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Report

Brain Plasticity in the Adult: Modulation of Function in Amblyopia with rTMS

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Summary

Amblyopia is a cortically based visual disorder caused by disruption of vision during a critical early developmental period. It is often thought to be a largely intractable problem in adult patients because of a lack of neuronal plasticity after this critical period [1]; however, recent advances have suggested that plasticity is still present in the adult amblyopic visual cortex [2–6]. Here, we present data showing that repetitive transcranial magnetic stimulation (rTMS) of the visual cortex can temporarily improve contrast sensitivity in the amblyopic visual cortex. The results indicate continued plasticity of the amblyopic visual system in adulthood and open the way for a potential new therapeutic approach to the treatment of amblyopia.

Results and Discussion

Monocular amblyopia is the largest cause of monocular visual impairment in the adult population, with an incidence of 3%. Current treatment approaches emphasize patching or penalization of the nonamblyopic eye before 12 years of age [7]. There is no widely employed treatment available for individuals outside of this critical period [7, 8]. Plasticity has, however, been reported in visual cortex of adult humans [9] and animals [10] after the normal critical period [2, 5], suggesting that the visual cortex of adult amblyopes may possess some capacity for functional recovery. Supporting this idea are recent studies indicating that monocular perceptual training can significantly improve visual function in the amblyopic eye [3, 4, 6, 11–13] and results showing that function can be recovered in the deprived eye of post-critical-period animals [5]. This improvement in animals has been shown to be mediated in part by a decrease in intracortical inhibition (ICI) [5, 14]. There is therefore a growing body of evidence suggesting that post-critical-period plasticity is present in the amblyopic visual system. With these findings in mind, we conducted a study investigating whether visual plasticity, measured as a change in contrast-detection thresholds, could be manipulated by repetitive transcranial magnetic stimulation (rTMS), a noninvasive technique for stimulating the visual cortex. The exact mechanisms through which rTMS affects stimulated regions of cortex are currently unclear; however, there is evidence to suggest that the excitability of the region remains altered for a period of time after the offset of the stimulation, with low stimulation frequencies ($\leq$1 Hz) decreasing excitability and higher frequencies increasing excitability [15]. Furthermore, the effects of TMS have been shown to interact with the current activity state of the stimulated neurons in visual cortex [16–19]. Because the amblyopic eye has been shown to evoke lower levels of activity in the human visual striate and extrastriate cortex than its fellow fixing counterpart [20], rTMS may differentially influence the neural populations subserving the amblyopic and nonamblyopic eyes. In addition, rTMS has been shown to reduce ICI; however, these effects have only been shown in motor cortex and have yet to be conclusively demonstrated [15].

In order to gain insight into the possible underlying mechanisms of any effect of rTMS on amblyopia, we tested two different stimulation regimes, a low-frequency stimulation of 1 Hz and a higher-frequency stimulation of 10 Hz. TMS was administered with a MagStim Rapid2 biphasic stimulator and a MagStim figure-8 air-cooled coil. During rTMS administration, we used the BrainSight Frameless stereotaxic system to monitor coil position. Nine amblyopic participants were tested with the 1 Hz stimulation, six of whom were also tested with the 10 Hz stimulation (see Supplemental Experimental Procedures and Table S1, available online). In addition, five control participants with normal vision were tested for the 10 Hz condition.

To quantify any effects of rTMS on amblyopic vision, we measured contrast sensitivity to one low-spatial-frequency grating and one high-spatial-frequency grating (see Table S1 for details) directly before (T0), directly after (T1), and 30 min after (T2) rTMS of the primary visual cortex. Spatial frequencies were selected on the basis of the severity of the amblyopia and consequent visibility of Gabor patches. Contrast sensitivity was measured with a staircase technique converging on 71% correct detection threshold, with three threshold measurements taken for each participant per eye/spatial frequency combination within each block of measurements (T0–T2). This method of measurement was used because it provided the best tradeoff between accuracy and speed of measurement as necessitated by the transient nature of rTMS effects [21]. To control for non-rTMS-related changes in contrast sensitivity, we built a number of controls into our study. First, we tested high- and low-spatial-frequency contrast sensitivity in both the amblyopic and the nonamblyopic (fellow fixing) eye of our patients in all experimental sessions. This provided a measure of the effect of rTMS on normally functioning components of the visual system. Fellow fixing eyes do not show pronounced contrast-sensitivity deficits. In addition, amblyopic eyes typically do not show a pronounced deficit at low spatial frequencies [22]. Therefore, we had one

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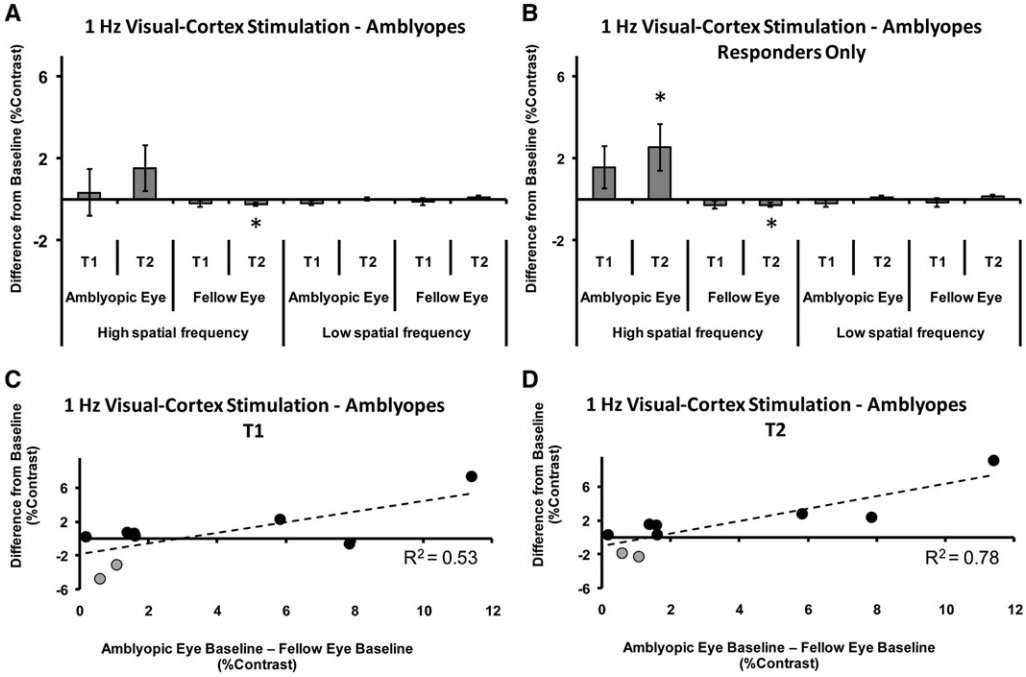

Figure 1. Effects of 1 Hz rTMS over Visual Cortex on Contrast Detection for Amblyopic Participants

For both the amblyopic eye and the fellow fixing eye, measurements were made before rTMS (T0), directly after rTMS (T1), and 30 min after rTMS (T2) for a high spatial frequency and for a low spatial frequency. Data for T1 and T2 were normalized to the baseline (T0 − T1 and T0 − T2) and plotted on the y axis as a change in percentage of contrast relative to T0. A positive difference therefore indicates an improvement in contrast sensitivity (more contrast required before rTMS than after). Error bars represent ± 1 standard error of the mean (SEM); n = 9. Nonparametric statistics were used because data were not normally distributed. Group data are shown in Figure 1A. For the fellow-fixing-eye, high-spatial-frequency condition, Friedman's test showed a significant difference in the ranks of contrast-detection thresholds for the three different time points (chi-square = 8.22, $p < 0.05$). A Wilcoxon signed-ranks test showed a significant decrease in contrast sensitivity from T0 to T2 ($Z = 2.55$, $p < 0.01$). No other conditions were significant. Figure 1B shows the group averages with the two nonresponding participants removed. For the amblyopic-eye, high-spatial-frequency condition, Friedman's test showed a significant difference in the ranks of contrast-detection thresholds for the three different time points (chi-square = 10.29, $p < 0.01$). A Wilcoxon signed-ranks test showed a significant difference between T0 and T2 ($Z = 2.37$, $p < 0.05$). Figures 1C and 1D show the normalized data for the amblyopic eye for each participant at T1 and T2, respectively, plotted as a function of the difference between the two eyes at the baseline (T0 for the amblyopic eye − T0 for the fellow fixing eye). Nonresponding participants are shown in gray. The positive correlation was marginal for T1 (rho = 0.60, $p = 0.09$) and reliable for T2 (rho = 0.77, $p < 0.05$).

experimental condition (amblyopic eye, high spatial frequency) and three control conditions in which no improvement was anticipated (amblyopic eye, low spatial frequency and the low and high spatial frequencies for the fellow fixing eye). Second, we ran a control experimental condition in which rTMS was delivered over motor cortex. In this condition, the patients experienced all the peripheral effects induced by rTMS, including in this case a twitch in the left first dorsal interosseous (FDI) muscle, but with no direct neural changes in visual cortex. Visual-cortex rTMS was delivered over an optimal phosphene location close to the occipital poles. This location was independently identified in each patient. For all control observers, we used a high-spatial-frequency stimulus of 20 cpd to allow for clear differences in performance between the low- and high-spatial-frequency conditions. Although this precluded a direct comparison with the amblyopic-eye data, such a control was built into the amblyopia experiment itself through testing of the fellow fixing eye.

Ignoring any individual differences within our amblyopic population, we found no effect in our averaged results of 1 Hz visual-cortex stimulation on any of the amblyopic-eye conditions (Figure 1A). A closer inspection of the data revealed that seven of nine patients had responded to the stimulation at one or both of the two post-rTMS time points, and if these results were considered alone, the effect of rTMS was reliable at T2 (Figure 1B). However, we have not been able to identify any distinguishing features for the nonresponders that would allow us to consider them as a clearly separate population. Interestingly, although the magnitude of the change was small, seven of nine and eight of nine participants showed a reduction in contrast sensitivity at T1 and T2, respectively, for the nonamblyopic-eye, high-spatial-frequency condition (Figures 1A and 1B). The reduction was reliable for T2. No other conditions showed reliable rTMS-induced changes. Individual data are shown in Figures 1C and 1D for T1 and T2, respectively, plotted as the absolute change from the baseline in the amblyopic eye as a function of the difference in baseline performance between the two eyes (amblyopic eye pre-rTMS baseline − fellow fixing eye pre-rTMS baseline). The nonresponding participants are shown in gray. The positive correlations (marginal at T1, reliable at T2) suggest that the larger the absolute difference between the two eyes at the baseline, the greater the effect of rTMS on the amblyopic eye. For 10 Hz stimulation, the result was clearer; all six participants tested showed an improved contrast sensitivity at T1 and T2 (Figure 2A). Importantly, both participants that did not respond to the 1 Hz stimulation did show a response to the 10 Hz stimulation. The absolute amount of improvement was positively correlated with the difference in the baseline between the two eyes (Figures 2B and 2C). Although this correlation was driven predominantly by the most extreme data point, the pattern is consistent with the 1 Hz data. A comparison of Figure 1C and Figure 1D with

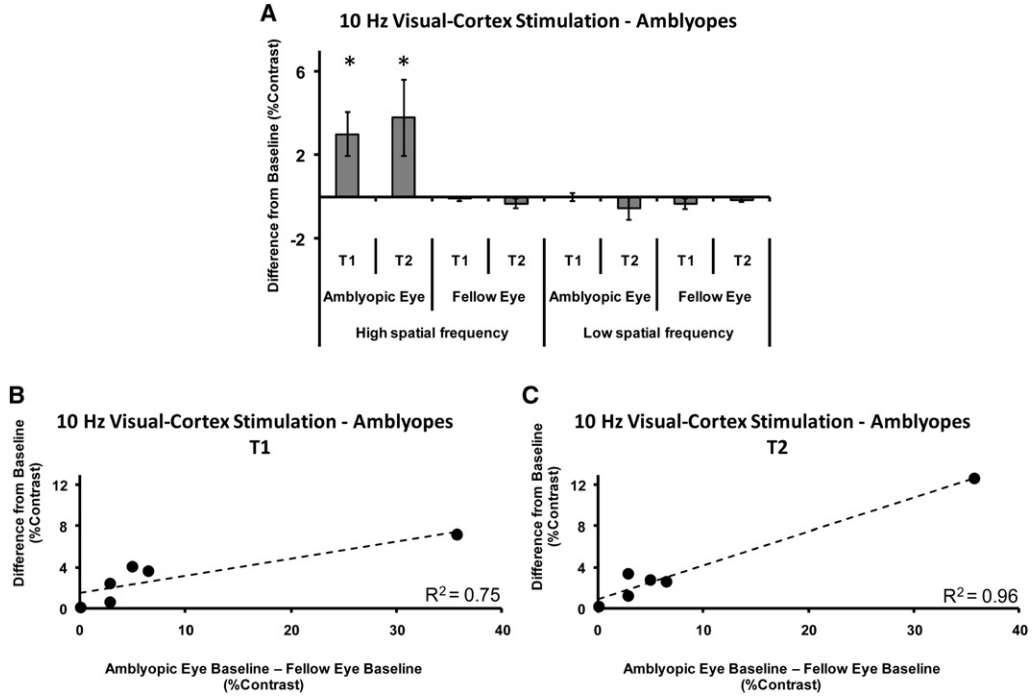

Figure 2. Effects of 10 Hz rTMS over Visual Cortex on Contrast Sensitivity for Amblyopic Participants

Group (Figure 2A) and individual data (Figures 2B and 2C) are presented as in Figure 1 (n = 6). For the amblyopic-eye, high-spatial-frequency condition, Friedman's test showed a significant difference in the ranks of contrast-detection thresholds for the three different time points (chi-square = 9.33, $p < 0.01$). A Wilcoxon signed-ranks test showed a significant difference between T0 and T1 and T0 and T2 ($Z = 2.20$, $p < 0.05$ for both). The positive correlation (Figures 2B and 2C) was reliable at T1 (rho = 0.89, $p < 0.05$) but not at T2 (because of the use of nonparametric statistics, rho = 0.60, $p = 0.21$). Error bars represent ± 1 SEM.

Figure 2B and Figure 2C shows a difference in the baselines between the two conditions for the most extreme data point (participant A.M.). This participant had to be tested at different spatial frequencies in the 10 Hz condition because of a sustained improvement in contrast sensitivity in the amblyopic eye after the 1 Hz rTMS (see Table S1). This improvement cannot be attributed only to the rTMS intervention, however, because A.M. had been recruited for a perceptual-training experiment in the intervening time between rTMS sessions. For all other participants, there was no significant change in baseline sensitivity across the different stimulation sessions ($p > 0.05$), which were separated by at least 1 week, indicating that the effects of rTMS were transient. Delivery of 1 Hz rTMS over motor cortex elicited no reliable changes in contrast sensitivity for the amblyopic observers (Figure 3A). Data from five control participants for 10 Hz visual-cortex stimulation are shown in Figure 3B. Interestingly, the results show a small increase in contrast sensitivity for the nondominant eye at T1 only. Although these results are less pronounced and more transient than the amblyopic-patient data, they do suggest that 10 Hz rTMS-induced changes can be measured in normal visual cortex.

For all amblyopic participants, 10 Hz rTMS over visual cortex improved contrast detection for high spatial frequencies in the amblyopic eye directly after and 30 min after rTMS. The 1 Hz rTMS had less consistent effects, although the data suggest that this intervention may also be effective if the difference in function between the eyes is large. Intersubject variability is a documented phenomenon in rTMS studies, particularly with shorter stimulation trains [23], and may therefore have been a factor here for the 1 Hz -stimulation paradigm.

With our currently evolving but incomplete understanding of rTMS, it is not possible to conclusively identify the mechanisms responsible for the rTMS-based improvement in visual function that we report here. However, we can assume that explanations based simply on global excitation or inhibition are unlikely to be satisfactory because both 1 Hz and 10 Hz stimulation were effective in the majority of subjects. This, therefore, implicates mechanisms requiring either (1) more complex changes in the relative excitation and inhibition of separate neural populations or (2) changes in ICI. The most parsimonious explanation is that rTMS acts to equate the excitability of the neurons subserving each eye. The direction of the change in the relative excitability of the populations of these neurons is still an open question. Although 1 Hz stimulation is thought to decrease excitability, it has been demonstrated that if a neural population is inhibited prior to rTMS (as may be the case for amblyopic-eye neurons), the effects of subsequent rTMS can be reversed [17, 24]. Despite these considerations, the concept of promoting equality in neural excitability between the two eyes is still consistent with the efficacy of both 1 Hz and 10 Hz rTMS demonstrated in this study and the idea that rTMS preferentially acts to return a neural system to equilibrium [25]. This explanation is also partially supported by the small but reliable reduction in sensitivity in the fellow fixing eye after 1 Hz rTMS; i.e., rTMS had opposite effects on the two eyes of amblyopes for high spatial frequencies. A similar but not statistically reliable trend was also present in the 10 Hz data.

A second possibility is that rTMS acts to reduce ICI, an effect that has been demonstrated in the motor cortex for both 1 Hz and 10 Hz stimulation [26, 27]. In motor cortex, higher

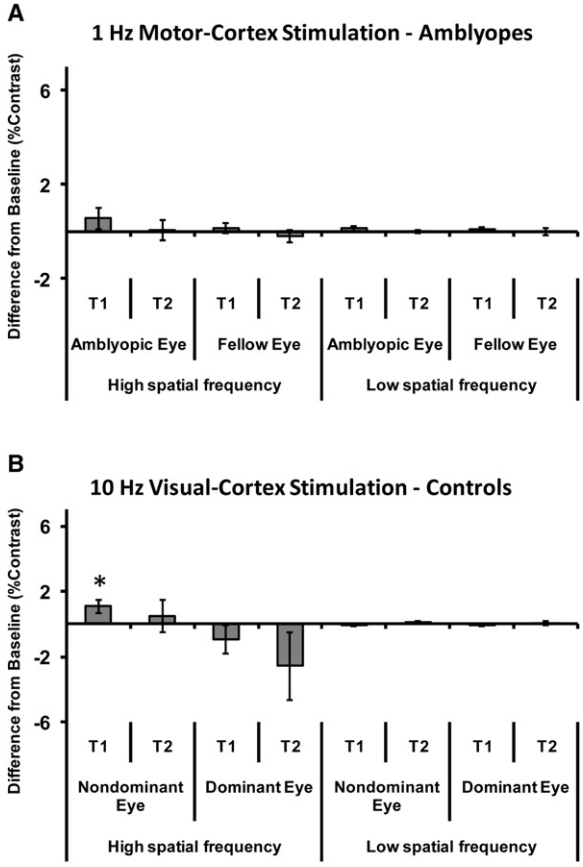

Figure 3. Additional Control Data

Aside from the within-subject controls built into the study (fellow-fixing-eye data and testing of low spatial frequencies for the amblyopic eye), additional controls were conducted. Figure 3A shows the effects of 1 Hz stimulation of motor cortex on the contrast sensitivity of amblyopes. There were no reliable changes from the baseline. Figure 3B shows the mean effects of 10 Hz stimulation over visual cortex for five control subjects. Friedman's tests were nonsignificant for all conditions; however, all participants (five out of five) showed an improvement at T2 for the nondominant-eye, high-spatial-frequency condition at T1 ($T0 < T1$, $Z = 2.02$, $p < 0.05$). Error bars represent ± 1 SEM.

stimulation frequencies do appear to be more effective at modulating ICI [15]. Such an effect may account for the finding that for two of our participants, 10 Hz stimulation was more effective than 1 Hz stimulation. An explanation based on ICI would link our results with recent animal investigations highlighting the importance of reductions of ICI to recovery from visual deprivation [5]. Unfortunately, it is not possible to measure ICI in visual cortex with a subjective phosphene report [28]. In addition, differences in stimulation parameters and the stimulation site make comparisons with previous motor-cortex studies speculative. Our current data set therefore cannot conclusively identify the mechanism by which rTMS is acting on the visual system to alter contrast sensitivity, but some candidate mechanisms can be identified. Further work with neuroimaging techniques is required to investigate this issue and the neural effects of rTMS in general. In addition, studies employing alternative stimulation regimes, such as theta-burst stimulation [29] or 20 Hz stimulation [23], may shed further light on the underlying mechanisms. We have shown that stimulation of primary visual cortex is sufficient to induce an improvement in contrast sensitivity of the amblyopic eye; however, this does not rule out the possibility that stimulation of other extrastriate areas that are reciprocally connected to V1 [30] may have similar effects.

There are clear clinical implications for our findings; however, currently the data show only a transient effect, as evidenced by the lack of a difference between the baseline measurements on successive stimulation sessions separated by at least 1 week (see Supplemental Data for more detailed time-course measurements in three individual participants). This transience is consistent with the vast majority of effects associated with a single session of rTMS. There is some evidence that repeated sessions of rTMS elicit progressively larger responses in the cortex (although the duration of the effect remains unchanged) [31] and that longer-lasting effects of rTMS can be observed after repeated stimulation of visual cortex [32], implying that repeated administration of rTMS to the amblyopic cortex may result in larger, longer-lasting improvements. Of particular interest, however, may be the combination of rTMS with active training regimes [25], such as those previously shown to be beneficial to amblyopic vision [4]. It is also notable that contrast sensitivity is only one of many visual deficits found in the amblyopic eye [7]. It may be possible that measuring other types of visual function could reveal a more pronounced effect of rTMS on amblyopic vision.

Experimental Procedures

Psychophysics

Contrast sensitivity was measured with single 17° Gabor patches presented for 1 s within a Gaussian temporal envelope. Participants indicated whether the patches were oriented vertically or horizontally, and thresholds were measured with a two-down, one-up staircase technique. Note that because these patches were large, only a small region of increased acuity in the visual field would be needed for improved task performance. Stimuli were presented on a linearized Iyama Vision Master Pro monitor with a ViSaGe visual stimulus generator (Cambridge Research Systems). Participants performed the psychophysical task monocularly. An eye patch was used to occlude one eye.

Single-Pulse TMS

The methods used to define the optimal stimulation site for phosphene induction and to calculate phosphene thresholds have been explained previously [33]. In brief, using single-pulse stimulation, we chose an optimal location for inducing phosphenes [34, 35] close to the vertical meridian in posterior occipital cortex by positioning the coil over a range of locations above the inion. The average location for maximal phosphene induction was 2.5 cm above the inion (SD 1 cm) and 1 cm laterally from the midline (SD 0.1 cm; four of nine participants required a rightward lateral move of the coil) for the amblyopic participants and 2.4 cm above (SD 0.6 cm) and 0.7 cm laterally for the controls (one of five participants required a rightward lateral move of the coil). All participants reported phosphenes. Motor thresholds were measured with a comparable subjective-report-based technique (see Supplemental Experimental Procedures for details).

Repetitive TMS

The 1 Hz rTMS was delivered for 10 min (600 pulses) at 100% of threshold for the stimulated area (visual or motor cortex) [36]. The 10 Hz rTMS was delivered to visual cortex at 100% of motor threshold in 5 s trains separated by 45 s intertrain intervals (total 900 pulses) [24]. Our stimulation protocols differed not only in frequency of stimulation but also in intensity and duration because of differences in the tolerability of the two protocols (see Supplemental Experimental Procedures). One participant reported a (transient) headache after 1 Hz stimulation and withdrew from the study before completing the 10 Hz condition. Two additional patients were unavailable for the 10 Hz condition. All procedures were approved by the institutional ethics committee.

Supplemental Data

Supplemental Data include Supplemental Results, Experimental Procedures, one figure, and one table and can be found with this article online at http://www.current-biology.com/cgi/content/full/18/14/1067/DC1/.

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