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Award Number: W81XWH-10-1-1056

TITLE: A Behavioral Treatment for Traumatic Brain Injury-Associated Visual Dysfunction
Based on Adult Cortical Plasticity

PRINCIPAL INVESTIGATOR: Dr. Uri Polat

CONTRACTING ORGANIZATION:

Tel-Aviv University

Goldschleger Eye Research Institute, Sheba Medical Center

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14. ABSTRACT We have completed testing and training of two groups of control subjects, total of 42 subjects, the 2nd group using an improved training protocol (a modification that was not planned according to the original study design). There was a remarkable improvement in the objective measurements of the visual functions, both in the foveal and peripheral measurements, including subjective improvement reported by the subjects. The results of the modified training protocol were applied to TBI patients. We have presented the data in the 3rd International Workshop on Perceptual Learning in December 2012 and the full manuscript is under preparation on the data of all controls subjects. We have recruited 10 TBI patients so far and present their current results. There is already a pronounced improvement in their visual functions towards the levels of the normal control group, including in static contrast sensitivity and in lateral interactions, with the negative effect of lateral masking replaced by a slight positive effect of facilitation (i.e., detection threshold reduction). The subject also report subjective improvements in various visual functions, including reading, fixation on objects. In the methodological aspect, we have been able to establish the remote training protocol at the homes of the TBI participants, in addition to their weekly visits to the lab. We proceed with training and intensive screening the medical files to identify more potential TBI patients. We have submitted an abstract for presentation in the 10th World Congress on Brain Injury held by the International Brain Injury Association in March 2014 (attached). Note that the study period was extended by 1 year, until Sept 28 2014 (extension approval attached).		
15. SUBJECT TERMS Traumatic Brain Injury; Perceptual Learning; Behavioral Treatment; Visual Dysfunction; Cortical Plasticity		

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Introduction

Different traumatic brain injuries are associated with visual dysfunction (Chua, Ng, Yap & Bok, 2007). Tissue damage following stroke, car accident, etc. may result in visual scotomas or other severe visual deficits. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity (Fahle, 2002). A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. Plasticity is based on neuronal excitations and is affected by pharmacological changes in the balance between neuronal excitation or inhibition (He, Hodos & Quinlan, 2006, Maya Vetencourt, Sale, Viegi, Baroncelli, De Pasquale, O'Leary, Castren & Maffei, 2008, Rozas, Frank, Heynen, Morales, Bear & Kirkwood, 2001).

A method developed in our laboratory is a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in the visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied our paradigm to treat abnormal neuronal interactions in amblyopic adults (Polat, 2008, Polat, Ma-Naim, Belkin & Sagi, 2004). We were the first to show plasticity in adults with a visual deficit that was considered untreatable, see below. Using a similar paradigm, we also achieved a significant improvement in individuals with presbyopia, see below (Polat, 2009, Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin & Levi, 2012). Thus, our treatment induces visual enhancement of blurred or low-contrast images, an effect that is highly applicative for patients with visual dysfunction associated with TBI. Moreover, our recent study with similar paradigm resulted in improved visual functions in young subjects with normal vision in only 10 training sessions (Sterkin, Yehezkel & Polat, 2012). We have a highly efficient and practical treatment technique to improve vision. Thus, we can apply this proved effective training techniques to evoke plasticity in the damaged visual cortex of patients with TBI. The training paradigm is intended to reduce the extent of the damaged visual fields (i.e., "restitution training").

Body

During the last year, there has been additional improvement following training in the TBI patients, as shown in the examples below. There is also progress in TBI patient recruitment, and a waiting list of patients is formed, according to their schedule of other medical procedures, such as strabismus surgery, etc. and the needed period of 1 year after the traumatic event before they can begin their participation in the study. We are also in process of recruiting TBI patients from 2 additional medical rehabilitation facilities (the Tel Aviv Sourasky Medical Center Rehabilitation Department and the Beit Levenstein Raanana Hospital Rehabilitation Center) and from a separate rehabilitation facility within the Sheba medical center.

Patient's recruitment typically needs solutions of non-training issues. For example, in the initial phase of recruiting a new patient, we find that there is a need for a better optical

correction prior to training initiation. Since the cost of the new glasses is rather high, we have covered the cost of the glasses for the patient who needed a new optical correction. We also needed to wait a couple of weeks until he received and accustomed with the glasses. In other cases we encourage the patients to train at their home and we are helping them in instructions and training on computers. Sometimes we are also provide incentive (payment) if they meet a goal of minimal training sessions per month. In some cases, we cover the transportation expenses (taxi charges).

Control subjects: We have completed the training protocol in one group of 21 control subjects and are in the midst of training and post-testing of the second group of 21 control subjects that have been trained on a modified protocol. In total, there are 42 control subjects in the 2 training groups. Additional control subjects have been recruited and will be re-tested without training as a no-training control group. There was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. Importantly, there were no changes in the gaze position induced by training, indicating that the improvements in the visual functions induced by training cannot be accounted for by gaze stabilization mechanism, thus we can conclude that the changes occurred in the brain.

TBI patients: So far, we have recruited 10 TBI patients. We anticipated that the pre-treatment phase of the TBI patients will require personal adjustments for each patient. Indeed, due to different type of the injury of each patient, that involve cognitive and motor limitations, we were required to personalize the psychophysical testing to the abilities of each patient. For example, such adjustments were done in the presentation time of the stimuli, adding sounds to mark the presentation time and colored symbols to ease with the detection of the temporal interval. All these adjustments require continued programming modifications and retesting. Moreover, due to physical and transportation limitations, the amount of collected data in each session is limited compared to control data. As a result, the period of the pre-treatment sessions is much longer than initially anticipated. On the other hand, this period is also necessary and can be considered as instruction period that is needed for the patients to comprehend the training procedures.

Obviously, the adjustment of the pretesting is posing the requirement to re-test control subjects on the modified parameters that the TBI patients were tested in order to have normative data.

We are now performing part of the training at the TBI's homes, in addition to their weekly regular visits to the lab. This adjustment was suggested by the Review Expert Panel and is aimed to reduce the burden from the patients to arrive few times a week to the lab. To do so, we are helping them in purchasing computers, instructions on internet connection and other technical issues that needed to be resolved for remote training. We have installed the training program and are now receiving/sending the training sessions via the internet. One patient preferred to be trained on his i-Phone. We installed the Glassesoff Inc. application and are training him using a training program tailored to his abilities. In general, establishing efficient training protocol for TBI patients is very challenging and requiring creative solutions tailored to each patient. We anticipate that this solution will accelerate the pace of training. Moreover,

we anticipate that the acquired experience with the patients that are already training will accelerate the procedures with the further recruited patients.

Task 1. To apply behavioral training to healthy control individuals using our paradigm that is adapted for peripheral vision. This experiment will provide us with exact indications on potential effectiveness of the treatment and the amount of expected improvement in the target populations (months 1-12):

1a. Modification of the software for periphery (months 1-2).

Was accomplished as reported earlier.

1b. Adapting the eye-tracking system for the new setup (months 3-4).

Was accomplished as reported earlier.

1c. Creating of Matlab interface for interpretation of the eye-tracking results (months 3-4).

Was accomplished as reported earlier.

1d. Healthy participants recruitment and screening (months 3-9).

We have completed recruiting all control subjects.

1e. Baseline testing of the healthy participants (3-9)

Was accomplished as reported earlier (see section 1f below).

1f. Training of the healthy participants (months 3-12).

Twenty one control subjects finished the training. Based on their results, another group of 21 subjects was recruited and are now in the midst of training and post-testing on a modified protocol. Here we present the results of the participants that have already completed the post-test measurements. All measurements of the visual functions are shown before (pretest) and after (posttest) completing 20-30 training sessions (each session on a different day). All subjects in this group were trained in their homes.

The results were presented in the 3rd International Workshop on Perceptual Learning in December 2012 and a full manuscript is under preparation for publication based on the data of all controls subjects.

Here we present the results of the healthy control participants of the 2nd control group, in addition to the previously reported results of the 1st control group:

Lateral interactions in Transient Contrast Sensitivity:

In the first control group we have trained lateral interactions only in the vertical direction, however in the modified protocol reported here both the vertical and horizontal directions were trained, in order to make the protocol more applicable to scotoma reduction-orientated training protocol of TBI patients. Here we present the results of 7 of the 21 subjects in this group that have already completed the post-test.

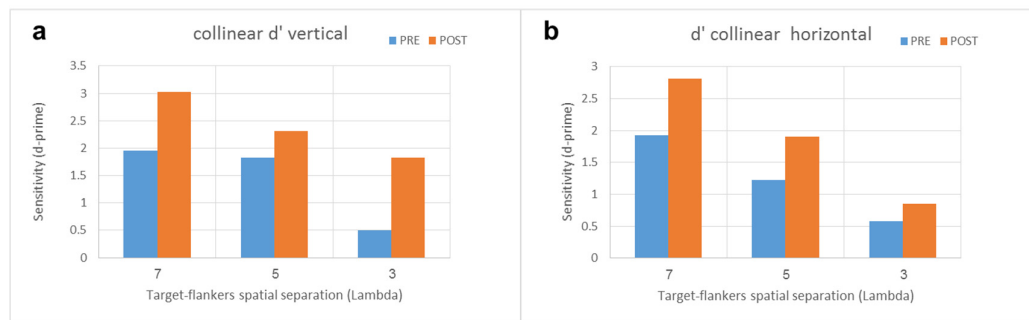


Figure 1 Lateral interactions. Contrast sensitivity facilitation measured with transient Gabor stimuli (D-prime) in healthy participants of the 2nd control group. Error bars, SEM. Higher values indicate improvement.

After training, there was a significant improvement in contrast sensitivity facilitation measured with transient Gabor stimuli with 3 different spatial separation between the low-contrast Gabor target and the flanking high-contrast collinear Gabors (Fig. 1, N=7, in periphery with the eccentricity of 4 degrees). The d-prime is a sensitivity measure calculated from the probabilities of Hit and False-alarm responses. The improvement was evident both for closer and for further spatial separations ($P < 0.04$). A similar pattern of results was observed for vertical (left panel) and horizontal (right panel) directions.

1g. Post-treatment testing of the healthy participants (6-12)

See section 1f above.

1h. Data analysis and summary of the first year of the project (months 9-12).

Was reported earlier.

Task 2. To apply behavioral training to patients with traumatic brain injury-associated visual dysfunction (months 3-36):

2a. Recruitment of patients for the "No treatment control group" (months 3-18).

So far, all but one of the recruited patients will participate in the "Treatment group". We will recruit patients for the "No treatment control group" during the coming year once we have the treatment group. The ones that can't participate in the training but pass the inclusion criteria will participate in the no-treatment group.

2b. Recruitment of patients for the "Treatment group" (months 3-30).

We have recruited 10 TBI patients so far. The results of representative TBI patients are presented in section 2d below. Other TBI patients are identified and are in the process of recruitment.

2c. Baseline testing of all the patients (months 3-30).

See section 2d below.

2d. Training of the patients of the "Treatment group" (months 12-30).

Here we present the results of representative TBI patients, in addition to the previously reported results as was presented in the three quarterly reports:

Subject AO:

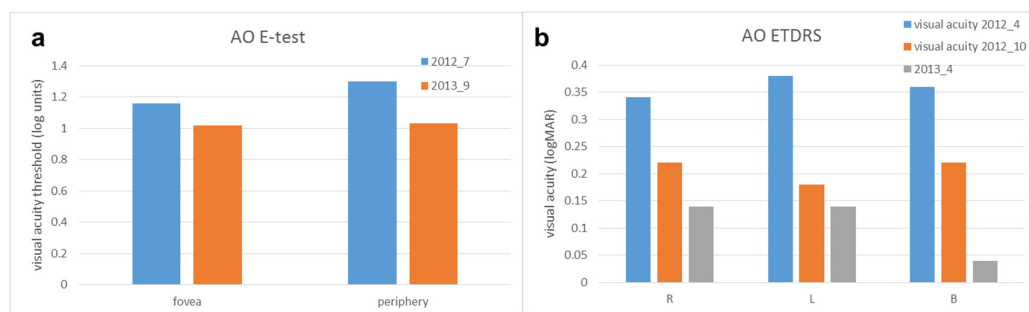


Figure 2 Visual acuity. Improvement on a) computerized visual acuity test and b) standard visual acuity chart (ETDRS) during on-going training (between April 2012 and September 2013) for a representative TBI patient AO. Lower values indicate improvement.

Figure 2 shows visual acuity measurements using the computerized visual acuity test and the ETDRS chart for the representative subject AO. Visual acuity in the normal controls before training is zero (20/20). There is a pronounced improvement in the visual acuity, of more than 3 ETDRS lines (above 100% improvement), towards the levels of the normal control group. The training phase continues.

This patient continues his training protocol and will be retested again.

Subject OS:

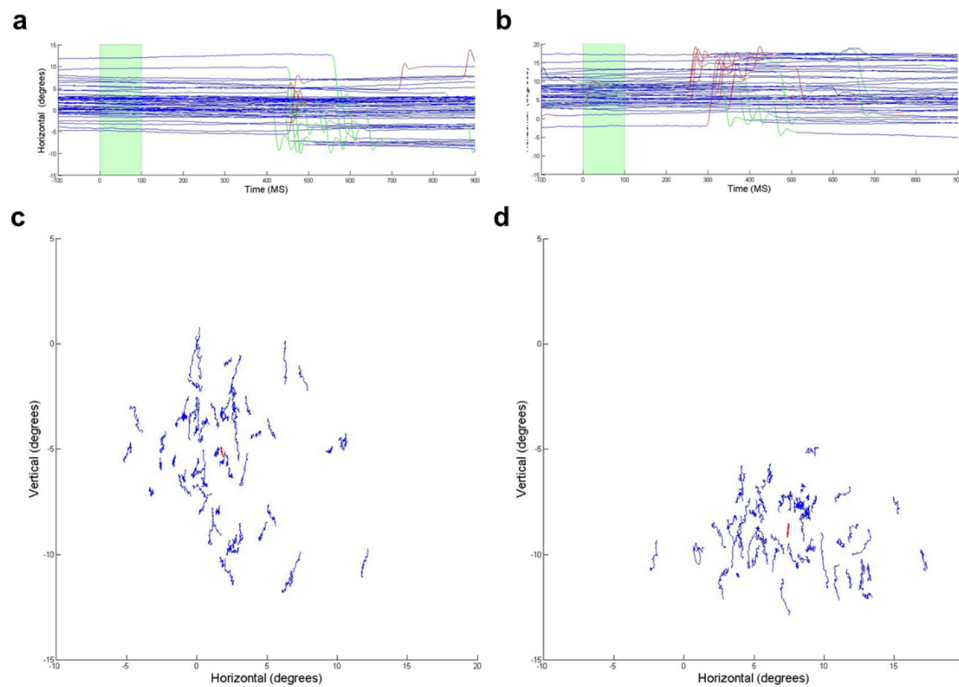


Figure 3 Eye movement trajectory. Eye position trajectory in the horizontal direction of a) pretest and b) posttest for a representative TBI patient OS. The green bars represent the stimulus presentation time, with the onset at 0. Each blue line represents the slow phase of eye movements, whereas the superimposed red and green sections are the fast saccadic movements in the left and right direction, respectively. 2-D trajectory of the same c) pre- and d) posttest measurements.

As can be clearly seen from Figure 3a and b, on average, in the posttest, the saccade onset time relative to the stimulus onset appears earlier. A different analysis showed that this trend is not due to any within session effect but rather a clear difference between the pre- and posttest measurements. Moreover, Figure 3c and d show that the spread of eye position is larger in the pretest in the vertical direction compared to posttest.

This patient continues his training protocol and will be retested again.

Subject IM:

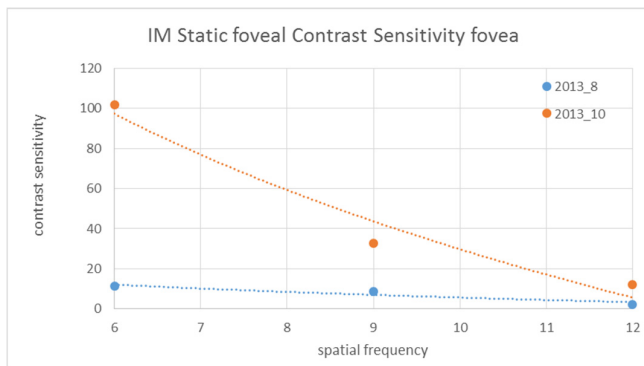


Figure 4 Contrast Sensitivity in the fovea. Improvement in contrast sensitivity measured using static foveal Gabor targets for a representative TBI patient IM. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

Figure 4 shows contrast sensitivity measurements for static targets for the representative subject at pretest and now. There is already a pronounced improvement for the 3 spatial frequencies (6, 9 and 12 cpd), towards the levels of the normal control group.

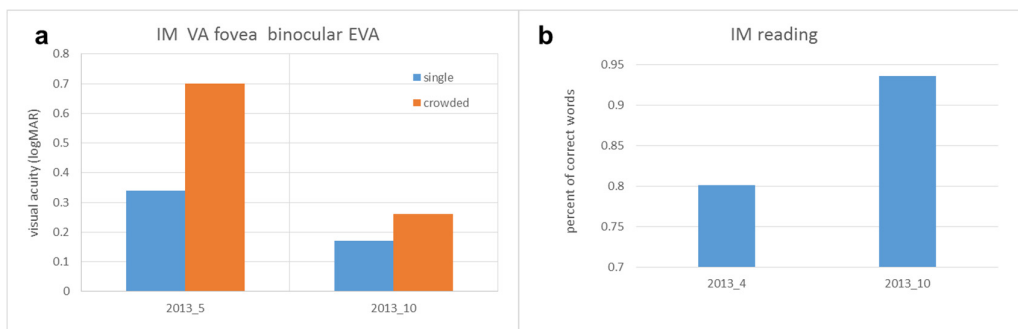


Figure 5 Visual acuity and reading. a) Improvement in visual acuity of letters measured in isolation and when surrounded by other letters for a representative TBI patient IM. Lower values indicate improvement. b) Improvement in single word covert reading for a representative TBI patient IM. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

Figure 5 shows a profound objective improvement in both the visual acuity measurements and the reading abilities of a representative TBI patient IM following training. These findings are accompanied by a profound subjectively reported improvement (both by the patient and the family).

This patient continues his training protocol and will be retested again.

Subject ZK:

Since the training methodology is based on *lateral interactions* between neurons, we tested the effects that flanking Gabors induced on the target Gabors for the spatial separation that induces a positive effect in normal controls ("facilitation", as published in Polat and Sagi,

1993). The positive effect of lateral interactions reduces the detection threshold of the target Gabor, whereas a negative effect, also termed "lateral masking", induces threshold elevation for the target detection.

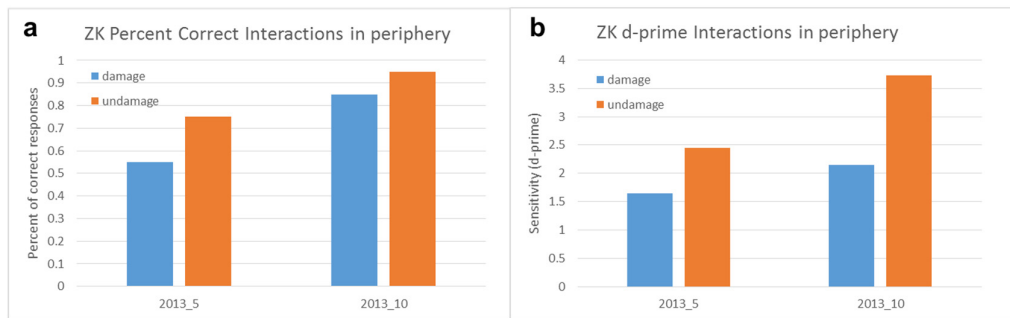


Figure 6 Improvement in contrast sensitivity due to lateral interactions measured using transient peripheral Gabor targets. Contrast sensitivity shown as a) percent of correct responses and b) sensitivity (d-prime) for a representative TBI patient ZK. The blue bars represent targets within the damaged visual field, whereas the red bars represent targets presented within the intact areas of the visual field. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

As shown in Figure 6, there is already a pronounced improvement in lateral interactions in the damaged visual field, towards the pattern that is found in the intact areas of the visual field.

This patient also showed a trend of the Visual Field improvement (i.e. a decrease in the scotoma area), as measured using a standard clinical Visual Field procedure of the Neuroophthalmologic unit of the Ophthalmology department in the Sheba Medical Center.

This patient continues his training protocol and will be retested again.

Key Research Accomplishments

- Accomplishment in the 1st and 2nd control group experiments.
- Achievement of a real outcome of improvement of visual functions that has an impact on the everyday functions.
- Validation of the training protocol suitability for patients.
- Recruitment of patients.
- Solving technological problems to enable training of patients at their homes
- Training of patients at their homes with measurable improvements.
- Intensive screening the medical files to identify more potential TBI patients.
- Engagement of 2 additional rehabilitation medical centers for potential TBI patients' recruitment acceleration.

Reportable Outcomes

- Data presentation in the 3rd International Workshop on Perceptual Learning in December 2012.
- Preparation of a manuscript for publication based on the data of all controls subjects.
- An abstract for presentation in the 10th World Congress on Brain Injury held by the International Brain Injury Association in March 2014.

Conclusion

Despite numerous technical difficulties, we have completed the initial pretests, the training and the posttests in the 1st control group and almost finished the post-testing measurements of the 2nd control group. There was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. After analyzing the posttest results, we have refined the protocol for training the TBI patients. Ten TBI patients were recruited to participate in the study. The patients that are training feel subjective improvement in the everyday life, supported by the reports of their family members. More participants were approached and are entering the study in the coming quarter, depending on their rehabilitation schedule and the limitation determined by the minimal elapsed period of one year after the TBI as required by the study protocol. Finally, we

anticipate that engaging 2 additional rehabilitation medical centers will accelerate the potential TBI patients' recruitment.

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Sterkin, A., Yehezkel, O., & Polat, U. (2012). Learning to be fast: gain accuracy with speed. *Vision Res*, 61, 115-124.

Appendices

10/28/13 10th World Congress on Brain Injury
<https://ibia.conference-services.net/abstracts.asp?sessionID={34D7BD19-1811-4E57-A543-E2939E745904}&action=finish¤t=23396&abstractID=78...> 1/2

ABSTRACT SUBMISSION

Title: Perceptual learning improves visual functions in TBI patients

Abstract No. 0694

Title Perceptual learning improves visual functions in TBI patients

Abstract

Different traumatic brain injuries are associated with visual dysfunction. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience dependent plasticity. A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. We developed a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied our paradigm, which induces visual improvement in amblyopia [lazy eye; Polat, Ma-Naim, Belkin and Sagi, D. (2004) Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci U S A*, 101(17): 6692-6697] and presbyopia [aging eye; Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin and Levi, (2012). Training the brain to overcome the effect of aging on the human eye. *Scientific Reports*, 2 (278)] an effect that is highly applicable for patients with visual dysfunction associated with TBI. Here we report on results obtained from TBI patients that were trained on contrast detection of Gabor targets under spatial and temporal masking conditions, targeting the improvement of collinear facilitation and temporal processing. They were trained on the fovea and periphery. The patients were trained on a PC computer from a distance of 1.5 meters, once or twice a week. Training improved lateral interactions (increased facilitation and diminished the lateral suppression when it existed) and improved visual functions such as contrast sensitivity, visual acuity, crowding, reaction time, vernier acuity, and reading. There was also improvement in the pattern of eye movements and fixation. Although the previously reliable visual field was not measurable, after training, the pattern of fixation enabled measurement of a reliable visual field. Thus, the visual improvements are not due to development of eye movement or a fixation strategy to overcome the visual deficiencies, rather they are due to real improvement of the neural network involved in visual processing in the brain.

Affiliations

(1) Tel-Aviv University, Tel-Aviv, Israel

(2) Bar-Ilan University, Ramat-Gan, Israel

(3) Sheba Medical Center, Ramat-Gan, Israel

Authors Maria Lev (1) Presenting

Anna Sterkin (1)

Ravid Doron (1)

Moshe Fried (1)

Yossi Mandel (2)

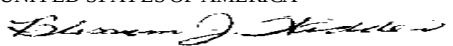
Ruth Huna-Baron (3)

Uri Polat (1)

Type Adult

Categories Neurorehabilitation – case reports/clinical research

Presentation Oral

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2. AMENDMENT/MODIFICATION NO. P00001		3. EFFECTIVE DATE 15-Apr-2013		4. REQUISITION/PURCHASE REQ. NO. W23RYX0173N616		5. PROJECT NO.(If applicable)	
6. ISSUED BY US ARMY MEDICAL RESEARCH ACQUISITION ACT DIRECTOR 820 CHANDLER STREET FORT DETRICK MD 21702-5014		CODE W81XWH		7. ADMINISTERED BY (If other than item 6) USA MED RESEARCH ACQ ACTIVITY ATTN: ELENA BANE 301-619-6871 ELENA.G.BANE.CIV@MAIL.MIL FORT DETRICK MD 21702-5014		CODE W81XWH	
8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code) TEL AVIV UNIVERSITY RAMAT AVIV TEL AVIV 69978				9A. AMENDMENT OF SOLICITATION NO.			
				9B. DATED (SEE ITEM 11)			
				X 10A. MOD. OF CONTRACT/ORDER NO. W81XWH-10-1-1056			
				X 10B. DATED (SEE ITEM 13) 28-Sep-2010			
CODE SF955		FACILITY CODE					
11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS							
☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer ☐ is extended, ☐ is not extended. Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.							
12. ACCOUNTING AND APPROPRIATION DATA (If required)							
13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.							
A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.							
B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).							
C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:							
X D. OTHER (Specify type of modification and authority) Bilateral; USMARRA General Terms & Conditions (see 23 Mar 2013 email signature)							
E. IMPORTANT: Contractor ☒ is not, ☐ is required to sign this document and return _____ copies to the issuing office.							
14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.) Modification Control Number: ebane1133311 Principal Investigator: Dr. Uri Polat Proposal Title: "A Behavioral Treatment for Traumatic Brain Injury - Associated Visual Dysfunction Based on Audit Cortical Plasticity" Period of Performance: 28 September 2010 - 27 October 2014 (research ends 27 September 2014) Total Award and Funded Amount: \$551,000.00. This modification is to provide a one-year no-cost extension (NCE), extending the POP end date to 27 October 2014 (research ends 27 September 2014), approved by the GOR via email dated 12 April 2013. See SUMMARY of CHANGES							
Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.							
15A. NAME AND TITLE OF SIGNER (Type or print)				16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print) BLOSSOM WIDDER / CONTRACTING OFFICER TEL: 301-619-7143 EMAIL: blossom.widder@us.army.mil			
15B. CONTRACTOR/OFFEROR (Signature of person authorized to sign)		15C. DATE SIGNED		16B. UNITED STATES OF AMERICA BY  (Signature of Contracting Officer)		16C. DATE SIGNED 18-Apr-2013	

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION 00010 - SOLICITATION CONTRACT FORM

CLIN 0001

The CLIN extended description has changed from Proposal #09224001, Period of Performance: 28 September 2010 - 27 October 2013 (Research ends 27 September 2013). The additional 30 days are for submission of the final report and Government acceptance. to Proposal #09224001, Period of Performance: 28 September 2010 - 27 October 2014 (Research ends 27 September 2014). The additional 30 days are for submission of the final report and Government acceptance..

DELIVERIES AND PERFORMANCE

The following Delivery Schedule item for CLIN 0001 has been changed from:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	UIC
POP 28-SEP-2010 TO 27-OCT-2013	N/A	USA MED RESEARCH MAT CMD TMED AND ADV TECH RSRCH CTR TATRC 504 SCOTT STREET FORT DETRICK MD 21702-5012 FOB: Destination	W90ERG

To:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	UIC
POP 28-SEP-2010 TO 27-OCT-2014	N/A	USA MED RESEARCH MAT CMD TMED AND ADV TECH RSRCH CTR TATRC 504 SCOTT STREET FORT DETRICK MD 21702-5012 FOB: Destination	W90ERG

(End of Summary of Changes)