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Applications of Perceptual Learning to Ophthalmology

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1. Introduction

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. While a central concern of Ophthalmology is to address diseases of the eye (e.g. ocular impairments), an equally important component of vision is how the brain processes information that is received from the eye.

Vision is a synergistic effect of eye sensing and brain processing mechanisms. Vision can be compared to a satellite dish with the eye representing the dish or the sensor receiving aspect of the system. The eye/sensor captures light signals and transfers these signals to the brain, which is our visual processor. Through a series of brain processing stages, the image is processed by perceptual, higher order cognitive, and then motor systems resulting in decisions and responses. Thus, vision deficits can be due to eye mechanics, brain processing problems or both. Research of Perceptual Learning provides some answers and solutions for brain processing issues. This research demonstrates that the adult visual system is sufficiently plastic to ameliorate effects of low vision, including amblyopia [1], presbyopia [2], macular degeneration [3], stroke [4, 5], and late-life recovery of visual function [6]. Likewise, normal sighted individuals have the potential to further improve their vision through Perceptual Learning. These visual gains are related to brain function improvement (plasticity).

In this chapter we review the field of Perceptual Learning and its promise to achieve better outcomes in clinical practice. The significance of the development of effective, low-cost therapies to treat brain-based low vision can be life-altering for millions of people worldwide.

2. Perceptual Learning

Perceptual Learning (PL) refers to a long lasting improvement in perceptual abilities as a result of experience. Research of this topic has undergone tremendous development over the last 30 years. Plasticity in the sensory systems was previously thought to occur only in early development. This view has been substantiated by studies of a “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 ocular dominance where early patching enables inputs from the open eye to take over much of primary visual cortex, however, in adult cats patching has little impact on connectivity [7, 8]. This data was used to support the hypothesis that the low-level sensory stages need to consistently process primitive sensory features; such as in vision, orientation, spatial frequency, and local motion. However, studies of perceptual learning show that even in adults, perceptual abilities can be sharpened with repeated exposure or training. For example, perceptual abilities, including elementary processes (e.g., contrast sensitivity [9] and visual acuity [1, 2, 10, 11]) can be strengthened through appropriate training approaches.

Perceptual Learning is exemplified by long-lasting improvement on simple but difficult perceptual tasks. The effects of perceptual learning have been shown to last months, even years [12-14]. The field of perceptual learning is one of growing interest largely due to the fact training on visual perception can be highly specific to the trained visual features and can give clues into the stages of processing at which learning occurs. For example, a series of studies conducted by Schoups and colleagues [15, 16] showed that training subjects (human and monkey) on an orientation discrimination task around a particular reference orientation yielded learning effects that failed to transfer to other stimulus orientations at the trained location or that same orientation at a different retinotopic location. They postulated that these learning effects were consistent with plasticity in neurons residing in primary visual cortex, which show a high degree of both retinotopic and orientation specificity. Physiological studies by this group confirmed these predictions with the demonstration of plasticity of orientation tuning across early visual cortex [15, 17]. Consistent with this, numerous behavioral studies show perceptual learning can be highly specific to a wide range of trained stimulus features including retinotopic location [18, 19], visual orientation [15, 20] and direction [12, 19], among others. Likewise, many neuroscientific studies provide evidence of sensory plasticity in all stages of visual processing through single-unit recording in monkeys [15, 21-23] and fMRI signal changes in humans [24-26].

An important caveat is that psychophysical studies of perceptual learning are only a rough tool for making inferences of the underlying neural structures. Accordingly, physiological studies demonstrating low-level perceptual learning typically fail to explain the magnitude of the behavioral changes [27] and some models of perceptual learning demonstrate that channel reweighting in the readout of sensory areas can account for some aspects of perceptual learning specificity without requiring plasticity in primary sensory areas [28-31]. Other studies have found plasticity in higher-level visual areas that were originally hypothesized to be lower level features [14, 32-34]. For instance, Law and Gold [33] failed to find plasticity in monkey area

middle temporal cortex (MT), but found learning effects in a later area (lateral intraparietal cortex; LIP) that largely explained behavioral changes after training in a visual motion task. Likewise, learning in visual area V4 has been found to be more robust than that in V1 [17, 22, 32, 35, 36]. Also, some aspects of learning could be taking place in other brain regions, an interesting case was recently found in which the superior colliculus [37, 38] and frontal brain areas [39] develop tuning to motion directions after extensive training. While the exact locus of visual plasticity in a given study is often an issue of significant controversy, as a whole these studies give indication that plasticity is likely occurring at all stages of visual processing; although with a distribution that varies across tasks and training paradigms.

3. Perceptual Learning as a method to improve vision

Software programs integrating perceptual learning are being utilized more frequently to optimize outcomes in specific visual conditions, both in research/clinical studies and commercially. Using computer generated visual stimuli presented in repetitive patterns, users interact with visual stimuli and the training process induces neurological visual system plasticity and patient benefits. The observed benefits can include increased neuro-adaptation to new visual environments, improved contrast sensitivity and increases in spatial or visual acuity. Recent research provides examples of perceptual learning techniques that result in visual improvements for a variety of visual conditions.

4. Amblyopia

Amblyopia results in a lack of stereovision and poor vision in the amblyopic eye (even after the optics of the eye, and misalignment between the eyes, are corrected). Amblyopia impacts 2-3% of the population and is conventionally considered untreatable in adults. The gold standard for treating amblyopia is to restore stereovision. To accomplish this, (1) cortical processing of the amblyopic eye needs to be strengthened, (2) suppression from the non-amblyopic eye needs to be lessened, and (3) binocular integration needs to process correctly in the visual system. Amblyopia is typically treated only children, where traditional approaches focusing on patching or the use of atropine in the non-amblyopic eye, with no treatment attempted in adults due to a believed lack of plasticity.

However, recently perceptual learning paradigms have been found to be effective in improving acuity and stereopsis in adults, and in children where traditional patching was unsuccessful [40-42]. More recently there has been focus on binocular interactions in amblyopia with push-pull trainings that put the eyes in competition successfully lessening suppression in the amblyopic eye [43, 44], or binocular integration, which trains the two eyes to work better together [45]. Perceptual learning techniques, or more recently commercial video games [46], have also been found to reduce crowding [47], and improve spatial frequency and contrast discrimination, which also transferred to untrained spatial frequencies in adults with amblyo-

pia [48]. Together these approaches have led to numerous examples which demonstrate substantial benefits in vision in the amblyopic eye and provide great promise for future perceptual learning based treatment approaches.

5. Age-related Macular Degeneration (AMD)

Age-related Macular Degeneration (AMD) is the leading cause of central low vision in adults. The prevalence of AMD increases after age 50, and is expected to affect nearly three million Americans by 2020 (*The Eye Diseases Prevalence Research Group, 2004*). AMD patients suffer a retinal disorder in which photoreceptors are damaged or displaced, resulting in visual field loss, spatial distortions to the visual field, and impairments of acuity and contrast sensitivity. Despite a range of treatments to arrest the progress of AMD, damage to the retina cannot be reversed, resulting in a need for effective visual training therapies. There are a number of studies that show both functional learning in the development of preferred looking points [49-51] and cortical reorganization in foveal responses to peripheral stimuli [3, 52]. Difficulty reading is a common complaint in AMD patients due to the central vision loss. Recently, Chung [53] demonstrated that perceptual learning could improve reading speed in these patients after training. Additionally, Liu et al [54] trained profoundly visually impaired individuals (including AMD, glaucoma, retinitis pigmentosa, and other conditions) on a visual search task. Search speed and accuracy improved after training, effects that remained for at least one month.

While, there are limited perceptual-learning studies in AMD patients and it is unclear the extent to which normally occurring reorganizations are driven through use-dependent mechanisms [55], there is significant potential benefit to applications of perceptual learning in AMD.

6. Age related visual decline

It is well documented that vision declines with age [56]. Deficits are seen in many aspects of vision including eye optics, luminance, contrast, orientation, motion processing, form, scene and depth perception, and optical flow. Recent research has found perceptual learning can improve visual performance in older individuals. For example, after training on a visual discrimination task older participants improved up to the same performance level of untrained college age participants, with improvements lasting at least 3 months after training [57]. Additionally, older individuals improved on a motion detection task (either drifting sine wave gratings or random dot motion), and learning transferred to the untrained motion type [58].

The most common age related visual deficit is presbyopia. Presbyopia is a progressive normal aging process where the elasticity of the lens of the eye is reduced [59]. Although the decrease in elasticity of lens starts at birth, this condition, noticed by most people in their early 40's, manifests as a reduced ability to focus on nearby stimuli and a reduction of contrast sensitivity

[2]. There is no cure for presbyopia. Typical treatments are reading glasses or multifocal lenses, contact lenses or more recently, surgery like the Laser-Assisted in Situ Keratomileusis (LASIK). While treatments do exist, their use can be inconvenient for some as many treatments are not ideal for all daily activities, or can represent a significant challenge to others. All treatment options of presbyopia induce further reduction in optical contrast [60, 61]. Additionally, the use of multifocal lenses (common form of therapy) introduces unnatural viewing conditions where the point of focus depends upon gaze angle and optical aberration in transition regions. Of note, encouraging research from Polat and colleagues [62] suggest perceptual learning can ameliorate the effects of presbyopia, and in some cases, enable mild presbyopes to read without glasses. After training on a contrast detection task using Gabor patches of a range of spatial frequencies participants improved near vision acuity, reading speed, contrast detection and discrimination without changing the optics of the eye.

In general, perceptual learning also shows great promise for conditions for which there are no standard treatments. These include the conditions mentioned above as well as other low-vision conditions such as glaucoma, night vision deficits, retinitis pigmentosa, low myopia, diabetes, etc., as well as a complement to medical technologies such as LASIK, intraocular lens implantations, retinal implants, and other treatments that yield improvements in vision but for which suboptimal cortical processing leaves patients without the full potential benefit of the optical improvements that they've gained.

7. Applying Perceptual Learning in ophthalmology practice

As eyecare technology advances, so do patient expectations. Optimizing outcomes and managing expectations is a consistent challenge in clinical practice. Eye practitioners agree that good vision promotes healthier lifestyles [63], aids educational processes [64] and visual impairment is detrimental to life itself [65, 66]. An international online survey sponsored by Bausch and Lomb called NSIGHT (Needs, Symptoms, Incidence, Global Eye Health Trends) found that "seeing better" was the most important consideration for choosing vision products. Patients prefer vision related products that emphasize vision improvement, therefore therapy goals need to involve products and methods to improve vision to a maximum. Clinicians pay tremendous attention to the "eye side" of the visual system but emerging research shows that we need to pay more attention to the neurological or brain processing aspect of vision which lies outside of conventional treatments.

Vision training is not a new phenomenon in Ophthalmology, eye exercises have been used for hundreds of years. The most common vision training procedures, currently and traditionally, focus on exercising the optics of the eye (e.g. flippers, prisms, and alternating fixation between distances). However these techniques lack reliable evidence of success [67]. Alternatively, recent perceptual learning based software intervention programs for eye related disorders have shown great promise and there is increasing evidence of their efficacy. Historically reserved for database and assessment tool functions, eyecare software is expanding rapidly into therapeutic interventions and treatment. Computer software is now finding real world

use in the visual world of binocular disorders, amblyopia, neuro-rehabilitation and visual enhancement. Researchers and software developers are encouraged by research showing that specific software use actualizes the potential of the visual system and translates into real life gains. Therefore, the science of improving brain processing is not only relevant but utilizing these tools to treat these disorders can prove life changing. With that said, not all computer programs produce positive visual benefits and the results derived from training can vary from individual to individual. In other words, a simple software program may create entertainment but does not necessarily create real world vision improvement.

Here, we highlight a few perceptual training products currently on the market that doctors are using to help patients.

GlassesOff is an iOS app that enhances contrast sensitivity. Studies have found that contrast sensitivity decreases in disease states but also diminishes with age [68, 69]. Therefore, presbyopia is a combination of both decreased accommodation but also decreased contrast sensitivity. GlassesOff reports several studies on their website related to their product. A recent study found acuity and contrast sensitivity improved in presbyopes after using GlassesOff for approximately 3 months [62]. A perceptual learning technique called “collinear facilitation” is utilized to strengthen neural connections and reduce visual noise. The reduction of visual noise then increases visual clarity. It claims a 90% success rate for dismissing glasses for reading. For more information see glassesoff.com.

Nova Vision is a home computer training program used to reduce visual field deficits and provide visual benefits to patients suffering from the effects of stroke and traumatic brain injury. Nova studies show that visual field can be expanded an additional 5% over time [70]. According to another study, 75% of the trainees reported improved mobility after training [71]. Ideal training consists of using the technology twice daily for 30 minutes a session for approximately 6 months. One can find more information at Novavision.com.

RevitalVision/NeuroVision was developed to aid doctors in the treatment of amblyopia, presbyopia and cataract surgery. RevitalVision has also been used to enhance the vision of sports athletes. Depending on the visual condition, the program requires 40 training sessions for the treatment of amblyopia and 20 sessions for other conditions. Three sessions are recommended weekly and each session lasts up to 30 minutes. Stated benefits include increased contrast sensitivity, enhanced visual acuity, reduction in haloes and improved sense of night vision [72]. The program is used at home on a Windows PC. Some doctors are prescribing the technology to patients to accelerate adaptation to altered visual states due to cataract or LASIK surgery. For more information see Revitalvision.com

ULTIMEYES is a recent application that works on a home computer (Windows PC, Apple Mac) or iOS or Android to train vision. Implementing recent neuroscience advances, ULTIMEYES training combines paired visual and auditory stimuli and was designed in a video-game like way, to make the training more enjoyable for the patient. Benefits include improved contrast sensitivity, enhanced visual acuity, increased night vision and a reduction of haloes. Training time requires 4 weekly sessions for a total of 30 sessions, and each training session takes approximately 25 minutes to complete. A recent study found improved acuity and

contrast sensitivity in normal sighted individuals after 2 months of ULTIMEYES training [10]. ULTIMEYES has also been used in the treatment of low vision conditions including presbyopia, amblyopia, post-LASIK rehabilitation, and post-cataract surgery rehabilitation (especially effective for multifocal patients), and with athletes for improved sports performance [11]. For more information see Ultimeyesvision.com.

This is not an exhaustive list of available technologies but gives the reader an idea of commercially available products using software technology to tune brain processing and create better visual performance.

8. Principles of Perceptual Learning

An important question in evaluating studies of PL, is how do we know *what* to learn? In other words, how does a neural system know which information is behaviorally relevant and which is not? Given that plasticity can occur in adult sensory systems, there must be some mechanism that gates what is learned (i.e. to control what aspects are allowed and what aspects are restricted). In the following sections, we review different mechanisms and approaches that help guide perceptual learning.

8.1. Attention

Attention refers to a set of fundamental mental process that selectively modulates the processing of relevant information over irrelevant information; it informs decisions, guides memory processes, and our executive control to direct resources to act upon the world. A common belief is that perceptual learning cannot occur without persistent and intensive attention to the feature to be learned [73]. Profound learning effects are often present for task-relevant features but are typically absent or very limited for the task-irrelevant and unattended features. For example, Ahissar and Hochstein [74] found no or little transfer of learning effects between two tasks that involved judgments on different stimulus attributes (either orientation of local elements or global shape) of the same stimuli. It was also reported that the ability of subjects to discriminate the orientation of a line did not improve when the brightness rather than orientation of the line was attended [75]. Additionally, a single-unit recording study in monkeys found neuronal plasticity manifested as a change in the orientation tuning curves of V1 cells with receptive fields overlapping the spatial location of the training task. No plasticity was found for cells with receptive fields overlapping the location of task-irrelevant stimuli presented at a different location from those relevant to the task [15]. While in the next section we'll discuss how attention to stimuli is not actually required to achieve on those stimuli, nonetheless attention plays an important role in selecting what we do (and do not) learn.

8.2. Reinforcement

Theories of reinforcement learning show that rewards and punishment sculpt when and what we learn. 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. For example, in a natural environment a target (e.g., a predator) to which one needs to direct attention is usually presented in the same or similar context. Thus, gaining higher sensitivity to features in such a context may lead one to more easily notice that he/she is in the environment in which a target tends to appear and to better recognize the target [e.g. 76].

Recent research demonstrates the fundamental importance of reinforcement processes in guiding perceptual learning. For example, the research paradigm of “task-irrelevant perceptual learning” shows that sensory plasticity occurs without attention being directed to the learned stimuli, and even for those that participants are not aware [19, 77-88]. Seitz and Watanabe [84] found that a sensitivity enhancement occurred as the result of temporal-pairing between the presentation of a subliminal, task-irrelevant, motion stimulus and a task-target. In this experiment, four different directions of motion were presented an equal number of times during the exposure stage, but a single direction of interest was consistently paired (temporally preceded and then overlapped) with the task-targets. Learning was found only for the motion-direction that was temporally-paired with the task-targets, not for the other motion-directions. Similar results were obtained when the luminance contrast of the dots (100% coherence) was made so low that the subjects did not notice the presentation of the motion stimuli [81]. These results suggest that task-irrelevant perceptual learning does not occur as a result of purely passive exposure, but that the irrelevant feature must be related to task performance. These results have led to the idea that plasticity is gated by confluence between a spatially diffusive task-related signal and a task-irrelevant feature signal [79]. Later research confirmed this idea by demonstrating that task-irrelevant perceptual learning can arise through pairing a stimulus with a liquid reward [80].

Seitz and Watanabe [79] 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, task-irrelevant perceptual learning has been shown to be a robust learning phenomenon that generalizes to a wide range of stimulus features, for example, motion processing [19], orientation processing [89], critical flicker fusion thresholds [82, 83], contour integration [90], auditory formant processing [91], and phonetic processing [92]. Importantly, task-irrelevant perceptual learning produces learning effects that are often as strong, and sometimes stronger, than learning effects produced through direct training [91, 93]. While the phenomenon of task-irrelevant perceptual learning has been studied in most detail in the case of low-level perceptual learning, recent research has identified a high-level, fast form, of task-irrelevant perceptual learning (fast-task-irrelevant perceptual learning) [94-101]. In this fast-task-irrelevant perceptual learning paradigm, participants conducted target detection tasks (looking for a target, letter, color, or word among a series of distractors), while also memorizing other stimuli (images, pictures) that were consistently paired with the stimuli of the target-detection task. Similar to task-irrelevant perceptual learning for low-level

perceptual learning, visual memory was enhanced for stimuli that were paired with the targets of the target-detection task. Thus task-irrelevant perceptual learning is arguably a basic mechanism of learning in the brain that spans multiple levels of processing and sensory modalities.

While we have discussed attention and reinforcement as separate processes, this distinction may be overly simplistic (e.g. [79, 86]). For example, the orienting of attention, in the direction of the target-arrow, has been linked with the acetylcholine neuromodulatory system [102]. The same neuromodulatory system has been suggested to have an important role in learning: some studies indicate that a reduction of the cholinergic input reduces cortical plasticity [103] and impairs learning [104-106]. However, other neuromodulatory systems, such as dopamine and norepinephrine have also been linked to both attention [107, 108] and to learning [109, 110]. Indeed, these three neuromodulators (acetylcholine, norepinephrine, and dopamine) have been linked to the three attentional systems described by Posner and Petersen (1990): the alerting network that involves temporal cueing and the maintenance of an alert state (norepinephrine; [111-113]; the orienting network that spatially selects information from sensory input (acetylcholine; [102]; and the executive control network that resolves conflict among responses (dopamine; [114]). These studies indicate that attention and reinforcement are deeply interrelated and that a good training approach should aim to direct both attention and reinforcement in a manner to promote learning.

8.3. Applying rules of synaptic plasticity

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) [115]. 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. Conversely, long-term depression (LTD) is induced by persistent low frequency electrical stimulation, resulting in weakened synaptic connections.

Recent research has established that non-invasive exposure-based stimulation protocols can be applied to the sensory systems and result in plasticity of the corresponding sensory cortices. 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 [116]. 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 [117]. Using a visual stimulation protocol Beste and colleagues [118] 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 orien-

tation 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. These studies of exposure-based learning provide a clear connection between the animal model and the human system, and suggest that approaches based upon knowledge of synaptic plasticity can be applied to improved perception in humans.

8.4. Multisensory facilitation

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 [119-123]. 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 subjects trained with auditory-visual stimuli exhibit a faster rate of learning and a higher degree of improvement than found in subjects trained in silence [124, 125]. Critically, these benefits of multisensory training are even found for perceptual tests *without* auditory signals. In other words, *multisensory training facilitates unisensory learning*. While, to date, most vision training procedures either don't include sounds as part of the task (other than as feedback) or include sounds that are not coordinated with visual stimuli, the advantage of multisensory training over visual-alone training is substantial; reducing the number of sessions required to reach asymptote by ~60%, while also raising the maximum performance [126]. We suggest that having complementary information about the target objects come from different sensory modalities allows the senses to work together to facilitate learning.

8.5. Promoting transfer of learning

Classically, a translational barrier to perceptual learning has been its high degree of specificity to trained stimulus features [127]; such as orientation [20], retinal location [128] or even the eye of training [80, 129]. For example training with a single visual stimulus at a single screen location can result in learning that is specific to that situation. While such studies have been informative regarding the mechanisms of learning, specificity limits therapeutic benefits.

Recent research suggests methods of how this "curse of specificity" can be overcome. Approaches that depart from the most simple training approaches, such as those using multi-stimulus training [130, 131] and off-the-shelf video games [132, 133] show a greater generalization of learning. For example, the recently developed technique of 'double training' found that the specific learning effects found in their paradigms can show broad transfer when

more than one stimulus attribute is trained at a time. Xiao, Zhang [131] trained participants on the Vernier discrimination task at a specific orientation at a specific location in the visual field, which normally yields location and orientation specific learning effects [129]. But when they subsequently trained a second orientation at a different spatial location, they found that the training induced changes for the second orientation transferred to the first location. Such findings of broad location transfer undermine the argument that this learning is due to plasticity in retinotopic visual areas.

There exist a growing number of studies that address how specificity, or its opposite, transfer, is controlled by different factors. In a discrimination task, Jeter, Doshier, Petrov and Lu [134] showed that transfer was observed in low-precision transfer tasks while specificity was observed in high-precision transfer tasks. Then, Jeter, Doshier, Liu and Lu [135] showed that specificity was the result of an extensive training, confirming more classical results [20, 128, 136], while a substantial transfer was observed at early in the training. Interestingly, another study, reported by Aberg, Tartaglia and Herzog [137] presented a series of experiments showing, in one hand, that the number of trials per session influenced the overall improvement of the participant's performance, and in another hand, the transfer depended on the number of trials presented during each session, not the total number of trials. Zhang *et al.*, [138] showed a peripheral orientation discrimination task transferred to new locations only after a pre-test was given to participants. These studies add to the double-training studies that show transfer after training multiple features or at multiple locations [130, 131]. Together these studies show that many factors (extent of training, blocking of trials, precision of training stimuli, diversity of training set, etc), influence the transfer of learning.

9. Conclusion

While extant applications of perceptual learning to Ophthalmology show great promise, a limitation of modern perceptual learning research is that learning is studied in very specific ways, focusing on one particular stimulus or factor. This narrow focus has limited understanding of the multiple learning factors that are present in natural settings and how these factors interact to determine the speed and nature of learning. We suggest a new paradigm of integrating perceptual learning methodologies into a coordinated approach that achieves a more comprehensive form of perceptual learning than typically studied in the lab. For example the approach used in the ULTIMEYES program combines many factors that are known to promote neural plasticity and generalization of learning [10, 11]. Furthermore, findings that playing off-the-shelf video games can improve vision [132, 133, 139] suggests another avenue of research where principles derived from video games should be combined with those from the field of perceptual learning to create an enriching user experience that encourages compliance with treatment while effectively optimizing how the brain process its ocular inputs.

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