technologically more complex being digital in nature and that although this approach was thought to solve the compliance problem associated with the patching approach, it does not. Kids not only have to put in the playtime (verified on the log files of the digital tablet) but also give their full attention,\textsuperscript{39} this is hard to document and has been thought to underlie the poor performance of this approach in a number of recent clinical trials.\textsuperscript{40–42}

**MONOCULAR ENDPOINT MEASURE**

**Why visual acuity?**

There is only a 1.41 benefit in visual acuity (0.15 log Mar) of having two eyes compared with one for normal individuals.\textsuperscript{43} This is a consequence of how information from the two eyes is combined in the early visual cortex. For example, in the case of an amblyope whose 20/200 vision has been improved to 20/20 from patching, which would be considered an incredible success, a monocular improvement of 1 LogMar (a factor of 10). Under binocular viewing, this 1 logmar improvement in monocular acuity due to patching therapy translates to only a 0.1 LogMar benefit binocularly. Furthermore, this small benefit is only realised if the patient has binocular combination, otherwise, there is no real-world functional benefit for what would be an incredibly successful monocular patching outcome. Additionally, while it is theoretically possible that the visual acuity loss could be the reason why stereopsis is reduced in the first place, this may not actually be the case as the visual acuity deficit is not significantly correlated with the stereo deficit, whereas suppression is.\textsuperscript{8} This suggests that it is suppression not visual acuity that limits stereopsis. Therefore, an acuity improvement in the amblyopic eye does not necessarily translate to improved binocular function (but see Lee and Isenberg\textsuperscript{44}). An argument that is often advanced in support of the importance of the visual acuity improvement is that if the good eye is lost from, for example, injury, then at least the patient will be left with a better functioning amblyopic eye. There is certainly a valid point. However, it is worth realising that the increased risk (x2) of losing an eye to injury is likely to be a direct consequence of not having binocular vision.\textsuperscript{45} Both patching and binocular therapy result in better acuity in the amblyopic eye; however, the latter specifically targets the restoration of binocular function.

**BINOCULAR ENDPOINT MEASURE**

**Fusion without stereopsis**

There are a number of real-world benefits of just having information from the two eyes able to be combined, even if the computation of retinal disparity (ie, stereopsis) has been irretrievably lost. First, the small benefit to overall binocular visual acuity outlined above. Second, a more functional binocular visual field,\textsuperscript{46,47} necessary for detecting and computing the trajectory of objects coming towards us in depth, this is a between-eye motion computation and probably does not rely on stereopsis per se.\textsuperscript{48} Very important in sport and for avoiding hazards, especially in protecting the fellow good eye from injury. This motion-in-depth computation is a low spatial resolution, binocularly based, velocity computation that is unrelated to and not impacted by visual acuity.

**Stereopsis**

The computation of retinal disparity resulting from the lateral separation of the two eyes gives us a fine-scale estimate of depth, which is very important for fine motor control and good hand–eye coordination\textsuperscript{49,50} that is intimately involved with how we interact with our environment using vision. This is deficient in amblyopes because of their loss of binocular function\textsuperscript{51,52} and it has been shown to recover to normal levels once their binocular vision is restored by binocular therapy.\textsuperscript{53} This has been shown using grasping tasks in the laboratory\textsuperscript{52,53–54} of the more practical Bruininks-Oseretsky Test of Motor Proficiency, which is in clinical use.\textsuperscript{38,51}

**Postural stability**

Our postural stability is worse when we only have one eye open and although stereopsis has not been controlled for, it is highly unlikely that stereopsis plays a major role.\textsuperscript{55} Amblyopes, particularly strabismics, are known to have postural instability,\textsuperscript{56} which is consistent with their loss of binocular vision in its most general form.

**Reading performance**

In normal, reading performance is better with two eyes compared with one.\textsuperscript{57} This is unlikely to be due to loss of stereopsis as reading is done at a single fixed plane. Amblyopes also experience reading difficulties, which could be due to their loss of binocular vision.\textsuperscript{58}
and the binocular control of reading eye movements. Patients with amblyopia read more slowly than their healthy peers under amblyopic eye viewing and binocular viewing conditions.69 60

Driving performance
Adrian and colleagues61 showed that racing car drivers under monocular condition are from 2.1 (95% CI 1.11 to 4.11; p=0.024) to 6.5 (95% CI 3.91 to 11.13; p=0.0001) times more likely to collide with target vehicles compared with their baseline (binocular) condition, depending on the driving situation. Furthermore, there was an average increase in reaction time from 64 ms (p=0.029) to 126 ms (p=0.015) under monocular condition, depending on the critical driving situation configuration. This study objectively demonstrates that monocularity has a significant negative impact on driving performance and safety. Concluding that amblyopes necessarily suffer from the full extent of these impairments needs to be taken with some caution. Amblyopes, unlike normal binocular individuals, rendered monocular, have had time for adaptations to occur (see Dakroub et al62). For example, the use of greater eye movements to compensate for a more restricted visual field and the use of greater head movements to derive depth from motion parallax to compensate for loss of stereopsis. Adaptations, not matter how effective, usually take time and are not instantaneous, this might cause problems in time-sensitive situations, like driving.

Other limitations of the binocular therapeutic approach
We are only at the beginning of understanding, which patients benefit maximally from this approach. The importance of age and previous treatment history are key issues. While it is true that patients of any age, even older adults who have a history of patching interventions can benefit from binocular therapy, there is a suggestion that younger, untreated patients exhibit larger benefits.63 Another important issue is the extent to which the patient complies with the therapy, this is just as important as it is for patching therapy but harder to quantify.40

In summary, in terms of real-world advantages, vision is of utmost importance; however, the visual acuity improvement of the amblyopic eye, given that there is a normally sighted fellow eye, will have little or no consequence for everyday life. Restoration of binocular vision, on the other hand, with or without an improvement in visual acuity of the amblyopic eye, has the potential for significant benefits for everyday vision, resulting in improved fine motor control, better peripheral detection of hazards, improved postural stability, better sporting performance and safer driving performance. All of these binocular benefits will help reduce the chances that there is any injury to the amblyopic eye. Without binocular vision, there is a factor of two increased risk of amblyopic eye injury.45 These benefits can be seen from studies where performance measures are compared for real-world activities for participants with binocular versus monocular vision. The improved fine motor control that is observed for amblyopes who have undergone binocular therapy being a good example.38 These deficiencies in real-world performance provide a simulation of what amblyopes experience and take us well beyond worrying about the visual acuity deficit in one eye. Restoration of binocular vision is not only the right thing to do from an aetiological perspective, but it is also the right thing to do from a real-world functional benefits perspective.

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