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Investigating the Links Between the Rules of Synaptic Plasticity at the Cellular Level and Behavior

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ABSTRACT OF THE DISSERTATION

Investigating the Links Between the Rules of Synaptic Plasticity at the Cellular Level and Behavior

by

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Dr. Aaron Seitz, Co-Chairperson
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Behavioral learning involves modifications to relevant synapses at the neural level, a process known as synaptic plasticity - the ability of the strength of the connections between synapses to change. These changes at the synaptic level are believed to underlie learning and memory. Perceptual learning (PL) is a type of learning that refers to a long lasting improvement in sensory perception as a result of practice or training. PL has been found for a variety of visual tasks, this type of learning also requires synaptic plasticity. However, PL studies typically require a significant amount of training, and concentrate on isolating a single mechanism, leading to great specificity of learning on the trained task. This focus on this specificity has defined the field, but is not
representative of ecological conditions. Combining many features is more representation of nature, and recent research suggests this type of training leads to more broad based perceptual benefits. This dissertation will investigate the links between the rules of plasticity at the cellular level and behavior in both a single mechanism, using exposure-based learning, and by combining several PL approaches into a video game framework.

Using the single PL mechanism, exposure-based learning, does not significantly alter behavior on a contrast discrimination task after limited training. Using an integrative approach that combines many perceptual learning mechanisms, including attention, reinforcement, multisensory stimuli, and multi-stimulus dimensions, broad-based benefits of vision were found in a healthy adult population. These results were extended into a highly specialized population, college baseball players. The improvements transferred not only to laboratory tests of vision, but also to improved offensive performance on the baseball field.

Overall, these results give evidence that rules of synaptic plasticity have efficacy when applied at the behavioral level using PL mechanisms. Work remains on establishing optimal training procedures and relating the training induced benefits to the underlying neural mechanisms. Integrating PL approaches that use longer training paradigms produce robust improvements to vision. These findings provide an exciting potential for PL based video-game training to be used as a diagnosis tool and therapeutic intervention to a variety of visual conditions.
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GENERAL INTRODUCTION

The purpose of this dissertation is to investigate the links between the rules of plasticity at the cellular level and behavior. Behavioral learning involves modifications to relevant synapses at the neural level, these changes become permanent memory traces and influence behavior (Mayford et al., 2012). Santiago Ramon y Cajal was the first to correctly postulate the mechanisms of learning and memory (Cajal, 1894). He speculated that strengthening the connections of existing neurons to improve the effectiveness of their communication is how memories are formed. This is now known as synaptic plasticity, the ability of the strength of the connections between synapses to change. It is now widely accepted that this process underlies learning and memory. In 1949 Donald Hebb provided a theory incorporating synaptic plasticity, or Hebbian learning, and subsequent memory formation (Hebb, 1949). This theory states that external events are represented by groups of activated neurons in a distributed network called a cell assembly. The activation of the network persists after the external stimulus is removed; this reverberating activity strengthens the connections within the network. Later, activation of a few cells in the network in response to partial stimulus exposure will activate the entire cell assembly, because these neurons tend to fire together.

The induction of synaptic plasticity at individual synapses involves a signaling cascade beginning with Ca\(^{2+}\) entering the synapse though N-methyl-D-aspartate (NMDA) receptors, phosphorylation mechanisms, and new protein synthesis (Caroni et al., 2012). Where the result is permanent architectural changes that can enhance synaptic strength and stabilize synapses. Some of these changes include: spine enlargement, restructuring
of the actin cytoskeleton, and insertion of post-synaptic density protein 95 (PSD-95) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Caroni et al., 2012). The reverse of these processes can also occur, and lead to a decreased synaptic efficacy. It is generally believed this structural plasticity occurs during learning, and allows for long-term memory storage. Strong evidence for this comes from songbird learning. Juvenile songbirds learn their species unique song from a tutor (Brainard & Doupe, 2002). This process involves memorization of the tutor song, producing motor commands to generate it’s own song, and using auditory feedback to compare it’s own song to the tutor’s. The neural correlates of this process have been well established (Brainard & Doupe, 2002), and lead to the rapid increase in spine size and stabilization.

Perceptual learning (PL) refers to a long lasting improvement in sensory perception as a result of practice or training. Some examples of PL in the visual system include: luminance contrast, (Adini et al., 2002; Furmanski et al., 2004) motion (Ball & Sekuler, 1982; Vaina et al., 1998) texture discrimination (Karni & Sagi, 1991; Ahissar & Hochstein, 1997), hyperacuity (Fahle & Edelman, 1993), stereoacuity (Fendick & Westheimer, 1983), global scene processing (Chun, 2000) and image/object recognition (Gold et al., 1999; Furmanski & Engel, 2000; Lin et al., 2010). Perceptual learning also requires synaptic plasticity.

The ability to induce plasticity in the visual system is strongest early in development during the “critical period”. The concept of a critical period states some processes develop early in life, and do not develop or develop to a lesser degree later in life. For example, classic experiments done in kittens demonstrate a critical period for

Itisnowcleartheadultvisualsystemexhibitsasignificantamountofplasticity. However, to induce this plasticity PL studies typically require a significant amount of training, and concentrate on isolating a single mechanism, leading to great specificity of learning on the trained task. This focus on specificity has been found for a number of factorsincluding,retinallocation(Karni&Sagi,1991),orientation(Fiorentini&Berardi, 1980),andspatialfrequency(Fiorentini&Berardi,1980).This specificity is thought to be evidence for plasticity in early visual cortices. This focus on specificity has defined the field, but is not representative of ecological conditions. We live in a multi stimulus, multi modal environment. Combining many features is more representative of nature, and recent researchsuggests this type of training leads to more broad based perceptual benefits. Forexample,Xiaoandcolleagues(Xiaoeetal.,2008)foundtransferoflearning tountrainedretinallocationsusingadoubletrainingtechnique.GreenandBavelier have
shown action video game training improves performance on a variety of tasks including, visual attention and spatial resolution (Green & Bavelier, 2003; 2006; 2007).

The goal of this dissertation is to examine the rules of synaptic plasticity at the behavioral level using PL paradigms, and how these can be applied to achieve practical benefits to vision. In Chapter 1 we will evaluate a single PL approach to induce plasticity and improve behavior. Here we use an exposure-based learning paradigm that has correlates to synaptic plasticity paradigms studied at the cellular level in the animal model with the goal of better understanding the required mechanisms involved in human synaptic plasticity. In Chapter 2 we will use what is known from many single PL mechanisms (including engagement of attention, reinforcement, multisensory stimuli, and multiple stimulus dimensions), and combine these approaches to produce a custom built perceptual-learning based video game with the goal of producing generalized improvements to vision. Once this video game training has been established as being effective in normal healthy adults (Chapter 2), we will determine if these visual improvements can transfer to functional improvements (Chapter 3). In Chapter 3 we applied our PL based video game to the University of California Riverside Men’s Baseball Team and evaluated vision improvements and also batting performance as a result of our training program. In these three chapters we hope to gain a better understanding of the links between synaptic plasticity and perceptual learning.
REFERENCES


Chapter 1: Exposure-Based Learning Effects on Contrast Discrimination

INTRODUCTION

The mechanisms of learning and memory can be studied at two levels, the behavioral level and the cellular level. At the cellular level, it is widely accepted that the process of synaptic plasticity underlies learning and memory. Synaptic plasticity is the ability of the strength of the connections between synapses to change, strengthening or weakening the connections of existing neurons to modulate the effectiveness of their communication. Bliss and Lomo discovered a method to experimentally induce a persistent synaptic plasticity termed long-term potentiation (LTP) (Bliss & Lomo, 1973). By inducing brief high frequency electrical stimulation in the perforant pathway of anaesthetized rabbits and recording in the dentate gyrus they discovered an increase of excitatory post-synaptic potentials (EPSPs) over baseline response that lasted up to 10 hours. The trigger for LTP induction is the influx of calcium through N-methyl-D-aspartate (NMDA) receptors into the post-synaptic neuron (Izumi et al., 1987). Conversely, long-term depression (LTD) is induced by persistent low frequency electrical stimulation, resulting in weakened synaptic connections. LTD also involves the influx of calcium, however the induction rate and concentration is less compared to LTP (Artola & Singer, 1993).

While most commonly studied in the animal model slice preparation, LTP has been observed in human hippocampal tissue (Beck et al., 2000). Using tissue obtained during a tumor removal, high frequency stimulation (HFS) to the perforant path induced LTP when recording field EPSPs from the dentate gyrus. This LTP is NMDA receptor
dependent, as the NMDA receptor antagonist D, L-2-amino-5-phosphonovaleric acid (AP5) prevents potentiation. LTP was also assessed in hippocampal tissue obtained from temporal lobe epilepsy patients, with the hippocampus being the seizure focal site. In a previous study it was shown that patients with a hippocampal seizure focus showed impaired verbal memory performance (Helmstaedter et al., 1997). When analyzed, the temporal lobe epilepsy tissue showed severely reduced LTP. Beck and colleagues (2000) provide evidence of NMDA receptor dependent LTP in the human hippocampus, and they suggest that impaired synaptic plasticity may contribute to deficient declarative memory seen in human temporal lobe epilepsy.

Evidence has emerged linking LTP and memory. Three examples support the link between LTP and memory. First, LTP is input specific; inputs that are not activated by the stimulation do not change. Second, LTP, like declarative memory, is associative. A weak stimulus alone is insufficient to induce LTP, however combined with a strong stimulus at a separate but convergent input will now induce LTP. Third, LTP is persistent; it can last up to several hours making it an attractive model for information storage (Bliss & Collingridge, 1993). Treatments that block LTP also block memory. Genetic deletion of NMDA receptors or the application of NMDA receptor antagonists prevents LTP induction and long-term memory formation (Morris et al., 1986; Tsien et al., 1996).

Electrical stimulation protocols that are used to induce plasticity at the synaptic level are highly invasive, and do not allow a systems level of analysis. To that end, there has been a recent effort in establishing non-invasive exposure-based stimulation protocols
that can be applied to the sensory systems that will result in plasticity of the corresponding sensory cortices. The idea here is the high frequency excitation of the sensory systems is analogous to high frequency electrical stimulation at the cellular level, where both will result in the induction of LTP. Currently the best evidence of this comes from the tactile domain. Applying high frequency (20 Hz) stimulation to the fingertips of monkey’s resulted in a larger area of representation in S1 of stimulated skin, compared to unstimulated skin (Recanzone et al., 1992). This provides evidence that topographic representations are altered by non-invasive exposure. Similar results have also been found in humans. Passive high frequency stimulation (HFS) (20 Hz) of the fingertip resulted in the behavioral improvement of a 2-point discrimination task, and low frequency stimulation (LFS) (1 Hz) decreased performance on this task (Ragert et al., 2008). Additionally, improvements on the behavioral task after HFS was correlated with cortical reorganization as assessed by mapping somatosensory evoked potentials. This effect was abolished by oral application of an NMDA receptor antagonist, indicating this effect shares similar requirements to cellular LTP and long-term memory formation as identified in the animal model (Dinse et al., 2003).

Evidence for exposure-based learning has also been found in the auditory system. High frequency presentation of auditory pips (13 Hz, 13 times/sec) resulted in an enhancement of the N1 component of the auditory evoked potential (Clapp et al., 2005a) in the auditory cortex, as confirmed by fMRI (Zaehle et al., 2007), which lasted for at least one hour.
These studies of exposure-based learning provide a clear connection between the animal model and the human system, and provide good evidence for early cortical processing areas as the location of this plasticity. There is less known about exposure-based learning in the visual system, however some evidence does exist. In a recent study (Sale et al.), rats were first trained on a visual discrimination task. Following behavioral tests, the brains were removed and theta burst stimulation (an electrical stimulation protocol typically used to induce LTP at the cellular level) was applied in either layer 4 or 2/3 of V1, and responses were recorded in layers 2/3. They were unable to induce LTP in V1 by electrical stimulation after training on the visual discrimination task. The authors conclude that perceptual learning on the discrimination task has induced plasticity, and is occluding further LTP. Additionally, Frankel et al. (2006) recorded visual evoked potentials (VEPs) from layer 4 of V1 in response to visual exposure of sine wave gratings. They found repeated presentations of gratings of the same orientation resulted in potentiated VEPs to that stimulus. Similar results have been found in the human system. Teyler and colleagues (2005) used a visual checkerboard “tetanus” (presented at 9 Hz) to persistently enhance the N1b visual evoked potential in normal humans. They replicated this experiment using fMRI and concluded the location of the potentiation response area was V2 (Clapp et al., 2005b). Like LTP in the animal model, this visually evoked potentiation is input specific. Presentation of an untrained stimulus, either different orientation or spatial frequency, did not produce an increased response (Teyler et al., 2005).
Using a visual stimulation protocol Beste et al. (2011) demonstrated behavioral changes on a change-detection task. Here, two bars were presented where a change could occur in the luminance of one bar, the orientation of one bar, the luminance and orientation of the same bar, or the luminance of one bar and the orientation of the other bar. The participants had to report a change in luminance, and ignore a change in orientation. The orientation change in the last condition was highly distracting, and made the luminance detection more difficult. A visual stimulation protocol consisted of alternating black and white bars flashing at either a high (20 Hz) or low (1 Hz) frequency with the goal of increasing or decreasing luminance saliency. The authors found a high frequency visual stimulation protocol improved the behavioral outcome on the detection task tested up to 10 days after induction. Conversely, a low frequency LTD-like protocol impaired performance.

While the required mechanisms involved in human synaptic plasticity are growing, there is still much that is unclear. Based on these results we wanted to expand the knowledge of synaptic plasticity in humans and investigate the rules of synaptic plasticity that operate at the level of behavior in the visual system. Where the goal was to alter visual behavior in human subjects using a non-invasive visual stimulation protocol. This paradigm, which correlates LTP and LTD studies at the cellular level in the animal model, takes advantage of what has been learned from previous research and builds on the knowledge of the field. Specifically, we hypothesized that high frequency visual stimulation will increase performance on a contrast discrimination task, and low frequency visual stimulation will decrease performance on a contrast discrimination task.
Contrast learning is a relevant target for exposure-based learning for several reasons. It is generally agreed that the location of contrast learning occurs low level in the visual system. This is consistent with successful exposure-based learning protocols in other sensory systems, including reorganization of S1 after tactile stimulation (Recanzone et al., 1992) and using other tasks in the human visual system (Clapp et al., 2005b). Additionally, contrast learning typically requires multiple training sessions and a large number of trials (Furmanski et al., 2004) (Li et al., 2009) (Yu et al., 2004). It is possible the stimulation like effect of exposure-based learning will increase plasticity and speed this learning process. Additionally, Beste et al. (2011) used a visual stimulation protocol of alternating luminance polarity in order to successfully manipulate luminance saliency in a change detection task. It is possible the effect of increasing or decreasing luminance detection is based on altering contrast sensitivity. We directly tested this by measuring performance on a contrast discrimination test after visual stimulation.

GENERAL METHODS

Participants

Participants were obtained from the University of California, Riverside undergraduate student pool. Participants were compensated by receiving 3 research credits; one per experimental hour. In addition, to ensure that the participants were properly motivated to perform the tasks, they were told that they would earn money at the end of the two-day experiment depending on how well they performed during the assigned tasks. Participants were paid of portion of $5.00 each day, for a maximum pay out of $10.00, depending on performance of the task.
**Apparatus**

Participants were seated 69.22 cm in front of a 24” CRT computer monitor; their heads were stabilized with a chin-rest and head bar. Visual stimuli were presented via an Apple Mac Mini running Matlab (Mathworks, Natick, MA) and Psychtoolbox Version 3 (Brainard, 1997; Pelli, 1997), using code custom written for the experiment. The monitor was connected to the computer through Bits++, a digital video processor manufactured by Cambridge Research Systems, which increases the dynamic range of the computer’s graphics system and allowed us to present a fuller range of contrasts ($2^{14}$ levels) for the visual stimuli. Bits++ interfaces with the Psychophysics Toolbox.

**Design**

The experiments consisted of 2 identical sessions, conducted at the same time on consecutive days. Experiments consisted of three segments - Pre-training Test, Training, and Post-training Test – presented in that order. The same general procedures were used to accomplish all studies, however the Training protocols were altered to accomplish each study. Each participant ran through the entirety of the experiment twice, which were run at the same time on consecutive days, each session lasted approximately 1.5 hours. This protocol allowed the evaluation of both short and longer-term plasticity effects, as well as establishing the stability and possible enhancement or decrement of visual performance.
Training

Stimuli: The stimuli presented to the participants consisted of visual stimuli chosen to stimulate primary visual areas. The main visual stimuli consisted of horizontally or vertically oriented bars. The bars had a length: width ratio of 1:2.86 (modeled after the high saliency condition in (Beste et al., 2011)). The background on the computer screen was always the midpoint of the maximum and minimum luminance display values, i.e., grey.

Visual stimulation protocols: Visual stimuli were presented according to LTP- and LTD-like protocols, similar to those used by Beste et al. (2011). LTP protocols require a high frequency visual stimulation. This protocol consisted of presenting the visual stimuli of opposite luminance polarity (black vs. white) in rapid bursts of 20 Hz flashes. The changes in luminance polarity occurred for 5 seconds, followed by 5 seconds of no stimuli presentation. This sequence (5 seconds on, 5 seconds off) was repeated for a total of 40 minutes. LTD protocols require a low frequency visual stimulation. This protocol consisted of continuously presenting the visual stimuli of opposite luminance polarity at 1 Hz flashes (Figure 1). The entire stimulation period lasted 40 minutes, however every 7 minutes training paused to allow the participant to rest their eyes. When the participant was ready, the session would resume.

Fixation Task: The participants performed a distracting fixation task, while the stimuli were presented according to the stimulation protocol for each study (see below). The black fixation point with a radius of 0.03 cycles/deg was presented in the center of the screen, and flashed white at random intervals (0.3% of the total time). Every time this
flash occurred, the participant was required to press the spacebar on a keyboard connected to the experimental computer. The flash was very brief (10 ms), subtle, and temporally unpredictable. The task required the participants to keep their attention on the fixation point, thus ensuring the stimuli remained in approximately the same retinal area.

*Pre- and Post-Training Tests*

Before and after each Training segment, the participant was tested on their sensitivity in discriminating low-contrast variants of the visual stimuli. The Pre- and Post-Training tests lasted approximately 10 minutes each. Other than the contrast, the stimuli of a horizontally or vertically oriented bar was identical to the stimuli presented during Training. The participant kept their gaze on a fixation point in the center of the screen. While they were thus fixated, two presentations would occur. The fixation dot turned into the number “1” briefly (300 ms), and then the number “2” (for 300 ms). When either the number “1” was on the screen, or when the number “2” was on the screen, the stimulus would appear for 300 ms (Figure 2). A visual stimulus would be present in one of the presentations but not the other. The stimuli was counter-balanced to be presented either horizontally or vertically, and to the right or left of the central fixation dot, with 60 trials per combination. The participant was required to respond to these presentations by pressing “1” or “2” on a keyboard corresponding to whether they saw the stimulus during the first or second presentation. As the test continued, the contrast of the visual stimuli adapted to the participants threshold using a three-up/one-down staircase procedure. Contrast was adjusted via the Bits++ video processor, which allows for high-resolution contrast corrections.
Analysis

For all stimulation protocols, the threshold for correctly responding to the visual stimuli was calculated for both Pre- and Post-Training tests by the average of the last 5 threshold reversals. A reversal is defined as a change in direction of contrast performance. Within each test, the threshold for visual stimuli was calculated for each possible combination of orientation and visual field of presentation. Results were analyzed using ANOVA (IBM SPSS Statistics 20.0) and T-test (Microsoft Excel, 2008) to compare results across conditions.

Study 1: Unilateral High Frequency or Low Frequency Stimulation

METHODS

This experiment consisted of 2 identical sessions, run at the same time on consecutive days. The experiment consisted of 3 segments: Pre-Training Test, Training, and Post-Training Test, presented in that order. During the experiment, a total of four tests of contrast discrimination were conducted – Session 1 Pre-test, Session 1 Post-test, Session 2 Pre-test, Session 2 Post-test. For the Training, participants were assigned to either a High Frequency Stimulation (HFS, n = 13) or Low Frequency Stimulation (LFS, n = 13) Training condition (Figure 3).

During the Pre-Training tests, visual stimuli were presented in one of two presentations, counterbalanced across orientations (horizontal or vertical) and visual fields (right or left of fixation). Contrast discrimination thresholds of the stimuli were determined using a three-up/one-down staircase procedure that started at a 10% contrast
level above the participant’s threshold, with a total of 120 trials. This created a baseline measurement of each participant’s contrast threshold.

During Training, visual stimuli consisted of a single horizontally or vertically oriented rectangular bar placed to the right or left of a central fixation point. This stimulus flashed according to either the high or low frequency stimulation protocol. Orientation, visual field, and stimulation frequency of the stimuli were counterbalanced amongst participants, and thus became the trained stimuli for each participant.

The Post-Training test was identical to the Pre-Training test and occurred immediately following the Training procedure. Contrast thresholds were determined for the stimulus that was the same orientation and visual field as during the Training procedure, and for stimulus that was different than presented during the Training. Therefore, we can compare the Trained and Untrained stimuli thresholds to that of the baseline Pre-Training test. We hypothesized the HFS protocol would increase sensitivity to visual stimuli when tested in the same orientation and visual field of training, and the LFS protocol would decrease sensitivity to visual stimuli when tested in the same orientation and visual field of training.

RESULTS

The stimulation protocols failed to produce significant changes in contrast discrimination performance. A repeated measures ANOVA was conducted to compare the effect of high frequency stimulation on contrast discrimination tested at four time points. In the HFS condition (Figure 4), there was no main effect of contrast threshold
Test (F(3,72) = 1.26, p = 0.30), Trained/Untrained stimuli Condition (F(1,24) = 0.60, p = 0.81) or an interaction of Test x Condition (F(3,72) = 0.514, p = 0.67).

Looking at the overall pattern of the results, performance from Pre-Training to Post-Training tests declined immediately after stimulation in both sessions (Figure 4, Table 1). T-tests revealed this decrease in performance was not statistically significant (Session 1: Pre/Post, p = 0.23. Session 2: Pre/Post, p = 0.22). This result is the opposite pattern to what we predicted from LTP studies at the cellular level. However, after 24 hours the pattern of performance does match our hypothesis (increased contrast sensitivity), but is not statistically significant (Session 1 Pre-test/Session 2 Pre-test, p = 0.39).

In the LFS condition (Figure 5), a repeated measures ANOVA was conducted to compare the effect of low frequency stimulation on contrast discrimination tested at four time points. Results revealed there was no main effect of contrast threshold Test (F(3,66) = 0.762, p = 0.52), or an interaction of Test x Condition (F(3,66) = 0.275, p = 0.84). A trend was seen for the main effect of Condition (Trained vs. Untrained stimuli) (F(1,22) = 3.64, p = 0.07). This may indicate a possible difference between the Trained and Untrained conditions, however it may also reflect baseline differences. Individual pairwise comparisons of each test between conditions did not reveal any significant differences (all p > 0.25). Additionally, performance from Pre-Training to Post-Training tests (within each Session), in the Trained condition decreased during each session (Figure 5, Table 2). This decrease in performance is more consistent with the results found in LTD studies at the cellular level, and supports our hypothesis. However, these contrast
threshold differences were not statistically significant (Session 1 Pre/Post, \( p = 0.63 \). Session 2 Pre/Post, \( p = 0.31 \)). After 24 hours, performance returned to baseline (Session 1 Pre-test/Session 2 Pre-test, \( p = 0.85 \)). There were no statistically significant differences from baseline performance on any tests on the Untrained stimuli after either HFS (Figure 4) or LFS (Figure 5) (all \( p > 0.25 \)).

In summary, the results of Study 1 found no significant effects of stimulation on contrast discrimination performance, after high or low frequency visual stimulation. Taking the overall pattern of results into account, there is some evidence to show that the stimulation protocol may have been weakly altering contrast discrimination behavior in the participants tested. First, immediately after low frequency stimulation, contrast discrimination performance slightly decreased (Table 2). These agree with the results we would expect to see after LFS, however the same pattern occurred after HFS - the opposite of what was hypothesized. This could indicate possible fatigue effects of the study procedure on the participants. Second, 24 hours after HFS contrast discrimination performance marginally decreased from baseline, indicating weak longer-term effects of the stimulation. Third, in the LFS condition, contrast discrimination thresholds were slightly higher for the stimuli that was Trained, versus the Untrained stimuli (Table 2). This result correctly supports our hypothesis, but was not statistically significant. Overall, this pattern of results is suggestive of an effect of stimulation, but failed to reach a statistically significant level. The design of this study was not powerful enough to show a significant effect, if one does in fact exist. This led us to create a more powerful within
subjects design, where participants received simultaneous High and Low frequency stimulation.

**Study 2: Simultaneous High Frequency or Low Frequency Stimulation**

**METHODS**

Based on the results of the previous experiment we modified the stimulation protocol where participants (n = 12) received both High frequency and Low frequency stimulation simultaneously during the Training condition. This allowed us to increase power and reduce variance related to individual differences. We also added a no stimulation Control condition (n = 7). As in Study 1, this experiment consisted of 2 identical sessions, at the same time on consecutive days. The experiment consisted of 3 segments: Pre-Training Test, Training, and Post-Training Test, presented in that order (Figure 6). Again, a total of four tests of contrast discrimination were conducted – Session 1 Pre-test, Session 1 Post-test, Session 2 Pre-test, Session 2 Post-test.

Pre – and Post – Training tests were conducted on low contrast variants of visual stimuli to determine contrast discrimination thresholds, as described above. Contrast discrimination thresholds of the stimuli were determined using two separate three-up/one-down staircase procedures, one that started above the participant’s threshold (10% contrast), one that started below (0.01% contrast) for a total of 240 trials.

During the Training, stimulation was presented bilaterally. One hemifield received HFS, the other hemifield received LFS. High and Low frequency stimulation location (right vs. left visual fields) was balanced across participants and consistent over
both sessions. To ensure proper separation of visual fields participants performed a fixation task – described above. Participants in the Control condition did not receive stimulation, and only performed the fixation task. We hypothesized the HFS protocol would increase the sensitivity to visual stimuli and LFS protocol would decrease the sensitivity to visual stimuli when delivered simultaneously and tested in the same orientation and hemisphere of Training. We also hypothesized no change in contrast discrimination performance in the Control condition.

RESULTS

The stimulation protocols failed to produce significant changes in contrast discrimination performance, however the results are trending in the predicted direction. A 3x4 repeated measures ANOVA was conducted to compare the effects of exposure-based leaning on contrast discrimination thresholds after HFS, LFS, or Control conditions. Results revealed no main effect for Condition (F(2,26) = 0.232, p = 0.80), or a significant interaction of Test x Condition (F(6,78) = 0.760, p = 0.60). However, there was a main effect of contrast threshold Test (F(3,78) = 3.314, p = 0.02). Pairwise comparisons revealed this significance is driven by the contrast threshold difference when tested after 24 hours compared to baseline (Session 1/Session 2 Pre-test, p = 0.01. Session 1 Post-test/Session 2 Pre-test, p = 0.03). These significant results are collapsed across all conditions (HFS, LFS, and Control), and reveals that as a whole participant’s improved when tested after 24 hours (Figure 7). With the Control condition removed, and only comparing the HFS and LFS conditions, a repeated measures ANOVA revealed the significant effect of Test disappears (F(1,20) = 2.603, p = 0.12).
In the HFS condition, contrast discrimination performance improved immediately and 24 hours after stimulation (Figure 8, Table 3) compared to baseline (Session 1 Pre/Post, p = 0.77, Session 1 Pre-test/Session 2 Pre-test, p = 0.11), indicating a slightly better performance than baseline, but failing to reach statistical significance.

In the LFS condition, performance from Pre-Training to Post-Training tests declined during each session (Figure 8, Table 3). This decrease in performance is of the predicted pattern, however contrast threshold differences were not statistically significant (Session 1 Pre/Post, p = 0.49, Session 2 Pre/Post, p = 0.49). After 24 hours performance returned towards baseline (Session 1 Pre-test/Session 2 Pre-test, p = 0.69).

Participants in the Control condition did not receive stimulation and instead only performed the fixation task. The fixation task failed to produce significant changes in contrast discrimination performance. However, contrast discrimination performance improved after 24 hours (Figure 8, Table 3). While not statistically significant (Session 1 Pre-test/Session 2 Pre-test, p = 0.42), this indicates some task learning.

**COMBINED RESULTS**

The previous studies individually failed to produce significant changes in contrast discrimination performance after exposure-based learning. However, the results are suggestive of an effect of stimulation and support the predicted pattern of our hypothesis, where HFS would increase performance on a contrast discrimination task and LFS would decrease performance on a contrast discrimination task. Here we examined the results of
exposure-based learning experiments as a whole, where we combined all the data from each condition in both studies (Figure 9, Table 4).

A 3x4 repeated measures ANOVA was used to compare the effects of exposure-based leaning on contrast discrimination thresholds after HFS (n = 25), LFS (n = 25), or Control (n = 7) conditions. Results revealed no main effect of contrast discrimination Test (F(3,150) = 1.810, p = 0.15), or a significant interaction of Test x Condition (F(6,150) = 0.632, p = 0.71). There was a trend of a main effect of Condition (HFS, LFS, or Control) (F(2,50) = 2.649, p = 0.08).

However, after removing the Control condition from the repeated measures ANOVA results revealed a significant difference between the High and Low frequency stimulation Conditions (F(1,45) = 4.985, p = 0.03). T-tests revealed this significance is driven by Session 2 tests (Session 2 Pre-test HFS/LFS, p = 0.04. Session 2 Post-test HFS/LFS, p = 0.03). This would suggest a period of consolidation or multiple stimulation sessions are necessary to produce the effect. The ANOVA also revealed there was a trend for the main effect of contrast discrimination Test (F(3,135) = 2.157, p = 0.10). There was not a significant interaction of Test x Condition when the Control condition was removed (F(3,135) = 1.008, p = 0.39).

These results could indicate a component of task learning that is revealed by the Control participants. This effect becomes more visible when we subtract baseline performance (Session 1 Pre-test) from the subsequent contrast discrimination tests (Figure 10). We see both the HFS and Control conditions improved on the Session 2 tests, however there was more variability in the HFS group. Notably, the LFS group did
not show this improvement after 24 hours, or did to a lesser extent. While the Control participants did not receive stimulation, they did participate in the contrast discrimination tests. Exposure to those tests could facilitate a small amount of contrast learning on its own.

Perceptual tasks often improve with training, and changes in neural circuitry are underlying these improvements. Task learning on the other hand, involves mechanisms unrelated to plasticity. Instead, improvements are based on task related principles, including a better understanding and familiarity of the procedure. There is debate in the field whether contrast discrimination can be improved with practice. Some studies do not find contrast learning (Dorais & Sagi, 1997; Adini et al., 2002), while others argue practice does enable contrast learning (Yu et al., 2004) similar to the improvements seen in many other visual tasks. While we cannot be clear on the cause of our results, it is ambiguous whether they are related to our synaptic plasticity hypothesis.

**Study 3: Change Detection Task Replication**

While our results suggest there is some evidence our exposure-based learning protocols may have been weakly altering contrast discrimination behavior in the participants tested, after many versions and combining all data we lacked the robust results found by Hubert Dinse’s group (Beste et al., 2011). The Training segments are very similar in these two studies, including the stimulation frequency, duration, and stimuli. However, there are several differences between this and the current study. As a behavioral measurement, Beste and colleagues use a change detection task, while we used a contrast discrimination task. It is generally believed a change detection task is a
higher level process involving attention, where a contrast discrimination task relies on low level visual brain area. In our previous studies we assessed the effects of stimulation immediately after training and after 24 hours. Beste assessed behavioral changes 90 minutes, 24 hours, and 10 days after stimulation. It is unclear if these differences in procedure were the reason we failed to see an exposure-based learning effect published by Beste et al (2011). Therefore, in order to better compare our results we conducted another study where we replaced the contrast discrimination task in our design, for the change-detection task used by Beste et al (2011) into the Training segment of our experimental paradigm.

METHODS

This experiment consisted of 2 identical sessions, at the same time on consecutive days. The experiment consisted of 3 segments: Pre-Training Test, Training, and Post-Training Test, presented in that order. Here participants were assigned to either a High frequency stimulation (HFS, n = 18) or Low frequency stimulation (LFS, n = 25) Training condition (Figure 11).

Pre and Post-tests consisted of a change-detection task similar to that used by Beste et al. (2011), where the task of the participant was to detect the change in luminance polarity from the first presentation to the second presentation. During each trial of the change-detection task (Figure 12) participants kept their gaze on a fixation dot in the center of the screen. Stimuli were presented on either side (1 degree) of fixation. Stimuli varied in luminance polarity (black vs. white) and orientation (horizontal vs. vertical), all combinations of the stimuli were counterbalanced during the first
presentation. After being presented for 200 ms, the stimuli were removed and the fixation dot only appeared for 50 ms. In the next frame stimuli reappeared for 200 ms on either side of the fixation dot. There were four possible conditions of the second presentation, where 1) the luminance of one stimuli changed, 2) the orientation of one stimuli changed, 3) the luminance and orientation of the same stimuli changed, or 4) the luminance of one stimuli changed and the orientation of the other stimuli changed. Task difficulty was further manipulated by adjusting the length: width ratios of the stimuli (high saliency condition - 1:2.41, low saliency condition – 1:1.35). The 4th condition with high saliency was the most difficult, as the change in orientation distracted from the luminance polarity change – on which the participant responded. Each test lasted approximately 15 minutes with a total of 512 trials (128 per condition, with 4 conditions at 2 levels of saliency).

During the Training, stimulation was presented bilaterally. Both hemifields received either High or Low frequency stimulation. All stimuli were presented at high saliency. High or Low frequency stimulation was balanced across participants and was consistent over both sessions. To ensure proper separation of visual fields participant’s performed a fixation task – described in the general methods. We hypothesized the High frequency visual stimulation protocol would increase luminance change detection, and the Low frequency visual stimulation protocol would decrease luminance change detection when tested in the same orientation and saliency of training.

RESULTS

Results revealed HFS significantly increased luminance detection for both the high and low saliency conditions when tested after 24 hours (Session 1 Pre-test/Session 2
Pre-test high saliency \( p = 0.01 \), low saliency \( p = 0.008 \) and immediately after stimulation on day 2 (Session 1 Pre-test/Session 2 Post-test high saliency \( p = 0.005 \), low saliency \( p = 0.002 \)) compared to baseline (Figure 13A, Table 5). These results support our hypothesis that high frequency visual stimulation increased performance on a change detection task, and match the results obtained by Beste et al (2011).

However, similar results were found after LFS (Figure 14A, Table 6). In the high saliency condition, luminance detection performance increased compared to baseline when tested after 24 hours (Session 1 Pre-test/Session 2 Pre-test \( p = 0.05 \), Session 1 Pre-test/Session 2 Post-test \( p = 0.02 \)) and immediately after stimulation on day 1 (Session 1 Pre/Post \( p = 0.04 \)), and following stimulation on day 2 (Session 1 Pre-test/Session 2 Post-test \( p = 0.01 \)) in the low saliency condition. These results do not match our hypothesis that low frequency visual stimulation would decrease luminance change detection, and are the opposite of the results found by Beste and colleagues (2011). Where they found a significant decrease in luminance detection performance after LFS when tested after 90 minutes. These results seem to be more consistent with learning across tests, rather than an effect of stimulation.

**DISCUSSION**

Our results indicate two sessions of exposure-based learning stimulation protocols do not significantly alter behavior on a contrast discrimination task. This protocol was based on LTP and LTD-like electrical stimulation protocols typically used at the cellular level in the animal model to evaluate modifications of synaptic plasticity. Here, robust increases or decreases are found after high or low frequency stimulation, respectively.
We failed to find robust alterations at the behavioral level, however our results indicate weak alterations that may suggest a behavioral effect of visual stimulation. When we combined the results of the slightly different versions of our protocol, we found a significant difference between the high frequency and low frequency stimulation conditions. Specifically, after two sessions of high frequency visual stimulation participants improved their performance on a contrast discrimination task. Likewise, after two sessions of low frequency visual stimulation participants decreased their performance on a contrast discrimination task. These results suggest the temporal dynamics of the visual stimulation may have opposing effects on behavior, and are consistent with the opposing cellular response properties seen after LTP and LTD protocols. However, we cannot provide strong evidence for this effect.

We did not find a significant change from baseline performance after visual stimulation. These results do not match previous exposure-based learning studies. Using a visual checkerboard “tetanus”, Teyler et al. (2005) potentiated visually evoked responses, and that this LTP-like effect was located in V2 (Clapp et al., 2005a). Beste et al (2011) found a change in a luminance detection task after high or low frequency visual stimulation. We attempted to replicate this effect using the same paradigm, but did not find the bi-directional modification of behavior.

There is debate in the field whether contrast discrimination can be improved with practice. Some studies do not find contrast learning after training (Dorais & Sagi, 1997; Adini et al., 2002). Other studies do find contrast learning, but a large amount of training is required. Furmansi et al (2004) found improved performance on the detection of low-
contrast patterns after one month and 14,000 training trials. Yu and colleagues (2004) found improvement on a similar task after at least 8 hours of training. Li et al (2009) found improvement along the full contrast sensitivity curve after 50 hours of training over 9 weeks. There is less evidence for fast contrast learning. Adini et al (2002) found improved contrast discrimination after 3 days and 1,500-3,000 trials of training. It is possible we see only weak improvements in our contrast discrimination task as a result of exposure-based learning due to the time course required for plasticity as a result of contrast learning, and longer training would lead to more robust effects.

A possible explanation for the results seen in Studies 1, 2, and 3 could be related to testing effects. Where participants improved on task related principles that allowed them to respond more consistently and better reflects their true sensitivity. This could include a better understanding and familiarity of the procedure, better attention at the time of stimulus presentation, remembering what they saw, learning the correct response keys, etc. These can all result in benefits that lead to session-to-session improvements unrelated to our manipulation. This can be seen in the Study 2 Control participants. These participants did not receive stimulation and instead only performed the fixation task. Contrast discrimination performance improved slightly after 24 hours (Table 3). While not statistically significant (Session 1 Pre-test/Session 2 Pre-test, p = 0.42), this indicates some improvement on the task. Also, all participants in Study 3 improved luminance detection performance from test-to-test, regardless of stimulation condition.

The results seen in Studies 1 and 2 could also be related to fatigue or adaptation effects. In Study 1, all participants contrast discrimination performance decreased
immediately after stimulation in both sessions. This could indicate possible fatigue effects of the study procedure on the participants. Alternatively, these results could be the consequence of adaptation. Contrast adaption is known to occur at many levels of the visual system (Solomon et al., 2004), and performance on the change-detection task improved within the session.
REFERENCES


Figure 1. The stimulation protocol consists of rectangles flashing unilaterally or bilaterally, at a frequency of 20 Hz or 1 Hz.
Figure 2. In the contrast discrimination tests, the number 1, then the number 2 flashed briefly (200 ms) on the screen. The stimuli appeared during one of the presentations. The participant responded if they saw the rectangle during the first or second presentation. The contrast level of the stimuli adjusted to the participant's threshold.
Figure 3. Experimental design of Study 1 consisted of two identical sessions at the same time on consecutive day. Each session consists of 3 segments: Contrast discrimination Pre-Training Test, unilateral High or Low frequency stimulation Training, and Contrast discrimination Post-Training Test.
Figure 4. Contrast discrimination performance in the HFS condition tested at four timepoints for the Trained and Untrained stimuli. Error bars represent within subject standard error.
Figure 5. Contrast discrimination performance in the LFS condition tested at four timepoints for the Trained and Untrained stimuli. Error bars represent within subject standard error.
Figure 6. Experimental design of Study 2 consisted of two identical sessions at the same time on consecutive day. Each session consists of 3 segments: Contrast discrimination Pre-Training Test, bilateral High and Low frequency stimulation Training or Control, and Contrast discrimination Post-Training Test.
Figure 7. Contrast discrimination performance of all participants in the HFS, LFS, and control conditions tested at four timepoints. Error bars represent within subject standard error.
Figure 8. Contrast discrimination performance of the HFS, LFS, and Control conditions tested at four timepoints. Error bars represent within subject standard error.
Figure 9. Combined contrast discrimination performance in the HFS, LFS and Control conditions in Studies 1 and 2. Contrast discrimination performance was tested at four timepoints. Error bars represent within subject standard error.
Figure 10. Contrast discrimination performance in the HFS, LFS and Control conditions subtracted from the Session 1 Pre-test (baseline). Error bars represent within subject standard error.
Figure 11. Experimental design of Study 3 consisted of two identical sessions at the same time on consecutive day. Each session consists of 3 segments: Change detection Pre-Training Test, bilateral High or Low frequency stimulation Training, and Change detection Post-Training Test.
Figure 12. Change detection task. Participants fixated at the center of the screen, stimuli were presented on either side of fixation and varied in luminance polarity and orientation. Stimuli reappeared on either side of the fixation dot. There were four possible conditions of the second presentation, 1) the luminance of one stimuli changed, 2) the orientation of one stimuli changed, 3) the luminance and orientation of the same stimuli changed, or 4) the luminance of one stimuli changed and the orientation of the other stimuli changed.
Figure 13. Contrast discrimination performance in the HFS condition tested at four timepoints for the high and low saliency conditions. Error bars represent within subject standard error.
Figure 14. Contrast discrimination performance in the LFS condition tested at four timepoints for the high and low saliency conditions. Error bars represent within subject standard error.
Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Trained</th>
<th>Untrained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S1 Pre-test</strong></td>
<td>0.6129 ± 0.105</td>
<td>0.6757 ± 0.100</td>
</tr>
<tr>
<td><strong>S1 Post-test</strong></td>
<td>0.8044 ± 0.112</td>
<td>0.6426 ± 0.112</td>
</tr>
<tr>
<td><strong>S2 Pre-test</strong></td>
<td>0.4939 ± 0.085</td>
<td>0.5526 ± 0.126</td>
</tr>
<tr>
<td><strong>S2 Post-test</strong></td>
<td>0.6388 ± 0.077</td>
<td>0.6065 ± 0.107</td>
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Table 2.

Table of Mean Weber Contrast: Study 1 LFS condition

<table>
<thead>
<tr>
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<th>Trained</th>
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<tr>
<td>S1 Pre-test</td>
<td>0.8289 ± 0.131</td>
<td>0.6823 ± 0.101</td>
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<tr>
<td>S1 Post-test</td>
<td>0.9594 ± 0.235</td>
<td>0.8157 ± 0.108</td>
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<tr>
<td>S2 Pre-test</td>
<td>0.7993 ± 0.084</td>
<td>0.6343 ± 0.119</td>
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<td>S2 Post-test</td>
<td>1.0183 ± 0.191</td>
<td>0.6363 ± 0.114</td>
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Table 3.

Table of Mean Weber Contrast: Study 2

<table>
<thead>
<tr>
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<th>Control</th>
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<tr>
<td><strong>S1 Pre-test</strong></td>
<td>0.8843 ± 0.076</td>
<td>0.8381 ± 0.060</td>
<td>0.9625 ± 0.172</td>
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<td><strong>S1 Post-test</strong></td>
<td>0.8515 ± 0.082</td>
<td>0.8945 ± 0.054</td>
<td>0.9570 ± 0.107</td>
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<td><strong>S2 Pre-test</strong></td>
<td>0.7240 ± 0.059</td>
<td>0.7839 ± 0.119</td>
<td>0.7983 ± 0.095</td>
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<td><strong>S2 Post-test</strong></td>
<td>0.7596 ± 0.062</td>
<td>0.8808 ± 0.073</td>
<td>0.8596 ± 0.056</td>
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Table 4.

Table of Mean Weber Contrast: Combined Results

<table>
<thead>
<tr>
<th></th>
<th>HFS</th>
<th>LFS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 Pre-test</td>
<td>0.7432 ± 0.070</td>
<td>0.8333 ± 0.073</td>
<td>0.7955 ± 0.047</td>
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<tr>
<td>S1 Post-test</td>
<td>0.8260 ± 0.070</td>
<td>0.9297 ± 0.127</td>
<td>0.8526 ± 0.026</td>
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<td>S2 Pre-test</td>
<td>0.6043 ± 0.057</td>
<td>0.7916 ± 0.071</td>
<td>0.7098 ± 0.042</td>
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<tr>
<td>S2 Post-test</td>
<td>0.6968 ± 0.051</td>
<td>0.9495 ± 0.101</td>
<td>0.8382 ± 0.061</td>
</tr>
</tbody>
</table>
Table 5.

Table of Mean Percent Correct: Study 3 HFS condition

<table>
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<tr>
<th></th>
<th>High Saliency</th>
<th>Low Saliency</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 Pre-test</td>
<td>74.74% ± 2.88</td>
<td>86.46% ± 1.24</td>
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<tr>
<td>S1 Post-test</td>
<td>80.04% ± 2.84</td>
<td>89.42% ± 1.62</td>
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<tr>
<td>S2 Pre-test</td>
<td>84.11% ± 2.05</td>
<td>91.41% ± 1.23</td>
</tr>
<tr>
<td>S2 Post-test</td>
<td>85.24% ± 2.58</td>
<td>92.53% ± 1.32</td>
</tr>
</tbody>
</table>
Table 6.

<table>
<thead>
<tr>
<th></th>
<th>High Saliency</th>
<th>Low Saliency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S1 Pre-test</strong></td>
<td>68.44% ± 3.02</td>
<td>86.00% ± 1.63</td>
</tr>
<tr>
<td><strong>S1 Post-test</strong></td>
<td>74.19% ± 2.97</td>
<td>90.50% ± 1.38</td>
</tr>
<tr>
<td><strong>S2 Pre-test</strong></td>
<td>77.56% ± 3.31</td>
<td>89.31% ± 1.96</td>
</tr>
<tr>
<td><strong>S2 Post-test</strong></td>
<td>78.65% ± 3.16</td>
<td>91.47% ± 1.53</td>
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Chapter 2: A perceptual learning based video game produces broad-based visual benefits

This chapter is currently in submission to the academic journal Vision Research.

INTRODUCTION

Over 100 million people worldwide suffer from low-vision; visual impairments that cannot be corrected by spectacles. Our knowledge of the world is derived from our perceptions, and an individual’s ability to navigate his/her surroundings or engage in activities of daily living such as walking, reading, watching TV, and driving, naturally relies on his/her ability to process sensory information. Thus deficits in visual abilities, due to disease, injury, stroke or aging, can have significant negative impacts on all aspects of an individual’s life. Likewise, an enhancement of visual abilities can have substantial positive benefits to one’s lifestyle. Visual deficits can generally be categorized as those related to the properties of the eye, for which there are numerous innovative corrective approaches, and those related to brain processing of visual information, for which understanding, and thus appropriate therapies, is very limited. The lack of appropriate approaches to treat brain-based aspects of low-vision is a serious problem since in many cases a component of the individual’s low-vision is related to sub-optimal brain processing (Polat, 2009).

Research in the field of perceptual learning provides promise to address components of low-vision. Improvements have been identified for a wide set of perceptual abilities; from perception of elementary features (e.g. luminance contrast
(Adini et al., 2002; Furmanski et al., 2004) motion (Ball & Sekuler, 1982; Vaina et al.,
1998) and line-orientation (Karni & Sagi, 1991; Ahissar & Hochstein, 1997) to global
scene processing (Chun, 2000) and image recognition (Gold et al., 1999; Lin et al.,
2010). Recent advances in the field of perceptual learning show great promise for
rehabilitation from a diverse set of vision disorders. For example, recently work on PL
has been translated to develop treatments of amblyopia (Levi & Li, 2009), presbyopia
(Polat, 2009), macular degeneration (Baker et al., 2005), stroke (Vaina & Gross, 2004;
Huxlin et al., 2009), and late-life recovery of visual function (Ostrovsky et al., 2006).
However, weeks or more of training can be needed to obtain significant perceptual
benefits (Furmanski et al., 2004; Li et al., 2008). Furthermore, perceptual learning can be
very specific to the trained stimulus features (Fahle, 2005). Focus on this specificity has
defined the field and has limited the development of training strategies that lead to broad
based benefits to visual processing.

A limitation of most perceptual learning approaches is their emphasis on isolating
a single feature. Almost all current techniques train a small set of stimulus features and
use stimuli of a single sensory modality. It is also common to employ tasks that are not
motivating to participants and require difficult stimulus discriminations for which
subjects make many errors and have low confidence of their accuracy. To achieve
effective therapies for low-vision populations research of perceptual learning needs to
shift focus from isolating mechanisms of learning to that of integrating multiple learning
approaches. Few studies that have done this shows that training on multiple stimulus
dimensions (Xiao et al., 2008), or with off-the-shelf video-games (Green & Bavelier,
2003), dramatically improves the extent to which learning generalizes to untrained conditions. Furthermore, research shows that learning is the greatest when using multisensory stimuli (Shams & Seitz, 2008), motivating tasks (Shibata et al., 2009), settings where participants understand the accuracy of their responses (Ahissar & Hochstein, 1997) and receive consistent reinforcement to the stimuli that are to be learned (Seitz & Watanabe, 2009). These data suggest the coordinated engagement of attention, delivery of reinforcement, use of multisensory stimuli, and training multiple stimulus dimensions individually enhance learning. Currently, there is limited research into how combining these features will effect broad-based enhancements in patients’ visual abilities.

One approach to achieving this end has been in the adoption of commercial video games as a tool to induce perceptual learning (Green & Bavelier, 2003). For example, Green and Bavelier (2003) showed that training with action video games positively impacts a wide range of visual skills including useful field of view, multiple object tracking, attentional blink, and performance in flanker compatibility tests. Furthermore, recent research has found that even basic visual abilities such as contrast sensitivity (Li et al., 2009) and acuity (Green & Bavelier, 2007; Li et al., 2011) improve after video game use. However, there exists some controversies regarding the mechanisms leading to these effects (Boot et al., 2011) and it is difficult to determine what aspects of the games lead to the observed learning effects. Thus while there is great promise in the video game approach, there is a need for games to be developed that allow a clearer link between game attributes and mechanisms of perceptual learning.
In the current study, we adopted an integrative approach where the goal is not to achieve highly specific learning but instead to achieve general improvements to vision. We combined multiple perceptual learning approaches (including engagement of attention, reinforcement, multisensory stimuli, and multiple stimulus dimensions) that have individually contributed to increasing the speed, magnitude and generality of learning into an integrated perceptual-learning video game. Training with this video game induced improvements in acuity and contrast sensitivity in participants. The use of this type of this custom video game framework built up from psychophysical approaches takes advantage of the benefits found from video game training while maintaining a tight link to psychophysical designs that enable understanding of mechanisms of perceptual learning.

MATERIALS AND METHODS

Participants

Thirty participants (18 male and 12 females; age range 18-55 years) were recruited and gave written consent to participate in experiments conforming to the guidelines of the University of California – Riverside Human Research Review Board. They were all healthy and had normal or corrected-to-normal visual acuity. None of them reported any neurological, psychiatric disorders or medical problems.

Materials

For the test stimuli, an Apple Mac Mini running Matlab (Mathworks, Natick, MA) or a Dell PC both with Psychtoolbox Version 3 (Brainard, 1997; Pelli, 1997) was
used to generate the stimuli and control the experiment. Participants sat on a height adjustable chair 5 feet from a 24” SonyTrinitron CRT monitor (resolution: 1600 x 1200 at 100 Hz) or a 23” LED Samsung Monitor (resolution: 1920 x 1080 at 100 Hz). Gaze position on the screen was tracked with the use of an eye-tracker (EyeLink 1000, SR Research ®).

For the training sessions, custom written software (Carrot NT, Los Angeles, CA) that runs on Apple OS X and Windows personal computers was used and participants had their head-position fixed with a headrest, but eye-movements were not tracked during training.

Testing Procedures

*Foveal Vision Tests* – Sixteen participants completed the foveal visual assessments, 8 in the Training Group and 8 Control Group. Tests were conduced twice for each participant on separate days: before and after training for participants in the Training Group, and at least 24 hours apart for the Control Group. An Optec Functional Visual Analyzer (Stereo Optical Company, Chicago, IL USA) was used to measure *foveal visual acuity* and a *contrast sensitivity function (CSF)*. In the CSF assessment, contrast thresholds of Gabors of 5 different spatial frequencies (1.5, 3, 6, 12, and 18 cycles/deg) were determined for each participant in each session using a staircase procedure.

*Peripheral Vision Tests* – Twenty-seven participants were tested on peripheral vision, 14 in the Training Group and 13 in the Control Group. Tests were conduced twice
for each participant on separate days: before and after training for participants in the Training Group, and at least 24 hours apart for the Control Group. For 16 of the participants (8 Trained, 8 Control) a gaze contingent display was utilized to ensure that stimuli were properly positioned on the retina. The participant had to fixate on a centrally presented red dot for 500 ms in order for each trial to begin. This was controlled by the use of an eye-tracker (EyeLink 1000, SR Research ®). In the other participants similar results were obtained without the eye-tracker given the brief unpredictable presentation of the stimuli.

Peripheral vision tests consisted of a measurement of acuity, and a measurement of contrast sensitivity. In the Acuity Test, Landolt C stimuli (using the Sloan Font size 32) were presented for 200 ms in 3 different eccentricities (2°, 5°, 10°) for each of 8 different angles (22.5°, 67.5°, 112.5°, 157.5°, 202.5°, 247.5°, 292.5°, 337.5°) around the circle. The task of the participant was to respond to the direction of the opening of the letter C, right or left. The participant did not receive feedback on the accuracy of their response. After a correct response the size of the stimulus would decrease, or increase after an incorrect response following a three-down/one-up staircase. A separate staircase was run for 30 trials on each stimulus eccentricity/angle combination, for a total of 720 trials. The threshold was averaged across all the positions at each eccentricity, giving each eccentricity a separate threshold.

For the Contrast Test, the stimulus was a letter “O”. The task of the participant was to respond to the location on the screen of the “O”, left or right of the fixation point. The participant did not receive feedback on the accuracy of their response. The stimuli
were presented for 200 ms at 3 different eccentricities (2°, 5°, 10°) for each of 8 different angles (22.5°, 67.5°, 112.5°, 157.5°, 202.5°, 247.5°, 292.5°, 337.5°) around the circle. The stimuli contrast started at 17%, after a correct response the contrast of the stimulus would decrease, or increase after an incorrect response following a three-down/one-up staircase. A separate staircase was run for 30 trials on each stimulus eccentricity/angle combination, for a total of 720 trials. The threshold was averaged across all the positions at each eccentricity, giving each eccentricity a separate threshold.

Training Procedures

Fourteen participants conducted 24 sessions on the video-game based vision training program. We define this program as a “video-game” rather than a traditional psychophysical paradigm because the goal here is to entertain as well as evaluate an experimental manipulation. The program was set up like a game, where levels progressed in difficulty throughout training. Many parameters were adaptive to a participant’s performance, including level progression, stimuli contrast and stimuli number. Sessions were conducted on separate days with an average of 4 sessions per week. Each training session lasted approximately 30 minutes. Stimuli consisted of Gabor patches at 6 spatial frequencies (2, 4, 8, 16, 32, 64 cycles/deg), and 8 orientations (22.5°, 67.5°, 112.5°, 157.5°, 202.5°, 247.5°, 292.5°, 337.5°).

Calibration - At the beginning of each session a calibration was run where participants were shown a display containing visual Gabor Stimuli of 7 contrast values spanning between suprathreshold and subthreshold, (these were adaptively determined across sessions based on previous performance levels) for each of the 6 spatial
frequencies. This calibration determined the initial contrast values for each spatial frequency to be displayed during the training exercises.

Participants ran 8-12 training exercises in each session that ran approximately 2 minutes each (number of training exercises varied depending on participants’ rate of performance). Exercises alternated between Static (simultaneous) and Dynamic (sequential) types. The goal of the exercises was to click on all the Gabors as quickly as possible. Separate staircases were run on each spatial frequency. Gabors not selected during the time limit would start flickering at a 20 Hz frequency. Previous research (Godde et al., 2000; Dinse et al., 2006; Seitz & Dinse, 2007; Beste et al., 2011) shows that a visual stimulus flickering at 20 Hz is sufficient to induce learning even when there is no training task on those stimuli. The delay before flickering onset is so that the adaptive procedures can track the pre-flicking thresholds. If targets were still not selected while flickering, contrast increased until selected. This allowed participants to successfully select all targets.

The first few exercises consisted of only Gabor targets, as the training progressed distractors were added (Figure 15). The session number the distractors were added varied for each participant based on their performance. However, once distractors were added all subsequent sessions contained distractors. Before each exercise that included distractors participants were given instructions, including an example, of a correct Gabor target and an incorrect distractor. Throughout training distractors became more similar to the targets (starting of as blobs, then oriented patterns, then noise patches of the same spatial frequency of the Gabors, etc.). Participants were instructed not to select distractors, on
penalty of losing points. Participants received more points when they clicked on Gabors at lower-contrast and thus their scores corresponded with their performance in the sessions.

During the exercises, when a target was selected a sound was played through speakers where interaural level differences were used to co-locate the sound with the just selected visual target. Here, low-frequency tones corresponded with stimuli at the bottom of the screen and high-frequencies tones corresponded to stimuli at the top of the screen. Thus the horizontal and vertical locations on the screen each corresponded to a unique tone. The sounds provide an important cue to the location of the visual stimuli and such multisensory facilitation has been shown to boost learning (Shams & Seitz, 2008).

*Static Exercise* - An array of Gabors of a single randomly determined orientation and one of the 6 spatial frequencies would appear all at once randomly across the screen. The contrast of the Gabors and number of Gabors was adaptively determined. The contrast was decreased by 5% of the current contrast-level whenever 80% of the displayed Gabors were selected within a 2.5 second per Gabor time limit, and increased whenever fewer than 40% of Gabors were selected within this time limit. The number was adaptively determined to approximate what participants could select within 20 seconds.

*Dynamic Exercises* - Gabors would fade in one at a time at a random location on the screen. For each 20 second miniround all the Gabors would appear in a randomly chosen orientation/spatial frequency combination. A Gabor would appear sequentially every 2.5 seconds, or as soon the previous Gabor was selected. The contrast of the
Gabors was adaptively determined using a three–down/one–up staircase. In addition to a tone being played when the Gabor was selected, a separate unique tone corresponding to the target location would be played at the onset time of each Gabor. This tone cued the location where the Gabor appeared on the screen. In exercises that contained distractors, the distractors appeared all at once on the screen while Gabors faded in sequentially.

RESULTS

We first examined foveal vision in our participants. Independent tests of foveal acuity and a CSF were run in 16 participants (8 Training, 8 Control) using an Optec Functional Visual Analyzer. For foveal acuity, we found that acuity went from 19.25 ± 1.5 to 16.7 ± 0.8, a t-test showed this to be significant (p = 0.026). However, no such benefits were found in the control group (21.0 ± 2.4 to 20.8 ± 1.7, p = 0.85). We examined the CSF at 5 spatial frequencies (1.5, 3, 6, 12, and 18 cycles/deg). Results are shown in Figure 16, contrast sensitivity improvements were significant at each SF (p = 0.002, 0.033, 0.011, 0.013, 0.003, respectively). For the control group, no significant changes in contrast sensitivity were found (p = 0.08, 0.20, 0.97, 1.0, 0.30, respectively).

Next, we examined peripheral acuity in 27 participants (14 Training, 13 Control), 16 (8 Trained, 8 Control) of which used a gaze-contingent display to ensure accurate fixation on each trial. Using Landolt C’s to assess peripheral acuity (Figure 17), significant benefits of training were confirmed with a two-way repeated measures ANOVA (Eccentricity X Session) showing a main effects of Session for acuity (F(13) = 4.7, p = 0.025), no such benefits were found in the control group (p = 0.97). These
benefits to acuity in the trained group were significant at each of the eccentricities tested (2° p = 0.016, 5° p = 0.018, 10° p = 0.044).

Peripheral contrast sensitivity (Figure 18) was measured with a letter “O” presented at each eccentricity (scaled logarithmically to account for cortical magnification factor), also using gaze-contingent displays. Of note, while the percent contrast might be expected to be lowest at the smallest eccentricity (closest to the fovea), our results exhibit the opposite pattern. This is likely due to our scaling inadvertently decreasing the difficulty of the task as eccentricity increases, however our tests of interest are improvement from pre-test to post-test, and these baseline differences across eccentricity are not of concern. For the trained group, a two-way repeated measures ANOVA revealed a main effect of Session for contrast sensitivity (F(13) = 6.8, p = 0.012), however, no changes were found in the control group (p = 0.58). For the trained group these benefits were significant at 2° (p = 0.003) and 10° (p = 0.014) and showed a trend for 5° (p = 0.096).

DISCUSSION

This study shows broad-based benefits of vision in a healthy adult population through an integrative approach that combines many perceptual learning mechanisms, including attention, reinforcement, multisensory stimuli, and multi-stimulus dimensions. Our results demonstrate a broad improvement of vision that transfers outside the context of the training task (untrained stimuli) to a different task on the trained stimuli (the CSF assessment) and then to poster-based eye-charts presented on a wall. The magnitude of the effects that we observe rival those found using off-the-shelf video games with acuity
(Green & Bavelier, 2003), however unlike Green and Bavelier (2003), our acuity measures were found with self-paced standard eye-charts. As opposed to off the shelf video games, our program uses a custom video game framework built up from psychophysical approaches where multiple perceptual learning principles can be further added or subtracted in the future to better understand the contribution of each feature. Additionally, our results match results of Li et al (2009) showing improvement along the full contrast sensitivity curve, however, unlike Li et al (2009), our study involved no time restriction in the viewing of the stimuli while measuring the CSF. Furthermore, to our knowledge, we are the first to show broad-based improvements that also include peripheral acuity and contrast sensitivity using a single training approach. This research is the first steps in contributing to training approaches for variety of individuals, the next steps include comparing these results to those of sham training.

Perceptual learning research demonstrates that the adult visual system is sufficiently plastic to ameliorate effects of amblyopia (Levi & Li, 2009), presbyopia (Polat, 2009), macular degeneration (Baker et al., 2005), stroke (Huxlin et al., 2009), and late-life recovery of visual function (Ostrovsky et al., 2006). Benefits of contrast sensitivity can be found across a range of spatial frequencies when used as training for suboptimal vision (Huang et al., 2008; Zhou et al., 2012). However, benefits are slow to form (Furmanski et al., 2004; Li et al., 2008), even extensive training can fail to result in visual improvement (Ahissar & Hochstein, 1997), and benefits are typically highly specific to the trained stimulus features (Fahle, 2005). While recent breakthroughs demonstrate the utility of principles such as the coordination of attention and
reinforcement (Seitz & Watanabe, 2003; Seitz & Watanabe, 2005; Seitz & Watanabe, 2009), use of multisensory stimuli (Shams & Seitz, 2008), and training multiple stimulus dimensions (Xiao et al., 2008), in enhancing learning, little research integrates these principles into a combined approach. As such, the status quo in treating brain-based low vision is to adapt standard perceptual learning procedures to be used with clinical populations. This turns a strength of modern perceptual learning research, the use of simple approaches to cleanly identify individual mechanisms of learning, into a weakness, where conventional therapies train small sets of stimulus features, use stimuli of a single sensory modality, employ tasks that are not motivating to participants and require difficult stimulus discriminations for which participants make many errors and have low confidence of their accuracy. The current approach combines multiple perceptual learning principles (including engagement of attention, reinforcement, multisensory stimuli, and multiple stimulus dimensions) and shows great promise in overcoming these limitations.

The current training was motivated by recent research under the guise of task-irrelevant learning (TIL), in which sensory plasticity occurs without attention being directed to the learned stimuli (Watanabe et al., 2001; Watanabe et al., 2002; Seitz & Watanabe, 2003; Seitz et al., 2005a; Seitz & Watanabe, 2005; Seitz et al., 2005b; Seitz et al., 2005c; 2006b; Seitz & Watanabe, 2008; Tsushima et al., 2008; Seitz et al., 2009; Seitz & Watanabe, 2009), shows that reinforcement is key to visual learning. Seitz & Watanabe (Seitz & Watanabe, 2005) suggested a model of perceptual learning where learning results from interactions between spatially diffusive task-driven signals and
bottom-up stimulus signals. Namely, that learning is gated by behaviorally relevant events (rewards, punishment, novelty, etc). At these times reinforcement signals are released to better learn aspects of the environment (even those for which the organism is not consciously aware) that are predictive or co-vary with the event. By now, TIL has been shown to be a robust learning phenomenon that generalizes to a wide range of stimulus features, for example, motion processing (Watanabe et al., 2002), orientation processing (Nishina et al., 2007), critical flicker fusion thresholds (Seitz et al., 2005c; 2006b), contour integration (Rosenthal & Humphreys, 2010), auditory formant processing (Seitz et al., 2010), phonetic processing (Vlahou et al., 2009) and memorization of complex objects (Lin et al., 2010; Swallow & Jiang, 2010; 2011). Importantly, TIL produces learning effects that are often as strong, and sometimes stronger, than learning effects produced through direct training (Seitz et al., 2010; Vlahou et al., in press). Thus TIL is arguably a basic mechanism of learning in the brain that spans multiple levels of processing and sensory modalities.

Additionally, we took advantage of recent findings of the multisensory facilitation of learning in which it has been found that learning is faster and greater when training with stimuli that are coordinated across the senses (Shams & Seitz, 2008). The human brain has evolved to learn and operate optimally in natural environments in which behavior is guided by information integrated across multiple sensory modalities. Crossmodal interactions are ubiquitous in the nervous system and occur even at early stages of perceptual processing (Shimojo & Shams, 2001; Calvert et al., 2004; Schroeder & Foxe, 2005; Ghazanfar & Schroeder, 2006; Driver & Noesselt, 2008). Until recently,
however, all studies of perceptual learning focused on training with one sensory modality. This unisensory training fails to tap into natural learning mechanisms that have evolved to optimize behavior in a multisensory environment. Recent research shows that participants trained with auditory-visual stimuli exhibit a faster rate of learning and a higher degree of improvement than found in participants trained in silence (Seitz et al., 2006a; Kim et al., 2008). Critically, these benefits of multisensory training are even found for perceptual tests without auditory signals. In other words, multisensory training facilitates unisensory learning. The advantage of multisensory training over visual-alone training was substantial; it reduced the number of sessions required to reach asymptote by ~60%, while also raising the maximum performance.

CONCLUSION

Our ability to navigate the world and engage in activities of daily living such as walking, reading, watching TV, and driving, relies on our ability to process visual information. Perceptual learning, therefore, has profound importance to health and well-being. Recent advances in the field of perceptual learning have shown great promise for rehabilitation from a diverse set of disorders. We found robust improvements in both foveal and peripheral acuity and contrast sensitivity after only 12 hours of training. Our research can contribute to training approaches for typically developed individuals, as well as rehabilitative approaches in individuals with low-vision. Furthermore, visual training programs have great potential to aid individuals, such as athletes looking to optimize their visual skills. Thus research into visual therapies has great potential to benefit a diverse range of individuals.
REFERENCES


Figure 15. Game screenshot - Static search with distractors. Participants should select the targets, and ignore the distractors. As levels progress distractors will look more and more like targets.
Figure 16. Contrast Sensitivity Function. Average CSF on pretest (blue) and posttest (red) for experimental and control group. Error bars represent within subject standard error.
Figure 17. Peripheral Acuity. Average acuity thresholds (based on 20/20 values) on pretest (blue) and posttest (red) for experimental and control group. Error bars represent within subject standard error.
Figure 18. Peripheral Contrast Sensitivity. Average contrast thresholds on pretest (blue) and posttest (red) for experimental and control group. Error bars represent within subject standard error.
Chapter 3: Improved Vision and on Field Performance in Baseball through Perceptual Learning

This chapter is currently in submission to the academic journal Current Biology.

Perception is the window through which we understand all information about our environment. Research in the field of perceptual learning demonstrates that vision can be improved in both normally seeing (Fiorentini & Berardi, 1980; Green & Bavelier, 2007) and visually impaired individuals (Polat, 2009). However, a limitation of most perceptual learning approaches is that they emphasize simplistic approaches to target specific mechanisms, often giving rise to learning effects that fail to generalize beyond experimental testing conditions (Fahle, 2005). In the current study, we adopted an integrative approach where the goal is not to achieve highly specific learning, but instead to achieve general improvements to vision. We combined multiple perceptual learning approaches, such as training with a diverse set of stimuli (Xiao et al., 2008), optimized stimulus presentation (Beste et al., 2011), multisensory facilitation (Shams & Seitz, 2008), motivating tasks (Shibata et al., 2009), maximizing participant performance-confidence (Ahissar & Hochstein, 1997) and consistently reinforcing training stimuli (Seitz & Watanabe, 2009), which have individually contributed to increasing the speed (Seitz et al., 2006), magnitude (Seitz et al., 2006; Vlahou et al., 2012) and generality of learning (Green & Bavelier, 2007; Xiao et al., 2008) with the goal of creating an integrated perceptual learning based-training program that would powerfully generalize to real world tasks.
The efficacy of this integrated training approach was tested in the University of California Riverside (UCR) Baseball Team. Vision is essential in the world of competitive sports. Research suggests elite baseball batters use various kinds of sensory information to be successful at the plate, but the most weight is given to visual feedback (Gray, 2009). Therefore, suboptimal vision makes the already difficult task of batting much more challenging. A limited amount of research has investigated the benefits of vision training on sporting performance in both elite and novice athletes. Most standard vision training programs focus on exercising the ocular muscles, and while generally accepted as being beneficial, the research supporting such claims are mixed (Wood & Abernethy, 1997; Abernethy & Wood, 2001; Clark et al., 2012). Testing our integrated training program in baseball players enabled analysis of real world performance, in this case batting performance, in addition to standards measures of vision.

We applied the integrated training program to the UCR Men’s Baseball Team prior to the start of the 2013 season. Nineteen players completed 30, 25-minute sessions, each on a different day, of the integrated training program (see supplemental methods for details) and served as the Trained group, while eighteen players served as an Untrained control group. Both before and after the training phase, visual acuity (using Snellen charts) was measured in both the Trained and Untrained groups.

Players in the Trained group, showed impressive improvements in visual acuity (measured at 20 feet), with an average of 31% improvement in binocular acuity (Figure 19). These changes were significantly greater than those of the players in the Untrained group (F = 31.13, p < 0.0001). The Trained group moved from a pre-training mean value
of 20/13 ± 0.69 SE to a post-training value of 20/10 ± 0.59, whereas the Untrained group had a pre-training mean value of 20/16 ± 1.4 and a post-training value of 20/16 ± 1.2. Of note, the pre-training differences were not significant between Trained and Untrained players (t = 0.8774, p = 0.39 t-test). Strikingly, 15 of 19 Trained players showed improved binocular acuity, the 4 Trained players not showing improvements in the binocular test improved in one or both of the eyes individually. These monocular improvements likely translated to less than one line change in binocular vision, the minimum change we could measure in our tests. Impressively, 7 of the Trained players reached 20/7.5 Snellen acuity in far binocular acuity after training. Similar improvements were also found in near vision for the Trained, but not Untrained, players (Figure 20).

For the Trained players we also measured contrast sensitivity functions (CSFs) at the beginning and end of training using a computerized assessment that staircased contrast in an orientation matching task for centrally presented Gabor patches of 6 different spatial frequencies (1.5, 3, 6, 12.5, 25 and 50 cycles/deg). Results are shown in Figure 21, where we found significant improvement in CSF (F = 25.4, p = 0.0001) demonstrating that contrast sensitivity as well as acuity benefitted from training.

The vision tests demonstrate a broad improvement of vision that transfers outside the context of the testing task (fast paced computer exercises) to a different task on the trained stimuli (the CSF assessment) and then to poster-based eye-charts presented on a wall. However, the question remains of whether these vision improvements as assessed by laboratory tests translate to real world benefits for the Trained players.
To address this point we analyzed batting statistics from the 2012 Big West Baseball season (ending 4 months prior to training), and the 2013 Big West Baseball season (beginning 2 months after training), a comparison used in previous research (Clark et al., 2012). Eleven of the 19 Trained players played in both the 2012 and 2013 seasons and subsequent analyses focus on these players. It is important to recognize that college players typically do improve from one year to the next; and this improvement needs to be recognized and incorporated into our estimation of the treatment effect. To address this concern, we identified 78 non-UCR players in the Big West league who played in both the 2012 and 2013 seasons and used their data as a baseline for the typical year-to-year improvements expected in this population of players.

As a first metric of batting performance we examined strike-outs (SOs). Being able to see the ball would seem a prerequisite to hitting it, and one might expect improved vision to decrease the number of SOs. The SOs of the Trained UCR players decreased from 22.1% of plate appearances to 17.7% of plate appearances, a reduction of 4.4% ± 2.0 SE with 10 (11) players showing a reduction in SOs. This was significantly greater than that of the rest of league (p = 0.013, permutation test, see methods for details) whose SOs decreased from 16.0% of plate appearances to 15.4% of plate appearances, a reduction in SOs of 0.4% ± 0.71 SE with only about half the league, 42 (78), showing improvement.

Next, we examined Runs Created (RC), a statistic initially described by Bill James (that includes key components of both on base and slugging percentage) (James, 2003), as a measure of overall batting performance. In 2013, the 11 Trained UCR players
created 212.34 runs, estimated by the basic runs created formula (Reference.Com, 2013b), and used 1130 outs (At Bats minus Hits), yielding 0.188 RC per out (Table 7). In the previous year, prior to training, these same 11 players created only 0.140 runs per out (RC = 125.44, Outs = 896). To evaluate this improvement of 0.048 RC/Out, we calculated the difference in the collective RC/Out of these two years for the league baseline group, who showed a difference of 0.011 (RC/Out values of 0.169 and 0.180 in 2012 and 2013, respectively). Had UCR players improved at the league rate, their expected RC/Out would have been 0.151 (0.140 + 0.011) and not 0.188 as observed. Projecting the 0.151 RC/Out into the UCR players’ performance over the course of their 2013 season of 1130 outs, the RC estimate is 170.63, or 41.71 RC less than when estimated on their actual performance. To evaluate the effect of treating 11 UCR batters, we need to evaluate the impact of this gain in RC on a metric easily understood: wins and losses.

The value, in terms of wins and losses, of adding some number of runs depends not only on the initial value (as adding runs is not linearly related to winning percentage), but also to the number of runs allowed (i.e., the runs scored by opponents). There is a so-called “Pythagorean” relation (Reference.Com, 2013a) between runs scored and runs allowed such that the ratio of the squares (most accurately, an exponent of 1.81 rather than 2) of runs created to the square (1.81) of runs allowed estimates the ratio of wins to losses. In 2013 UCR’s actual record was 22-32, a 0.407 winning percentage, whereas the Pythagorean estimate based on 286 runs scored and 364 runs allowed yields a winning percentage of 0.393, or a record of 21.2 wins and 32.8 losses in a 54 game season. If we
subtract the 41.71 RC that we attribute to treatment from the 286 runs scored, the Pythagorean estimate of winning percentage is 0.306 (16.5 wins, 37.5 losses). Thus, we estimate that treating the 11 UCR players may have gained the team 4 or 5 (21.2 vs 15.5) wins in the 2013 season as illustrated in Table 8.

While it is difficult to make a conclusive causal inference that the improvements in vision are solely responsible for the improved offensive performance shown by the trained players, the observed improvements are substantial and significantly greater than that experienced by players in the rest of the league in the same year. For example, a permutation test incorporating both SOs and RCs for Trained vs Baseline players shows a probability of 0.004 of getting such an improvement in offensive statistics by a chance draw of any random 11 players from the league (including the UCR players).

In summary, the integrated perceptual learning training program created broad based visual benefits in UCR baseball players. The improvements transferred not only to laboratory tests of vision, but also to improved offensive performance on the baseball field in the season after vision training. These data suggest that the curse of specificity in perceptual learning studies may be overcome by moving beyond traditional approaches that target single mechanisms of learning to instead integrate multiple principles with the goal of maximizing learning outcomes. This approach has potential to aid many individuals that rely on vision including not only athletes looking to optimize their visual skills but also individuals with low vision engaged in more everyday tasks.
**Supplementary Methods**

**Participants**

Participants included 37 members of the 2013 University of California Riverside (UCR) Men’s Baseball team (all male; age range 18-23). Nineteen position players participated in the vision training procedures and served as the Trained group, 18 pitchers served as the Untrained control group. All participants gave written consent to participate in experiments conforming to the guidelines of the UCR Human Research Review Board. They were all healthy and had normal or corrected-to-normal visual acuity. None of them reported any neurological, psychiatric disorders, or medical problems.

**Visual Assessments**

All participants conducted visual assessments. Visual acuity was measured with standard Snellen eye charts at a far distance (20’) and a near distance (16”). Right eye, left eye, and binocular measurements were made one week prior to vision training and one week to one month after vision training. All visual assessments and training sessions were conducted in the three months prior to the start of the 2013 UCR Men’s baseball season.

Contrast sensitivity function was measured on Trained players using custom software built in the ULTIMEYES™ vision-training program. Contrast threshold of Gabors of different spatial frequencies (1.5, 3, 6, 12.5, 25 and 50 cycles/deg) were determined for each subject using a staircase procedure.
Vision Training Program

Vision training consisted of video-game based custom software (written by Carrot Neurotechnology, Los Angeles, CA) called ULTIMEYES™ (UE). Participants in the Training condition conducted 30, 25 minute UE sessions, over the course of 8 weeks with an average of 4 sessions per week. All sessions were performed in the lab under the supervision of the experimenters, running on an Apple Mac Mini and a 23” LED Samsung Monitor (resolution 1920x1080 at 100 Hz).

Training procedures

UE stimuli consists of Gabor patches (game “targets”) at 6 spatial frequencies (1.5, 3, 6.3, 12.5, 25 and 50 cycles/deg), and 8 orientations (22.5°, 67.5°, 112.5°, 157.5°, 202.5°, 247.5°, 292.5°, or 337.5°). At the beginning of each training session participants performed a calibration for each spatial frequency where stimuli were presented at 7 contrast values ranging from suprathreshold to subthreshold. Levels were adaptively determined across sessions based on previous performance. This calibration determined the initial contrast value for each spatial frequency to be displayed during the training exercises.

Exercises alternated between Static and Dynamic types, each exercise runs approximately 2 minutes. Participants ran 8-12 exercises per training session, the number of exercises varied depending on participants rate of performance. The goal of the exercises was to click on all the Gabor targets as quickly as possible. The contrast of the targets was adaptively determined using a three–down/one–up staircase. The contrast was
decreased by 5% whenever 80% of the targets were selected within a 2.5 second per Gabor time limit, and increased whenever less than 40% of Gabors were selected within this time limit. Separate staircases were run on each spatial frequency. Gabors not selected during the time limit would start flickering at a 20 Hz frequency. If still not selected, contrast increased until selected. This allowed participants to successfully select all targets. The first few exercises consist of only Gabor targets, as the training progressed distractors were added. Throughout training distractors became more similar to the targets. Participants were instructed not to select distractors, on penalty of losing points. Participants received more points when they clicked on Gabors at lower-contrast and thus their scores corresponded with their performance in the sessions.

During the exercises, when a target was selected a sound was played through speakers where interaural level differences were used to co-locate the sound with the just selected visual target. Here, low-frequency tones corresponded with stimuli at the bottom of the screen and high-frequencies tones corresponded to stimuli at the top of the screen. Thus the horizontal and vertical locations on the screen each corresponded to a unique tone.

*Static exercise* - an array of targets of a single spatial frequency, at a randomly determined orientation were presented randomly on the screen all at once. The number of Gabor targets was adaptively determined to approximately what the participant could select within 20 seconds.

*Dynamic exercise* – targets of a randomly determined orientation/spatial frequency combination are presented one at a time at a random location on the screen. A
tone corresponding to the location of the target was played at the same time the target appeared on the screen. In addition to a tone being played when the Gabor was selected, a separate unique tone corresponding to the target location would be played at the onset time of each Gabor. This tone therefore gave a clue as to where the Gabor to be selected would appear on the screen.

Permutation Tests

Permutation tests were employed to compare the year-to-year improvement between the UCR Baseball Team and the rest of the Big West League. These tests consisted of randomly drawing 50,000 combinations of 11 players from the set 89 players (11 UCR players + 78 other Big West players) and calculating the average SOs and RCs for each of these groups. We then calculated the percentage of these groups that had fewer SOs ($p = 0.029$), more RCs ($p = 0.089$) or both ($p = 0.010$). While parametric tests produce similar results, one-tailed tests for SOs and RCs yield $p = 0.028$ and $p = 0.087$, respectively, the permutation test allows a convenient method to calculate the combined probability that takes into account possible correlations between SOs and RCs.
REFERENCES


Figure 19. Change in distance the same text can be read from the pre-test to the post-test measure at 20’ in the Trained and Untrained UCR players. Error bars represent within subject standard error.
Figure 20. Change in distance the same text can be read from the pre-test to the post-test measure at 16” in the Trained and Untrained UCR players. Error bars represent within subject standard error.
Figure 21. Change in Contrast Sensitivity Function in Trained Players. Y-axis, contrast sensitivity; higher score represents better ability to see low contrasts. X-axis, the spatial frequency. Error bars represent within subject standard error.
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Table 8.

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GENERAL DISCUSSION

The purpose of this dissertation was to investigate the links between the rules of plasticity at the cellular level and behavior in both a single mechanism, using exposure-based learning, and by combining several PL approaches into a video game framework. Using exposure-based learning, our results indicate limited training does not significantly alter behavior on a contrast discrimination task. We failed to find robust alterations at the behavioral level, this is in controversy with previous literature (Clapp et al., 2005b; Teyler et al., 2005; Beste et al., 2011; Clapp et al., 2012). However, our results indicate weak alterations that may suggest a behavioral effect of visual stimulation. After combining the results of two slightly different versions of our protocol, we find a significant difference between high frequency and low frequency stimulation conditions.

Using an integrative approach that combines many perceptual learning mechanisms, including attention, reinforcement, multisensory stimuli, and multi-stimulus dimensions, our results show broad-based benefits of vision in a healthy adult population. These results were extended into a highly specialized population, college baseball players. The improvements transferred not only to laboratory tests of vision, but also to improved offensive performance on the baseball field.

The overall results from this dissertation suggest, visual exposure-based learning does not robustly alter contrast discrimination, instead a longer training paradigm is necessary for contrast sensitivity improvements. This is consistent in the literature, many studies that find improvements in contrast sensitivity require long training procedures. Furmanski et al (2004) found improved performance on the detection of low-contrast
patterns after one month and 14,000 training trials. Yu and colleagues (2004) found improvement on a similar task after at least 8 hours of training. Li et al (2009) found improvement along the full contrast sensitivity curve after 50 hours of training over 9 weeks. There is less evidence for fast contrast learning. Adini et al (2002) found improved contrast discrimination after 3 days and 1,500-3,000 trials of training. Similarly, our perceptual-learning based video game consisted of approximately 12 hours of multi-stimulus dimensional training and improvements along the full contrast sensitivity curve were found.

Previous research has found exposure-based stimulation protocols can be applied to the sensory systems that result in plasticity of the corresponding sensory cortices (Recanzone et al., 1992; Dinse et al., 2003; Clapp et al., 2005a; Clapp et al., 2005b; Teyler et al., 2005; Zaehle et al., 2007; Ragert et al., 2008), there are several limitations as to why we did not find the same results. As previously mentioned the time course of contrast learning is traditionally slow, it may be the plasticity induced by exposure-based learning is not robust enough to produce behavioral results. To correct for this, future directions are to extend the exposure-based learning training. The results found after exposure-based learning may also be the explained by fatigue, adaptation or testing effects. Several alterations to the experimental design could address these issues. A greater number of shorter training sessions, along with more breaks in the training could ameliorate fatigue and adaptation effects. Introducing a suprathreshold contrast discrimination practice block would allow participants to become familiar with the testing procedures without interfering with contrast learning.
Integrative video game training was successful in inducing plasticity resulting in improved visual acuity and contrast sensitivity. However, a major limitation to this data is the lack of a training control condition. We evaluated pre and post-test differences in trained and untrained individuals, however the next steps are to develop a non-adaptive suprathreshold version of the vision training program. Additionally, we trained all position players of the UCR Men’s Baseball team. In the future we would like to have equal number of trained and untrained players matched by pre-training performance. Another limitation of this design is we were not able to evaluate the retainment of the improvements induced by our training. We would like to re-test the trained players after 6-12 months, in addition to immediately after training.

Our video game based vision training program combines many PL mechanisms (including attention, reinforcement, multisensory stimuli, and multi-stimulus dimensions), however a limitation to this approach is we do not know the contribution of each mechanism. Future directions include systematically removing one element at a time from the training program, and comparing all results. Additionally, the population we used for testing limited this study. Recent work using PL has been translated to develop treatments of amblyopia (Levi & Li, 2009), presbyopia (Polat, 2009), macular degeneration (Baker et al., 2005), stroke (Vaina & Gross, 2004; Huxlin et al., 2009), and late-life recovery of visual function (Ostrovsky et al., 2006). Future directions are to expand testing of our vision training program in these populations, and to create custom versions of the program that better address the specific needs of each population.
Overall, the results of this dissertation give evidence that rules of synaptic plasticity have efficacy when applied at the behavioral level using PL mechanisms. However, work remains on establishing the best training procedures and how to relate the visual benefits produced after training to the underlying neural mechanisms. Integrating many PL approaches and using longer training paradigms produce robust, generalized improvements to vision. These results indicate normal adults exhibit sufficient plasticity in the visual system at the cellular level, and this plasticity can be induced with behavioral training. These findings provide an exciting potential for PL based video-game training to be used as a diagnosis tool and therapeutic intervention to a variety of visual conditions.
REFERENCES


COMPLETE REFERENCE LIST


