New insights into amblyopia: Binocular therapy and noninvasive brain stimulation

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SUMMARY The current approach to the treatment of amblyopia is problematic for a number of reasons. First, it promotes recovery of monocular vision but because it is not designed to promote binocularity, its binocular outcomes often are disappointing. Second, compliance is poor and variable. Third, the effectiveness of the treatment is thought to decrease with increasing age. We discuss 2 new approaches aimed at recovering visual function in adults with amblyopia. The first is a binocular approach to amblyopia treatment that is showing promise in initial clinical studies. The second is still in development and involves the use of well-established noninvasive brain stimulation techniques to temporarily alter the balance of excitation and inhibition in the visual cortex. (J AAPOS 2013;17:89-93)

Our understanding of the degree of neural plasticity within the adult brain has changed greatly during the past decade. We once thought that the visual system went through an initial period of rapid development early in life that was complete by approximately 10 years of age, after which function was fixed.[1] We now know that the adult brain maintains some plasticity throughout life and that there are mechanisms that modulate this.[2,3] This opens up new possibilities for the treatment of a number of developmental disorders that we have previously considered untreatable in adulthood, including amblyopia.

Amblyopia is not generally treated beyond the age of 10 years in part because patching has been found to be much less effective after this age[4]; however, amblyopia can be treated in adults. The adult brain is to some extent plastic; furthermore, although patching can improve vision in older patients,[5] this is not theoretically an ideal way to restore binocular cortical function in amblyopic patients.

The site of the dysfunction in amblyopia is located in the visual cortex, and the vast majority of cortical neurons are binocular. Restoring the function of monocularly deprived animals is greatly facilitated by a short period of binocular stimulation,[6] presumably taking advantage of the innate binocular cortical circuits that characterize the mammalian visual system. We argue that taking a binocular approach to amblyopia treatment may offer a more principled and effective option and that recovery of cortical function in adulthood is an attainable goal. Indeed, adults with amblyopia can regain function temporarily as a result of transcranial magnetic brain stimulation, a method gaining popularity in modulating the mechanisms responsible for brain plasticity.

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A Binocular Treatment for Amblyopia

Patients with strabismic or ansiometropic amblyopia have a combination of reduced monocular vision and reduced or absent binocular function. Currently, treatment focuses on improving the vision of the amblyopic eye with the expectation that this will result in improved binocular function. We have framed the problem differently by proposing that a binocular disorder is the primary disorder and amblyopia is the consequence. This perspective allows us to approach the treatment of the condition in a radically different way. Rather than emphasizing patching, which may further disrupt binocular function, it would be preferable to re-establish binocular function and stereopsis. If this can be achieved, the visual acuity in the amblyopic eye would be expected to improve as a consequence of the new binocular status. Reestablishing binocular fusion requires a reduction of the suppression that was part and parcel of the original binocular disorder and whose long-term influence, according to this way of thinking, is the cause of amblyopia.[7] To summarize, if the conjecture that amblyopia is a disorder of binocular vision is accepted, then development of an appropriate treatment would require 3 steps: (1) confirmation of that patients with amblyopia have the ability to combine information between their eyes; (2) quantification of suppression; and (3) reduction of suppression and strengthening of fusion. All of the work described herein was approved by the institutional ethical review boards of McGill University and the University of Auckland and was conducted in accordance with the Declaration of Helsinki. All participants provided full written informed consent.

Amblyopic Patients' Capacity to Fuse

Although previous investigators have suggested that patients with amblyopia do not exhibit binocular summation at high spatial frequencies and therefore do not possess binocular capabilities,[8-11] we have shown more recently that once high spatial frequency stimuli shown to each eye are equated in terms of threshold contrast, normal levels of binocular summation can occur.[12] It would appear, therefore, that the contrast sensitivity deficit affecting the amblyopic eye has obscured the important fact that patients with amblyopia still possess functional binocular summation mechanisms.

Quantification of Suppression

If the contrast of an image shown to the fixing eye is reduced, then a point can be reached where the information from both eyes is combined, admittedly under artificial viewing conditions. The contrast at which this occurs, or more accurately, the interocular contrast ratio at which this occurs (the *relative*, not the absolute, contrast is important in this context) is a measure of how much suppression is operative. We call this the "balance point"[13]; the measure varies from subject to subject depending on their clinical characteristics.[7]

Treating Suppression and Restoring Binocular Vision

Our original study[14-16] reported the treatment of adults (7 patients with strabismus and 2 with mixed amblyopia) that had either been treated with patching as children or had not been previously treated. We used a global motion stimulus that we had originally adapted to measure suppression,[13] presented dichoptically using a mirror haploscope. During a period of training ranging from 1 to 3 hours a day, over the course of several weeks (20-60 hours total), the degree of suppression exhibited by these patients had reduced to the point where images of the same contrast could be combined between their eyes—something that was not possible at the beginning of treatment. Concurrently, visual acuity in the amblyopic eye improved; not to normal levels but significantly (mean improvement, 0.36 logMAR $\pm$ 0.19). These improvements occurred well beyond the age at which patching is thought to be effective (mean age, 40 years). What is surprising is that improvement was the result of binocular stimulation alone.

Of 9 patients, 8 also showed significant improvements in stereopsis, 6 progressing from no measurable stereopsis to normal levels for the clinical test we used (Randot test), others from having coarse to fine stereoscopic capabilities. A few participants showed no improvement. In the next phase of this research we set out to make our technique for measuring suppression clinically useful by moving to a head-mounted display and developing a rapid psychophysical approach to assess the extent of binocular combination. This resulted in both a space- and time-saving benefit.[17] In addition, we converted our global motion task to one that might, in the long term, be better at holding the attention of a young patient, namely, a version of the popular video game *Tetris* (Tetris Company, Honolulu, HI). The game is viewed dichoptically: the amblyopic eye sees only falling blocks that are of high, fixed contrast, and the fellow fixing eye sees only the more superficial ground plane blocks into which the falling blocks have to be keyed. These ground plane blocks are of low but variable contrast. The less relevant deeper ground plane blocks are seen by both eyes to aid fusion.

To succeed at the game, the patient must combine information from the two eyes, which initially can only be done if the contrast of the fixing eye is reduced sufficiently. The amount of contrast reduction depends on the amount of suppression, which is consistent with the principle established by our initial work using the global motion task. As long as the game is played successfully, the contrast of the images seen by the fixing eye is gradually increased, until it is the same as the amblyopic eye. Patients who reach this point can combine information from both eyes when the image contrast is the same for each eye, indicating a reduction of suppression. In our original study,[14] this usually required about 4-6 weeks of game playing for 1-2 hours daily. This video game treatment has been implemented both on the head-mounted display described previously[18] and on a handheld device (iPod, iPhone, iPad; Apple Inc, Cupertino, CA).[19] On the head-mounted display, children played for 1 hour daily for 5 days, whereas adults played the iPod game for 10 to 19 1-hour sessions during a period of 1-3 weeks. The initial results of this video game treatment have been very encouraging, even for patients beyond the age at which conventional patching is thought to be useful. For example, adults treated with our approach deployed on an iPod touch demonstrated stereopsis (Figure 1A) and visual acuity (Figure 1B) gains after only 4-6 weeks.[19] These improvements occurred as a result of directly targeting binocular vision because at no point during treatment was the fellow eye occluded. We have now devised an anaglyph version of the treatment that will work on a range of handheld platforms and allows for games other than *Tetris* to be played. These are currently being tested at other clinical sites in the UK, Canada, New Zealand, and the United States.

The Application of Repetitive Transcranial Magnetic Stimulation (rTMS) to Amblyopia

Transcranial magnetic stimulation (TMS) is an established, safe, and noninvasive technique for stimulating the human brain.[20,21] TMS is based on the principle of electromagnetic induction, whereby a brief magnetic field is generated within a plastic-coated coil of wire that is placed on the head above the cortical area to be stimulated. The magnetic field passes painlessly through the skull and induces a weak electrical current within the underlying region of cortex. If a series of pulses are

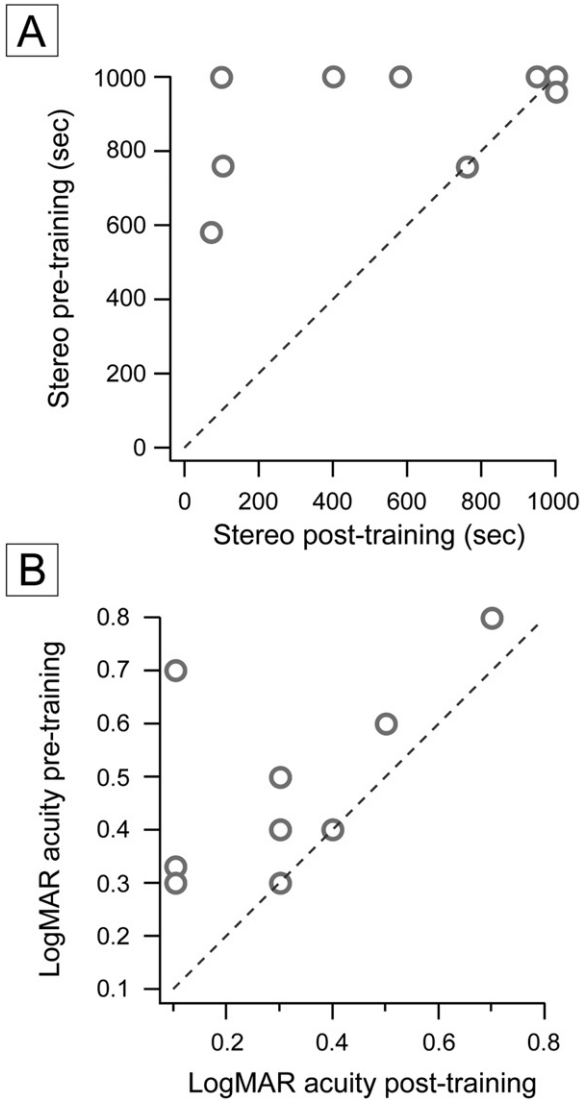

FIG 1. Results of the iPod treatment in 9 adult patients. A, stereopsis changes as a function of the treatment. B, monocular improvements in visual acuity as a result of restoring binocular function; points above the dashed unity line indicate an improvement. Replotted from To and colleagues.[19]

delivered to a cortical region, a technique known as rTMS, it is possible to temporarily alter the neural excitability of the stimulated region. Pulse trains of ≤1 Hz tend to decease excitability, whereas faster rates of delivery tend to increase excitability.[22] More complex stimulation sequences, which may have more pronounced effects on neural excitability, are being developed.[23] Because pathologic changes in the balance of neural excitation and inhibition within specific brain regions have been implicated in a number of neurologic and psychiatric disorders,[24] the use of rTMS as a potential treatment modality has been widely studied.[25,26] For example, rTMS of the left prefrontal cortex has been approved by the US Food and Drug Administration for the treatment of depression.[27] In addition, rTMS of the motor cortex may enhance recovery of motor function after stroke by redressing the disruption to inter-hemispheric inhibition that is thought to impede stroke recovery.[28]

The combination of impaired neural function and pathologic suppression characteristic of stroke has clear parallels with the current understanding of the neural basis of amblyopia.[29] Viewing through the amblyopic eye has been associated with reduced neural activity within the visual cortex,[30,31] and abnormal patterns of inhibition manifest as suppression of the amblyopic eye.[32,33] In this context, studies indicating that that the excitatory effects of rTMS are more pronounced for neural circuits that are inhibited (or suppressed), whereas the inhibitory effects of rTMS are more pronounced for neurons with greater levels of excitation[34-36] suggest that rTMS may differentially influence the cortical processing of inputs from the amblyopic and fellow eye by virtue of their differing levels of excitation and inhibition, even though inputs from both eyes project to common regions of the visual cortex.

We conducted the first study to assess the effect of rTMS on visual function in adult humans with amblyopia.[37] A group of 9 strabismic adults with amblyopia were recruited. Of these, 5 also had anisometropia, and 1 had a history of deprivation. Contrast sensitivity was measured for each eye for a high and a low spatial frequency grating target (spatial frequency was tailored according to the severity of amblyopia) using standard psychophysical techniques. Measurements were made directly before, after, and 30 minutes after rTMS. rTMS was delivered to the primary visual cortex and to the primary motor cortex as a control. Two spatial frequencies were used because amblyopia preferentially affects contrast sensitivity for high spatial frequencies[38] and therefore the low spatial frequency target acted as an additional control. Visual cortex rTMS improved contrast detection thresholds in 6 patients by an average of approximately 40% for the high spatial frequency target. This improvement was transient, with thresholds returning to baseline 1 week later. There were no reliable improvements for the low spatial frequency target, fellow eye viewing, or motor cortex stimulation. Two participants showed transient decreases in contrast sensitivity after 1 Hz rTMS but improvements after 10 Hz stimulation. The effects of rTMS on amblyopic eye and fellow eye contrast detection thresholds for the high spatial frequency target are shown in Figure 2A-B.

A control group of 5 participants with normal vision were also tested. The effects of 10 Hz rTMS on contrast sensitivity for a high spatial frequency target (20 cpd) varied with sensory eye dominance: rTMS tended to impair contrast sensitivity for the dominant eye directly after stimulation, whereas contrast sensitivity tended to improve for the nondominant eye directly after stimulation (Figure 2C). Recent evidence has suggested that eye dominance may relate to the balance of interocular suppression within the normal visual system,[39-41] suggesting that the mechanisms underlying the effects of rTMS on the

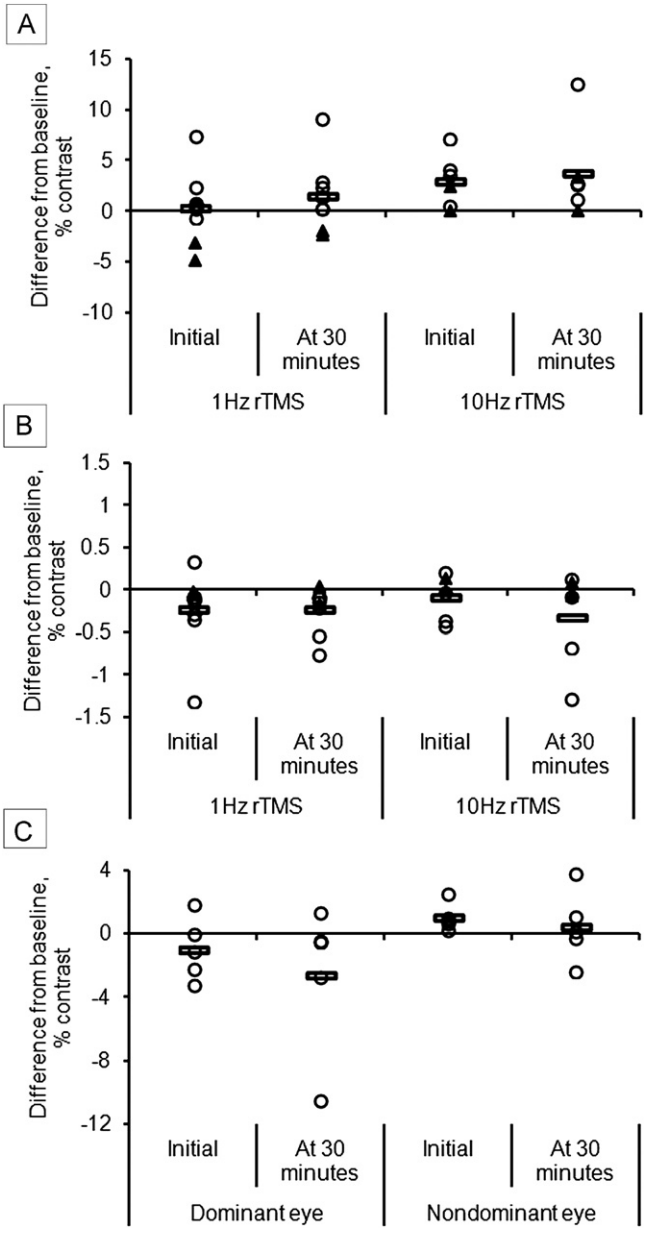

FIG 2. The effect of visual cortex rTMS on contrast detection thresholds for a high spatial frequency target directly after and 30 minutes after stimulation. Results are shown as pre-rTMS contrast threshold minus post-rTMS contrast threshold in units of percent contrast. Positive values indicate an improvement in contrast sensitivity (less contrast required after rTMS) and negative values indicate a reduction in contrast sensitivity. Data are shown for amblyopic eyes (A), fellow eyes (B), and control eyes (C). For observers with amblyopia, n = 9 for 1 Hz stimulation and n = 6 for 10 Hz stimulation. For control observers, n = 5, spatial frequency = 20 cpd and rTMS stimulation frequency = 10 Hz. Circular data points represent individual observers and filled triangles indicate the 2 participants who responded differently to 1 HZ and 10 Hz stimulation for amblyopic eye viewing. The horizontal bars show the mean for each condition. Note the differing scales in each plot, reflecting the larger changes induced by rTMS for amblyopic eye viewing. rTMS tended to increase contrast sensitivity for amblyopic eye viewing and nondominant eye viewing and decrease contrast sensitivity for fellow eye and dominant eye viewing. Data are replotted from Thompson and colleagues.[37]

normal and amblyopic visual system may have a common basis.

These results emphasize 2 key points. First, in agreement with a growing body of basic science literature, it appears that the adult human visual cortex does possess sufficient neural plasticity to allow for improved function in the amblyopic eye. Second, because of the brief nature of the rTMS intervention, it is likely that this improvement is mediated at least in part by neural systems that are already in place but suppressed within the visual cortex.

From a clinical perspective, the results of this initial study suggest that the application of noninvasive brain stimulation techniques to amblyopia in older patients deserves further investigation. The effects of repeated applications of rTMS currently are being investigated, and it is also possible that rTMS may enhance the effects of current treatments. Such effects have been reported for the combination of rTMS and physiotherapy in patients with stroke.[42] Finally, rTMS is not the only noninvasive brain stimulation technique available. Recent evidence suggests that a technique known as transcranial direct current stimulation can reduce gamma-aminobutyric acid–mediated suppressive interactions within the normal human visual cortex[43] and may therefore be applicable to amblyopia.

In conclusion, the current treatment principle for amblyopia involves restoring monocular function without any specific plan for reestablishing binocular function. The most widely used treatment method is patching of the fixing eye. Regardless of how one decides to fully activate the amblyopic eye, the problem remains that the approach is by its very nature monocular. If a binocular outcome is considered the ultimate goal of amblyopia therapy, then an approach that is fully binocular from the outset may be more effective. Here, we have described a binocular treatment based on strengthening binocular fusion at the expense of suppression with the goal of fully restoring functional binocular vision. Amblyopia is reduced as a secondary result of this treatment approach. The principle was established using a mirror haploscope and a global motion stimulus. It was translated to a head-mounted display in combination with either the dot motion stimulus or a *Tetris* video game. More recently we have carried out this treatment on a handheld device. In all cases, the treatment results are positive in terms of either monocular and/or binocular vision. Our initial work with noninvasive brain stimulation reinforces the concept that recovery of visual function in adults is possible and is gated by inhibitory mechanisms within early visual cortex.

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