Review

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Enhancement of visual perception by combining transcranial electrical stimulation and visual perceptual training

Abstract: The visual system remains highly malleable even after its maturity or impairment. Our visual function can be enhanced through many ways, such as transcranial electrical stimulation (tES) and visual perceptual learning (VPL). TES can change visual function rapidly, but its modulation effect is short-lived and unstable. By contrast, VPL can lead to a substantial and long-lasting improvement in visual function, but extensive training is typically required. Theoretically, visual function could be further improved in a shorter time frame by combining tES and VPL than by solely using tES or VPL. Vision enhancement by combining these two methods concurrently is both theoretically and practically significant. In this review, we firstly introduced the basic concept and possible mechanisms of VPL and tES; then we reviewed the current research progress of visual enhancement using the combination of two methods in both general and clinical population; finally, we discussed the limitations and future directions in this field. Our review provides a guide for future research and application of vision enhancement and restoration by combining VPL and tES.

Introduction

For both healthy and clinical populations, the visual system preserves a high capacity for plasticity even after maturity. To date, there are multiple methods that can induce visual plasticity, such as rapid visual stimulation [1], visual deprivation [2], action video game [3], visual perceptual learning (VPL) [4], and transcranial electrical stimulation (tES) techniques [5]. Since some methods which can induce neuroplasticity share similar principles (e.g., both VPL and tES are assumed to be able to induce long-term potentiation (LTP)-like plasticity [6, 7], applying multiple methods simultaneously to induce greater plasticity becomes feasible in practice. Therefore, in this review, we will focus on the current research progress of visual function enhancement by combing VPL and tES techniques in healthy adults as well as patients with neuro-ophthalmological disorders; in other words, VPL-induced vision enhancement further augmented by tES techniques.

Visual perceptual learning

Practice makes perfect. This principle is also applicable in sensory information processing. Repetitive practice on vi-

persistence, and (3) lack of generalization (or transfer). It has been well evidenced that performance on almost every visual task can be improved after extensive training, from detection or discrimination of basic stimulus feature to identification or recognition of complex image and natural stimulus [10], indicating that VPL is a ubiquitous phenomenon in visual science [11]. Next, the learning effect can last for a long time after the end of training. For example, in He et al.'s study on an orientation discrimination task, subjects' performance on the trained task achieved a substantial improvement and kept stable toward an asymptote after five training sessions and the acquired performance can be preserved even more than one year later after the initial training [9]. This long-term persistence of learning effect demonstrates that the encoded engram is transformed into long-term memory system after well-consolidation [12]. From the time scale of visual plasticity, the long-term persistence of VPL is a critical feature that is different from other forms of visual plasticity, such as visual adaptation [13]. Moreover, the long-term effect of plasticity is one of key factors that constrain the application of VPL in clinical practice [9]. Last, but certainly not least. The lack of generalization means that the learning effect in the trained condition cannot or only small partially transfer to untrained conditions (Figure 1). In other words, the effect of acquired learning is highly specific to the training settings. For example, in an orientation discrimination task, behavioral performance on the trained task increases with training, and manifests as a declined discrimination threshold (or raised accuracy), and/or reduced reaction time while performance on the untrained orthogonal orientation remains unchanged. Multiple factors have been found to be associated with the transfer of VPL, such as the task difficulty [14], task precision [15], task type [16], and training amount [17]. The lack of generalization makes VPL different from other forms of learning, such as language learning, and attracts a lot of interest [18].

Numerous studies have been conducted to explore the neural substrates of VPL. It has been suggested that VPL occurs at multiple loci in the brain, from subcortical nuclei to high-level cortical areas involved in decision-making or attention [19–24]. The occurrence of VPL is manifested in various forms, such as enhanced neural response [25, 26], refined neural representation [27, 28], sharpened tuning curve [29, 30], and channel reweighting from sensory inputs to decision units [20, 31–33]. For more information about the neural mechanisms of VPL, see Refs. [8, 34, 35].

VPL is a typical example of visual cortical plasticity in humans. Typically, the principle of VPL has not only been applied to improve visual skills in people with normal or corrected-to-normal vision, but also to rehabilitate vision for individuals with degraded or impaired vision, such as patients with amblyopia [36, 37], cortical blindness [38–40], age-related macular degeneration (AMD) [41, 42], myopia [43, 44], presbyopia [45, 46], and glaucoma [47–49]. In addition, VPL can be applied to enhance visual skills in some special scenarios, such as military action [50],
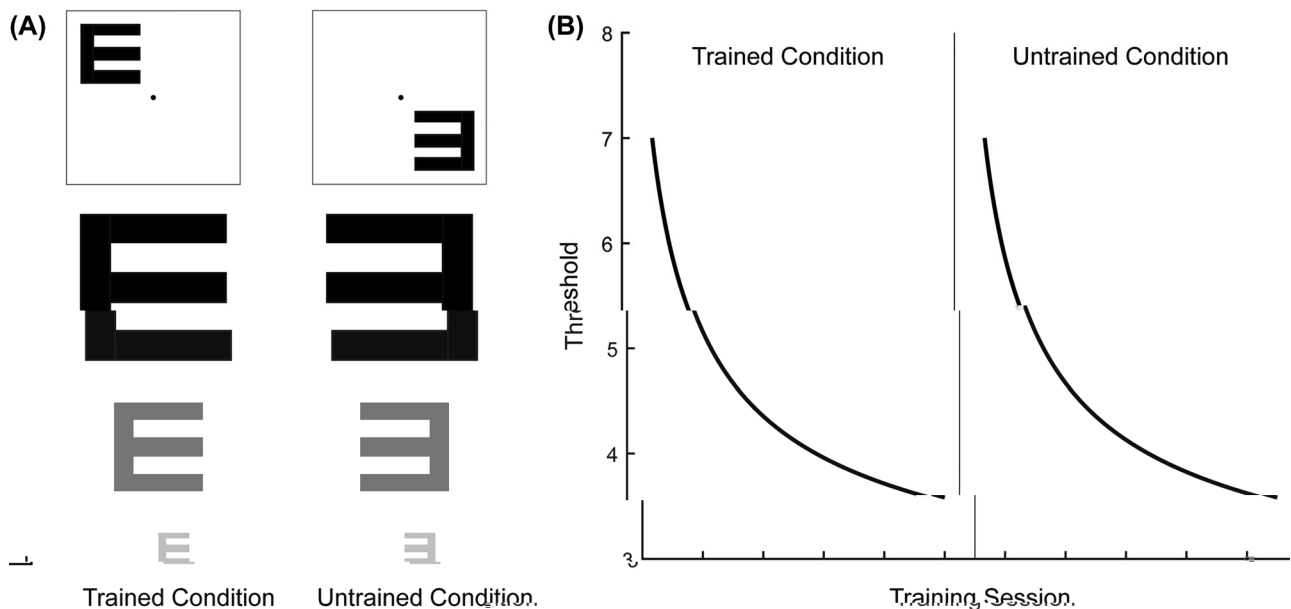
Figure 1: Illustration of the specificity of VPL. (A) During training, visual stimuli are presented at a given location, i.e., the trained location. Here tumbling 'E's are used as trained stimuli. The intensity of the trained stimulus, e.g., the size or contrast, is varying trial-by-trial. To investigate the transfer of learning, in the test condition, visual stimuli are presented at an untrained location and/or with a different orientation. (B) The learning curve in different conditions. In the trained condition, the intensity of stimulus declines with training. When another training is implemented at the initially untrained condition, the task performance on this condition returns to baseline at the early stage of training, i.e., the intensity of stimulus returns to a high value, which is equivalent to that in the initially trained condition. Then the intensity of stimulus in the later trained condition decreases with training.

diagnostic medical imaging [51], and sports training [52]. For more information about the application of VPL, see Refs. [53, 54].

Transcranial electrical stimulation

With the advancement of biomedical engineering, there has been an increase in the development of non-invasive brain stimulation (NIBS) techniques. As NIBS techniques can modify brain activities in a non-invasive and safe manner and enable researchers to causally modulate related behavioral performance, they can thus be used to probe causal links between cognitive processes and brain activities of specific cortical regions [55, 56]. In line with this, NIBS techniques can help us better understand the neural mechanism of brain function and can also enhance brain function for both healthy and clinical populations. NIBS techniques have been widely applied in both basic neuroscience as well as translational application studies across a broad range of fields including visual function [5, 57, 58]. NIBS techniques include a range of neuromodulation techniques, such as transcranial magnetic stimulation (TMS) techniques, transcranial electrical stimulation (tES) techniques, and transcranial focused ultrasound stimulation (tFUS) techniques [59]. Among NIBS techniques, tES techniques are particularly noteworthy. TES techniques apply weak electrical currents directly over the scalp and accordingly modify brain activity underneath the electrodes. According to the property of current flow, tES techniques can be classified into diverse types. In this review, we focus on the following three: transcranial direct current stimulation (tDCS) technique, transcranial alternating current stimulation (tACS) technique, and transcranial random noise stimulation (tRNS) technique (Figure 2).

TDCS

TDCS delivers direct constant currents of low intensity through one or multiple active electrode(s) [60]. The currents then pass through heads from active (anode) electrodes to reference (cathode) electrodes. According to polarity, tDCS can be divided into two subtypes, i.e., anodal tDCS and cathodal tDCS. TDCS can modify spontaneous and/or evoked brain activities in a polarity-specific manner. Anodal tDCS and cathodal tDCS is assumed to induce depolarization and hyperpolarization on the targeted neuronal populations and consequently increase and decrease the cortical excitability of stimulated brain regions, respectively [61, 62]. The changes in brain activity induced by tDCS were found to be dependent on the regulation of brain metabolite concentration. Specifically, anodal tDCS can decrease the concentration of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [63–65], and/or increase the concentration of excitatory neurotransmitter glutamate and glutamine (Glx) [66–68], while cathodal tDCS can decrease the concentration of glutamate [64, 65, 68]. The neuroplasticity induced by anodal and cathodal tDCS are thought to be manifested through the induction of long-term potentiation (LTP) and long-term depression (LTD)-like plasticity, respectively [69].

TACS

TACS releases alternating currents which oscillate at a given frequency [70]. Studies in human and non-human primates have demonstrated that tACS is able to entrain ongoing brain rhythms of targeted cortical areas in a frequency-specific manner. To date, it is still not completely understood how tACS modulates our brain oscillations. Studies found that
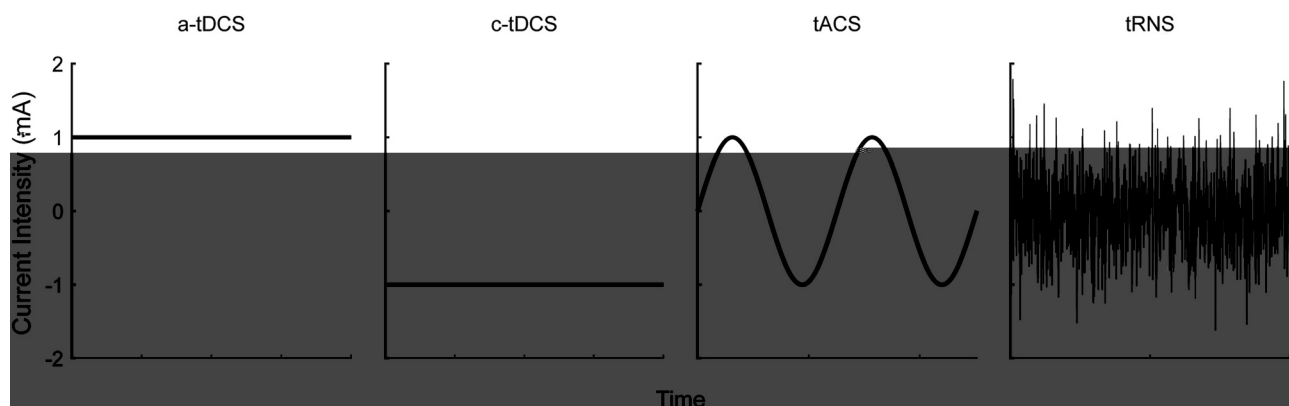
Figure 2: Illustration of different types of tES techniques. The current intensity of tDCS keeps constant with stimulation time. The current intensity of tACS changes at a constant alternating frequency. The current intensity of tRNS changes with stimulation time at random frequencies. tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; tRNS, transcranial random noise stimulation.

rhythmic alternating currents can alter the spike activity of the stimulated neurons, such as firing timing [71–73], firing rate [74, 75], and firing phase [76–78]. These findings suggest that the modification of spike activity induced by tACS plays a critical role in changing oscillatory activity of the stimulated neurons. Accordingly, changes in neural power spectra and/ or phase coherence were observed after tACS [79–82]. For example, in a human electroencephalographic (EEG) study, Zaehle et al. [83] found that individuals' endogenous alpha power was elevated by a 10-min tACS which was applied over the visual cortex at individuals' peak alpha frequencies. Similar frequency-specific entrainment in neural oscillation was also observed in other conditions, such as stimulation frequency bands [84], cortical regions [85], and neurophysiological methods [86].

TRNS

TRNS delivers alternating currents which oscillate at random frequencies (typically from 0.1 to 640 Hz), and it can be divided into low-frequency (0.1–100 Hz) tRNS and high-frequency (101–640 Hz) tRNS according to frequency range [87]. With respect to the neural mechanism underlying tRNS, two hypotheses have been proposed. The first one is the stochastic resonance hypothesis. The stochastic resonance refers to a phenomenon in which the ability to detect weak signals of a nonlinear system can be improved under the effect of weak random noise. In the neural system, an optimal amount of noise added to a subthreshold signal renders the stimulus above the system threshold [88], and gives rise to a higher signal-to-noise ratio [89]. TRNS is a powerful tool to add random neural noise to the stimulated cortical region [90, 91]. The alternative hypothesis is proposed based on the activation and inactivation of sodium channels. An *in vitro* electrophysiological study showed that extracellular voltage pulses applied to neurons can activate sodium inward current [92]. Moreover, in humans, a pharmacological study found that motor cortical excitability (indexed by motor evoked potential) can be inhibited by a sodium channel blocker if tRNS was administrated after the intake of drugs [93].

The application of VPL and tES in enhancing visual function

Though the exact working mechanisms of tES are still to be clarified, many studies have been conducted to further improve visual function by combining tES and VPL in both healthy and clinical populations.

The healthy adult

The process of learning and memory consists of at least three stages: encoding or acquisition, consolidation, and retrieval [94]. Theoretically, altering the neural activity at different stages of learning and memory, related task performance at corresponding stages can be modulated consequently. Therefore, modifying brain activity by tES at different timings relative to task execution is a feasible strategy to modulate learning performance at different stages of VPL. In most VPL studies, tES was either applied concurrently with perceptual training or before training, aiming to modulate the encoding or acquisition phase of learning, which might be modulated by both direct and indirect neurophysiological effect of tES. When tES is administrated during training, the encoding or acquisition phase of learning is expected to be directly modulated by external electrical fields (online effect). Considering the property of tES aftereffect, e.g., persistence after stimulation and cumulatively with stimulation [95, 96], tES applied before task execution was supposed to modulate the encoding or acquisition of learning (offline effect). More recently, tES was adopted after the initial training, a critical period of learning consolidation, to modulate VPL [97, 98].

This section looks at the advances in modulating visual performance on the trained task by tES in situations where neural activity and related perceptual performance at different stages of VPL was assumed to be changed.

TES administrated before and after task execution

TRNS

At present, among tES protocols concerning the working mechanisms involved in inducing neuroplasticity, tRNS is the least known. Still, when it comes to the efficacy in modulating VPL, tRNS is the most efficient tool to further enhance visual function when combined with visual perceptual training. Overall, compared with sham stimulation condition, studies found that while high-frequency tRNS (101–640 Hz) was effective in boosting VPL, no such facilitatory effect was found when low-frequency tRNS (0.1–100 Hz) was applied.

Enhancing visual function by combing VPL and tES was first implemented in an orientation discrimination learning study [99]. Specifically, a between-subjects design was adopted in this single-blind sham-controlled study.

Different types of tES techniques were applied, in one single training session consisting of multiple blocks, over the visual cortex while subjects were executing the trained task. The results showed that after training, subjects who were stimulated by high-frequency tRNS showed higher perceptual sensitivity than sham condition and other stimulation conditions, such as tDCS and low-frequency tRNS [99]. Moreover, in this seed study, subjects who were stimulated by high-frequency tRNS, had a higher performance on the trained task than in other stimulation conditions from the first training block on; however, the learning rate in the high-frequency tRNS group across all training blocks was not significantly higher than that of other stimulation groups [99]. While later studies found that with only one training session where tRNS was applied, the learning progress was faster than that in the sham condition, such as in the case of the visual temporal attention task [100] and the orientation discrimination task [101]. Notably, in VPL studies, one single session of training does not refine visual performance necessarily. Learning does not occur within one single training session, but through (between) sessions with nocturnal sleep or diurnal nap, such as in the texture discrimination task (TDT) and orientation discrimination task [102, 103]. Similarly, in the case of tES, the modulatory effects induced by tES with a number of sessions were better than that with those achieved by one session only. Thus, visual function will see a greater improvement when multi-session training or tES is implemented in comparison with when only one session intervention is administrated. This hypothesis was validated by later studies.

There is a growing number of studies that have found that tRNS is able to make subjects learn faster and finally gain more improvements when it was delivered concurrently with perceptual training across multiple sessions. For example, in a motion direction integration task, subjects were trained to identify the direction of moving stimuli in the period of 10 daily sessions. The results showed that subjects who received high-frequency tRNS during training had a higher learning rate and a higher improvement percentage on the trained task than that under control conditions (including sham stimulation, non-stimulation and active stimulation over other cortical areas). The enhanced performance could last up to at least six months after the training, which demonstrates the long-term persistence of tRNS-facilitated VPL. Similarly, the tRNS-facilitated VPL was also observed in other training tasks, from relatively simple tasks to complex tasks, such as the orientation discrimination task [104], numerosity judgment task or number acuity task [105, 106], and peripheral letter identification in crowding condition [107].

in several consecutive training sessions or in one single training session which constituted of multiple blocks. This null effect was found in the orientation discrimination task [99, 101], the motion direction integration task [110], and the motion direction discrimination task [111]. However, some studies found that anodal tDCS was effective in boosting VPL, such as in the orientation discrimination task [112], object identification task [113], and coarse dot identification task of Glass pattern [114]. Notably, in some studies, investigators found that VPL was inhibited by anodal tDCS, such as in orientation identification task [115] and visual search task [116]. Other studies found that the modulatory effects of anodal tDCS on VPL might be associated with stimulation timing relative to task execution [117]. Researchers found that if anodal tDCS was administrated prior to task execution, task performance could be modulated by tDCS which suggests that the offline effect of tDCS was effective in modulating VPL [116, 117]. The tDCS delivered prior to the trained task may induce priming effects which facilitate further changes in neuroplasticity.

Regarding cathodal tDCS, it is less adopted in VPL studies, given that cathodal tDCS is assumed to decrease cortical excitability of targeted brain regions and to inhibit related behavioral performance. In the field of VPL, researchers are more interested in further improving, instead of inhibiting or disrupting, visual perception. Only a few studies have been conducted to explore the role of cathodal tDCS in modulating VPL. To date, no study has shown that VPL can be disrupted or suppressed by cathodal tDCS [99, 116]. In contrast, some studies found that performance on the trained tasks could be further improved with cathodal tDCS [114, 118].

These results suggest that the direction of modulatory effects induced by tDCS are not simply determined by the polarity of tDCS, but might be associated with the mechanisms of the trained task [114].

TACS

One study has recently found that tACS was able to boost VPL effectively in a stimulation frequency and location-specific manner [9]. Specifically, He et al. found that when tACS at 10 Hz over the visual cortex was administrated during task execution, it could accelerate visual orientation discrimination learning and promote performance gains efficiently. But the facilitatory effects were absent when tACS was applied at other stimulation frequencies or over other cortical regions. In addition, the enhanced visual performance lasted more than one year after training [9].

TES administrated after task execution

TES applied following task execution was also efficient in modulating VPL. The physiological after-effects induced by

including both spatial and temporal vision, such as visual acuity [122], spatiotemporal contrast sensitivity function [123], visual motion [124], and visual search [125].

With respect to clinically translational application of VPL, the recovery of impaired vision for patients with amblyopia is the most successful one. It has been demonstrated that after extensively targeted training, multiple visual functions can be recovered, such as visual acuity [37], stereopsis [126, 127], contrast sensitivity function [37, 128], visual motion [129], binocular vision [130, 131], and letter identification [132, 133]. Moreover, different training methods were developed to recover vision for patients with amblyopia [134], such as monocular training [135], dichoptic training [127], and video game-based training [136].

The application of tES techniques during executing the trained task is a novel strategy that can further improve vision by boosting VPL. In a double-blind, sham-controlled cross-over study, Spiegel et al. first reported that anodal tDCS delivered over the visual cortex during a dichoptic video game training could lead subjects obtain more enhancement in stereoacuity than sham stimulation [137], suggesting that tES could enhance the therapeutic effects of perceptual learning-based treatment in amblyopia. Nevertheless, patients' impaired visual acuity, a clinical indicator of the greatest concern in ophthalmology, was not enhanced after this novel combination therapy. Whereas both visual acuity and contrast sensitivity function could be improved substantially in adults with amblyopia after extensive perceptual training in contrast detection with flankers [128]. The time course of vision recovery could be greatly shortened when

learning-like plasticity, Olma et al.'s study suggested that people with occipital stroke will obtain further improvement in visual performance when anodal tDCS was administered during training than in training without anodal tDCS [150]. While this facilitatory effect was not observed in a small sample study, in which anodal tDCS was applied over the middle temporal/V5 complex (hMT+/V5) (a motion-sensitive area) during training on a motion direction discrimination task [151]. It is still unclear what the cause for the discrepancy between the tDCS-boosted VPL studies mentioned above.

Previous studies found that tES applied during perceptual training might be able to accelerate vision recovery for patients with cortical blindness, such as having a larger expansion of visual fields and a better performance on visual tasks. However, it remains unclear how visual skills improved by this combination intervention. One possible underlying mechanism is that the spared neurons in the primary visual cortex (V1) are activated by repetitive stimuli and external electrical fields. Alternatively, under the effect of perceptual training and brain stimulation, the sub-cortical pathways of visual information processing are able to direct more projects to extrastriate cortex bypassing V1 more efficiently [4]. To develop efficient rehabilitation method, more studies with a larger sample size and a more rigorous experimental design should be adopted in the future.

Myopia

Myopia, also known as short-sightedness or near-sightedness, is typically associated with axial eye growth and refractive error development, and has been a leading public health issue in East Asia [152, 153]. Myopia, particularly for high myopia, can cause deficits in various visual functions and even blindness; more seriously, it is also associated with many serious complications [154, 155].

Studies that aim to enhance visual perception for patients with myopia via perceptual training and tES are scarce. Only several studies found that perceptual training could improve patient's uncorrected visual acuity and/or contrast sensitivity in patients with low or mild myopia with different training regimes [43, 44, 156–158], and the vision improvement could be retained for a long time [44, 156, 158] and even generalized to untrained conditions [43, 44]. Concerning the role of tES in modulating visual function in individuals with myopia, Camilleri et al. ever reported that eight daily sessions of high-frequency tRNS could increase uncorrected contrast sensitivity [138].

In Camilleri et al.'s study, when tES was delivered concurrently with perceptual training, patients obtained quicker and greater improvements in visual function than control conditions [138, 159]. Camilleri et al. found that patients with low myopia were not benefited from two weeks of contrast detection training solely, while their performance on both the trained and untrained tasks (i.e., uncorrected visual acuity and contrast sensitivity function) improved when high-frequency tRNS was administrated during training. Moreover, the amount of improvement in the trained tasks was comparable with that acquired after eight weeks of contrast detection training without tRNS [138]. This facilitatory effect of tRNS on VPL was replicated when one more control condition (i.e., training with sham stimulation) was involved in the study [159]. These studies demonstrate that tRNS can accelerate the time course of improving visual function via perceptual training for patients with low myopia. However, it is unclear whether patients with moderate or hyperopia will benefit from this intervention method, and whether patients with myopia will benefit from perceptual training with other types of tES techniques.

Future directions

Neural mechanisms

Undoubtedly, revealing the neural basis of visual function enhancement will be beneficial to the development of vision enhancement protocols. Visual function can be improved by either applying VPL or tES independently, or even improved to a larger extent by combining these two methods. It should be pointed out that the neural mechanisms underlying vision enhancement by these methods are still less understood, especially for the working mechanism of tES and its modulatory role in VPL, therefore hindering the design of precise and personalized vision enhancement protocols. Meanwhile, some studies obtained discrepant results that were opposite to the putative mechanisms of adopted tES techniques. The modulatory effects of tES on VPL may either be as a result of changes in specific circuits that involved in the trained tasks, or a general brain state (e.g., arousal or attention) by tES, or both. Furthermore, the mechanisms underlying vision enhancement in healthy adults, at least in some ways, are different to that of vision restoration in patients. If the working mechanisms underlying vision enhancement by the combination intervention are revealed, then protocols that can efficiently improve visual function should be developed.

Factors that influence modulatory effect

Over the last two decades, many meaningful research progresses have been made in both VPL and tES. However, not all intervention protocols yielded positive modulatory effect. Previous studies adopted different intervention protocols (such as, stimulation parameter and training method), which may cause inconsistent results. It has been found that many factors can affect the tES-induced modulatory effects, such as brain state [160], menstrual cycle [99], electrode location [9], stimulation timing [117], and paradigm of behavioral task [161]. Moreover, there are high variability in within-subjects and between-subjects in response to vision enhancement intervention methods. For instance, in a tDCS study, He et al. found that some subjects' visual contrast sensitivity functions were improved after one session of anodal tDCS, while opposite result was observed for other subjects, indicating that there was high inter-subject variability [161]. Additionally, for each single subject, changes in contrast sensitivity function before and after stimulation were inconsistent across different tDCS sessions, indicating that there was high intra-subject variability in responses to tDCS, and further suggesting that subjects' responses to anodal tDCS were possibly regulated by basal fabrics such as the instant brain state [161]. Therefore, with more influence factors being identified and controlled, the higher probability the response variability will be diminished, and the better modulatory effects will be achieved.

Translational application

As mentioned above, we have advances in promoting vision restoration clinically by combining VPL and tES, while some limitations exist in this field. First, a double-blind, randomized, placebo-/sham-controlled trial is still sparse. Single-blind design was adopted in most studies, and the sham condition was even absent in some studies. Moreover, the sample size was small in previous studies. To some extent, potential intervention bias was induced more likely. A more rigorous experimental design should be adopted to verify the therapeutic effect of combination intervene in recovering vision. Second, there are great individual differences in physiological and anatomical properties, though same method is adopted typically for each single subject, such that there were great between-subjects variability in responses to the intervene methods. For example, using tDCS with same stimulation configuration, there were prominent individual differences in responses to tDCS, and

thus there was no significant modulatory effect overall [162]. Developing a precise and personalized intervene protocol should be a critical step towards optimizing the therapeutic effect of this tES-aided VPL intervene in clinical practice. Finally, the combination of VPL and tES has been applied in limited conditions only. The tES-boosted VPL should be applied to improve visual skills at multiple stages of visual information processing across a wider range. Furthermore, improving visual function is not limited to recover vision for visually impaired or degraded people, but is also able to enhance task performance in special scenarios, such as military action [50], diagnostic medical imaging [51], and physical training [52].

Conclusions

Both visual perceptual training and tES techniques have been developed to enhance or restore vision for both healthy adults and people with visual impairments. Our visual perception can be further improved by combining extensive perceptual training and tES concurrently, showing prominent value in understanding neural mechanism of visual plasticity and practical application. However, more studies should be conducted in the future, especially to reveal the neural mechanisms underpinning the performance improvement by combing perceptual training and tES and to develop personalized rehabilitation protocols to make more people obtain benefits.

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References

1. Sumner RL, Spriggs MJ, Muthukumaraswamy SD, Kirk IJ. The role of Hebbian learning in human perception: a methodological and theoretical review of the human visual long-term potentiation paradigm. Neurosci Biobehav Rev 2020;115:220–37.
2. He HY, Ray B, Dennis K, Quinlan EM. Experience-dependent recovery of vision following chronic deprivation amblyopia. Nat Neurosci 2007;10:1134–6.

3. Bavelier D, Green CS, Pouget A, BavelierrPouget6(P)0(.A,)-9.erplasticit

44. Yan FF, Zhou J, Zhao W, Li M, Xi J, Lu ZL, et al. Perceptual learning improves neural processing in myopic vision. J Vis 2015; 15:12.

45. Liza SJ, Choe S, Kwon OS. Testing the efficacy of vision training for presbyopia: alternating-distance training does not facilitate vision improvement compared to fixed-distance training. Graefes Arch Clin Exp Ophthalmol 2022;260:1551–63.

46. Sterkin A, Levy Y, Pokroy R, Lev M, Levian L, Doron R, et al. Vision improvement in pilots with presbyopia following perceptual learning. Vis Res 2018;152:61–73.

47. Gudlin J, Mueller I, Thanos S, Sabel BA. Computer based vision restoration therapy in glaucoma patients: a small open pilot study. Restor Neurol Neurosci 2008;26:403–12.

48. Sabel BA, Gudlin J. Vision restoration training for glaucoma: a randomized clinical trial. JAMA Ophthalmol 2014;132:381–9.

49. Li B, Chu H, Yan L, Wiederhold BK, Wiederhold M, Lu Y. Individualized visual reality training improves visual acuity and visual field defects in patients with glaucoma: a preliminary study report. Cyberpsychol Behav Soc Netw 2020;23:179–84.

50. Falcone B, Coffman BA, Clark VP, Parasuraman R. Transcranial direct current stimulation augments perceptual sensitivity and 24-hour retention in a complex threat detection task. PLoS One 2012;7:e34993.

51. Alexander RG, Waite S, Macknik SL, Martinez-Conde S. What do radiologists look for? Advances and limitations of perceptual learning in radiologic search. J Vis 2020;20:17.

52. Deveau J, Ozer DJ, Seitz AR. Improved vision and on-field performance in baseball through perceptual learning. Curr Biol 2014;24:R146–7.

53. Deveau J, Lovcik G, Seitz AR. The therapeutic benefits of perceptual learning. Curr Trends Neurol 2013;7:39–49.

54. Lu ZL, Lin Z, Dosher BA. Translating perceptual learning from the laboratory to applications. Trends Cognit Sci 2016;20:561–3.

55. Polania R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. Nat Neurosci 2018; 21:174–87.

56. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37:1702–12.

57. Sabel BA, Thut G, Haueisen J, Henrich-Noack P, Herrmann CS, Hunold A, et al. Vision modulation, plasticity and restoration using non-invasive brain stimulation – an IFCN-sponsored review. Clin Neurophysiol 2020;131:887–911.

58. Zhang Y, Zhang Y, Cai P, Luo H, Fang F. The causal role of alpha-oscillations in feature binding. Proc Natl Acad Sci USA 2019;116: 17023–8.

59. Penton T, Catmur C, Banissy MJ, Bird G, Walsh V. Non-invasive stimulation of the social brain: the methodological challenges. Soc Cognit Affect Neurosci 2022;17:15–25.

60. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9.

61. Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol 2004;557:175–90.

62. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul 2017;10:51–8.

63. Antonenko D, Schubert F, Bohm F, Ittermann B, Aydin S, Hayek D, et al. tDCS-induced modulation of GABA levels and resting-state functional connectivity in older adults. J Neurosci 2017;37: 4065–73.

64. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical

but not β frequency sharpens multiple visual functions. Brain Stimul 2020;13:343–52.

81. Ruhnau P, Neuling T, Fusca M, Herrmann CS, Demarchi G, Weisz N. Eyes wide shut: transcranial alternating current stimulation drives alpha rhythm in a state dependent manner. Sci Rep 2016;6:27138.

82. Struber D, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. Brain Topogr 2014;27:158–71.

83. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One 2010;5:e13766.

84. Battaglini L, Ghiani A, Casco C, Ronconi L. Parietal tACS at beta frequency improves vision in a crowding regime. Neuroimage 2020;208:116451.

85. Pogosyan A, Gaynor LD, Eusebio A, Brown P. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 2009;19:1637–41.

86. Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. Nat Commun 2019;10:5427.

87. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 2008;28:14147–55.

88. van der Groen O, Tang MF, Wenderoth N, Mattingley JB. Stochastic resonance enhances the rate of evidence accumulation during combined brain stimulation and perceptual decision-making. PLoS Comput Biol 2018;14:e1006301.

89. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol 2004;115:267–81.

90. Pavan A, Ghin F, Contillo A, Milesi C, Campana G, Mather G. Modulatory mechanisms underlying high-frequency transcranial random noise stimulation (hf-tRNS): a combined stochastic resonance and equivalent noise approach. Brain Stimul 2019;12:967–77.

91. van der Groen O, Wenderoth N. Transcranial random noise stimulation of visual cortex: stochastic resonance enhances central mechanisms of perception. J Neurosci 2016;36:5289–98.

92. Schoen I, Fromherz P. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak capacitive currents on a silicon chip. J Neurophysiol 2008;100:346–57.

93. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci 2015;9:125.

94. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. Neuron 2004;44:121–33.

95. Kasten FH, Dowsett J, Herrmann CS. Sustained aftereffect of alpha-tACS lasts up to 70 min after stimulation. Front Hum Neurosci 2016;10:245.

96. Monte-Silva K, Kuo MF, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol 2010;103:1735–40.

97. He Q, Yang X-Y, Fang F. The role of anodal transcranial direct current stimulation (tDCS) in the consolidation of visual perceptual learning is mediated by the wake/sleep cycle. J Vis 2021;21:2346.

98. Yang XY, He Q, Fang F. Transcranial direct current stimulation over the visual cortex facilitates awake consolidation of visual perceptual learning. Brain Stimul 2022;15:380–2.

99. Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 2011;31:15416–23.

100. Tyler SC, Conto F, Battelli L. Rapid improvement on a temporal attention task within a single session of high-frequency transcranial random noise stimulation. J Cognit Neurosci 2018;30:656–66.

101. Fertonani A, Pirulli C, Bollini A, Miniussi C, Bortoletto M. Age-related changes in cortical connectivity influence the neuromodulatory effects of transcranial electrical stimulation. Neurobiol Aging 2019;82:77–87.

102. Karni A, Sagi D. The time course of learning a visual skill. Nature 1993;365:250–2.

103. Schoups AA, Vogels R, Orban GA. Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. J Physiol 1995;483:797–810.

104. Conto F, Edwards G, Tyler S, Parrott D, Grossman E, Battelli L. Attention network modulation via tRNS correlates with attention gain. Elife 2021;10:e63782.

105. Cappelletti M, Gessaroli E, Hithersay R, Mitolo M, Didino D, Kanai R, et al. Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. J Neurosci 2013;33:14899–907.

106. Cappelletti M, Pikkat H, Upstill E, Speekenbrink M, Walsh V. Learning to integrate versus inhibiting information is modulated by age. J Neurosci 2015;35:2213–25.

107. Contemori G, Trotter Y, Cottereau BR, Maniglia M. tRNS boosts perceptual learning in peripheral vision. Neuropsychologia 2019;125:129–36.

108. Womelsdorf T, Fries P. The role of neuronal synchronization in selective attention. Curr Opin Neurobiol 2007;17:154–60.

109. Peylo C, Hilla Y, Sauseng P. Cause or consequence? Alpha oscillations in visuospatial attention. Trends Neurosci 2021;44:705–13.

110. Herpich F, Melnick MD, Agosta S, Huxlin KR, Tadin 775-1.3728TD(B)-17.7Natt-e o t-n   lieni   (e)-9.3fc

115. Jia K, Frangou P, Karlaftis VM, Ziminski JJ, Giorgio J, Rideaux R, et al. Neurochemical and functional interactions for improved perceptual decisions through training. J Neurophysiol 2022;127: 900–12.

116. Grasso PA, Tonolli E, Miniussi C. Effects of different transcranial direct current stimulation protocols on visuo-spatial contextual learning formation: evidence of homeostatic regulatory mechanisms. Sci Rep 2020;10:4622.

117. Pirulli C, Fertonani A, Miniussi C. The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. Brain Stimul 2013;6:683–9.

118. Pirulli C, Fertonani A, Miniussi C. Is neural hyperpolarization by cathodal stimulation always detrimental at the behavioral level? Front Behav Neurosci 2014;8:226.

119. Inukai Y, Saito K, Sasaki R, Tsuiki S, Miyaguchi S, Kojima S, et al. Comparison of three non-invasive transcranial electrical stimulation methods for increasing cortical excitability. Front Hum Neurosci 2016;10:668.

120. Barrett BT, Bradley A, McGraw PV. Understanding the neural basis of amblyopia. Neuroscientist 2004;10:106–17.

121. Levi DM. Prentice award lecture 2011: removing the brakes on plasticity in the amblyopic brain. Optom Vis Sci 2012;89: 827–38.

122. Levi DM, Klein SA. Vernier acuity, crowding and amblyopia. Vis Res 1985;25:979–91.

123. Levi DM, Harwerth RS. Spatio-temporal interactions in anisometropic and strabismic amblyopia. Invest Ophthalmol Vis Sci 1977;16:90–5.

124. Simmers AJ, Ledgeway T, Hess RF, McGraw PV. Deficits to global motion processing in human amblyopia. Vis Res 2003; 43:729–38.

125. Tsirlin I, Colpa L, Goltz HC, Wong AMF. Visual search deficits in amblyopia. J Vis 2018;18:17.

126. Ding J, Levi DM. Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. Proc Natl Acad Sci USA 2011;108:E733–41.

127. Xi J, Jia WL, Feng LX, Lu ZL, Huang CB. Perceptual learning improves stereoacuity in amblyopia. Invest Ophthalmol Vis Sci 2014;55:2384–91.

128. Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. Proc Natl Acad Sci USA 2004; 101:6692–7.

129. Hou F, Huang CB, Tao L, Feng L, Zhou Y, Lu ZL. Training in contrast detection improves motion perception of sinewave gratings in amblyopia. Invest Ophthalmol Vis Sci 2011;52:6501–10.

130. Gu L, Deng S, Feng L, Yuan J, Chen Z, Yan J, et al. Effects of monocular perceptual learning on binocular visual processing in adolescent and adult amblyopia. iScience 2020;23:100875.

131. Jia W, Lan F, Zhao X, Lu ZL, Huang CB, Zhao W, et al. The effects of monocular training on binocular functions in anisometropic amblyopia. Vis Res 2018;152:74–83.

132. Chung ST, Li RW, Levi DM. Identification of contrast-defined letters benefits from perceptual learning in adults with amblyopia. Vis Res 2006;46:3853–61.

133. Yu D, Legge GE, Wagoner G, Chung STL. Training peripheral vision to read: boosting the speed of letter processing. Vis Res 2018;152:51–60.

134. Papageorgiou E, Asproudis I, Maconachie G, Tsironi EE, Gottlob I. The treatment of amblyopia: current practice and emerging trends. Graefes Arch Clin Exp Ophthalmol 2019;257: 1061–78.

135. Huang CB, Zhou Y, Lu ZL. Broad bandwidth of perceptual learning in the visual system of adults with anisometropic amblyopia. Proc Natl Acad Sci USA 2008;105:4068–73.

136. Deveau J, Lovcik G, Seitz AR. Broad-based visual benefits from training with an integrated perceptual-learning video game. Vis Res 2014;99:134–40.

137. Spiegel DP, Li J, Hess RF, Byblow WD, Deng D, Yu M, et al. Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia. Neurotherapeutics 2013; 10:831–9.

138. Camilleri R, Pavan A, Ghin F, Battaglini L, Campana G. Improvement of uncorrected visual acuity and contrast sensitivity with perceptual learning and transcranial random noise stimulation in individuals with mild myopia. Front Psychol 2014;5:1234.

139. Moret B, Camilleri R, Pavan A, Lo Giudice G, Veronese A, Rizzo R, et al. Differential effects of high-frequency transcranial random noise stimulation (hf-tRNS) on contrast sensitivity and visual acuity when combined with a short perceptual training in adults with amblyopia. Neuropsychologia 2018;114:125–33.

140. Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. Natural history of homonymous hemianopia. Neurology 2006;66: 901–5.

141. Das A, Huxlin KR. New approaches to visual rehabilitation for cortical blindness: outcomes and putative mechanisms. Neuroscientist 2010;16:374–87.

142. Kasten E, Wust S, Behrens-Baumann W, Sabel BA. Computer-based training for the treatment of partial blindness. Nat Med 1998;4:1083–7.

143. Cavanaugh MR, Huxlin KR. Visual discrimination training improves Humphrey perimetry in chronic cortically induced blindness. Neurology 2017;88:1856–64.

144. Raty S, Borrmann C, Granata G, Cardenas-Morales L, Schoenfeld A, Sailer M, et al. Non-invasive electrical brain stimulation for vision restoration after stroke: an exploratory randomized trial (REVIS). Restor Neurol Neurosci 2021;39:221–35.

145. Alber R, Moser H, Gall C, Sabel BA. Combined transcranial direct current stimulation and vision restoration training in subacute stroke rehabilitation: a pilot study. PM R 2017;9:787–94.

146. Halko MA, Datta A, Plow EB, Scaturro J, Bikson M, Merabet LB. Neuroplastic changes following rehabilitative training correlate with regional electrical field induced with tDCS. Article. NeuroImage 2011;57:885–91.

147. Plow EB, Obretenova SN, Fregni F, Pascual-Leone A, Merabet LB. Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical stimulation. Neurorehabil Neural Repair 2012;26:616–26.

148. Plow EB, Obretenova SN, Halko MA, Kenkel S, Jackson ML, Pascual-Leone A, et al. Combining visual rehabilitative training and noninvasive brain stimulation to enhance visual function in patients with hemianopia: a comparative case study. PM R 2011; 3:825–35.

149. Plow EB, Obretenova SN, Jackson ML, Merabet LB. Temporal profile of functional visual rehabilitative outcomes modulated by transcranial direct current stimulation. Neuromodulation 2012;15:367–73.

150. Olma MC, Dargie RA, Behrens JR, Kraft A, Irlbacher K, Fahle M, et al. Long-term effects of serial anodal tDCS on motion perception in subjects with occipital stroke measured in the unaffected visual hemifield. Front Hum Neurosci 2013;7:314.
151. Larcombe SJ, Kulyomina Y, Antonova N, Ajina S, Stagg CJ, Clatworthy PL, et al. Visual training in hemianopia alters neural activity in the absence of behavioural improvement: a pilot study. Ophthalmic Physiol Opt 2018;38:538–49.
152. Baird PN, Saw SM, Lanca C, Guggenheim JA, Smith EL III, Zhou X, et al. Myopia. Nat Rev Dis Primers 2020;6:99.
153. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.
154. Haarman AEG, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJM, Klaver CCW. The complications of myopia: a review and meta-analysis. Invest Ophthalmol Vis Sci 2020;61:49.
155. Verhoeven VJ, Wong KT, Buitendijk GH, Hofman A, Vingerling JR, Klaver CC. Visual consequences of refractive errors in the general population. Ophthalmology 2015;122:101–9.
156. Camilleri R, Pavan A, Ghin F, Campana G. Improving myopia via perceptual learning: is training with lateral masking the only (or the most) efficacious technique? Atten Percept Psychophys 2014;76:2485–94.
157. Durrie D, McMinn PS. Computer-based primary visual cortex training for treatment of low myopia and early presbyopia. Trans Am Ophthalmol Soc 2007;105:132–40.
158. Tan DT, Fong A. Efficacy of neural vision therapy to enhance contrast sensitivity function and visual acuity in low myopia. J Cataract Refract Surg 2008;34:570–7.
159. Camilleri R, Pavan A, Campana G. The application of online transcranial random noise stimulation and perceptual learning in the improvement of visual functions in mild myopia. Neuropsychologia 2016;89:225–31.
160. Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp 2019;40:904–15.
161. He Q, Lin BR, Zhao J, Shi YZ, Yan FF, Huang CB. No effects of anodal transcranial direct current stimulation on contrast sensitivity function. Restor Neurol Neurosci 2019;37:109–18.
162. Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. Brain Stimul 2015;8:1130–7.