



Review

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

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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.

Keywords: neuroplasticity; non-invasive brain stimulation; ophthalmology; perceptual learning; transcranial electrical stimulation; vision.

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 combining 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.

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Visual perceptual learning

Practice makes perfect. This principle is also applicable in sensory information processing. Repetitive practice on visual tasks can improve our ability to process visual sensory information and even in adults [8], this neural process is termed visual perceptual learning. Over the last three decades, VPL has been widely studied, and research has primarily focused on characteristics, cortical sites of occurrence, and manifestation of VPL [9].

Regarding the characteristics of VPL, there are three most prominent features: (1) ubiquity, (2) long-term

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],

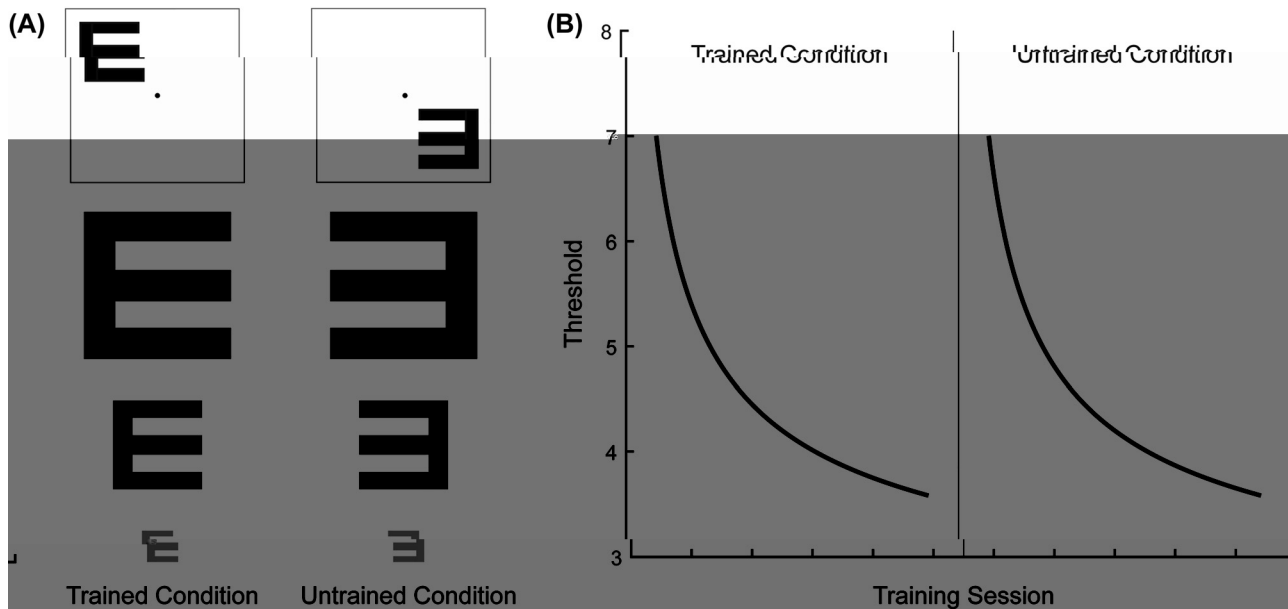


Figure 1: L. (A) D. H
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diagnostic medical imaging [51], and sports training [52]. For more information about the application of VPL, see Refs. [53, 54].

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

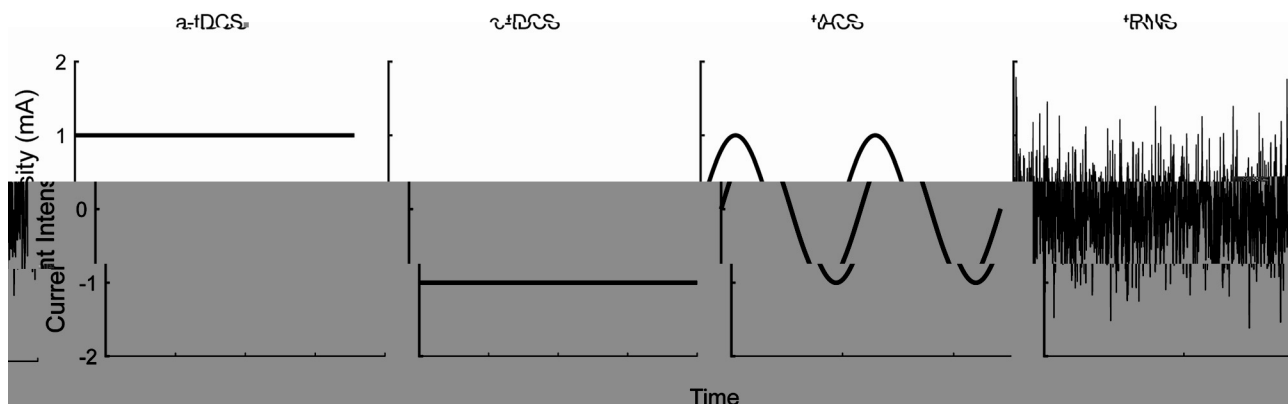


Figure 2: | DC AC N

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

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 administered. 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].

Interestingly, in addition to the tRNS-induced benefits in VPL mentioned above, tRNS delivered during training was

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 administered 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 administered 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 administered after task execution

TES applied following task execution was also efficient in modulating VPL. The physiological after-effects induced by tES do not dissipate immediately after the tES devices were switched off as the after-effects lasted at least 20 min after the termination of tES [5, 95, 119]. In line with this, some studies found that the tES applied before tasks could still modulate visual perception [117, 118]. Therefore, the after-effect of tES which is applied during executing the training task should be retained in the early awake consolidation stage. If the cortical regions involved in VPL are stimulated by tES during the early consolidation phase, the performance on the training task may be modulated. Indeed, this notion was confirmed by tDCS studies. Specifically, Yang et al. found that anodal tDCS applied over the visual cortex immediately after the training of TDT led performance on the trained task, even without extra training (i.e., offline gain occurred), had a greater improvement 12 h later; when sham tDCS was applied, no such modulatory effect was observed [98]. Similar results were also observed in an orientation discrimination task [97]. These studies demonstrated that VPL could be strengthened at the early stage of consolidation, even during wakefulness, which suggests that cortical excitability at the early awake consolidation stage is a key factor which influences the performance of VPL.

The clinical population

In visual impaired individuals, their visual function can be enhanced by both tES and VPL in numerous studies, but studies that aim to restore their visual function by combining tES and VPL are relative limited. So far, perceptual training coupled with tES has been primarily adopted to enhance or rehabilitate impaired vision in visually impaired people, including patients with amblyopia, cortical blindness, and myopia.

Amblyopia

Amblyopia is a developmental disorder that results from physiological changes in the visual cortex and impairs visual function in frequently one, or both, eye(s) despite full optical correction and the absence of obvious ocular pathology [120, 121]. People with amblyopia have deficits in many aspects of visual information processing, which range from relatively low-level to high-level vision,

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 training was implemented concurrently with high-frequency tRNS. Employing the training protocol, the same as that adopted by Polat et al., one study found that the amount of improvement in visual acuity and contrast sensitivity function after eight sessions of contrast detection training coupled with occipital high-frequency tRNS was equivalent to that obtained after 48 sessions of training without tRNS [138]. Moreover, the observed modulatory effect of tRNS could be retained at least six months after training [139].

Cortical blindness

Cortical blindness is chronic partial or complete loss of vision in one-half of the visual field after damage to the postchiasmatic visual pathways, including the primary visual cortex (V1) [4]. Though partial visual functions can be recovered spontaneously in the first several months after injury, the extent of visual recovery is still limited in cortical blindness [140]. Moreover, in the sub-acute phase (between three and six months after injury), little

improvement in visual function takes place to the extent that the deficits in vision are considered almost permanent [140, 141]. Unfortunately, at present there are no efficient rehabilitation methods that can enable the recovery of patients' visual fields, and thus without clinical intervention the deficits in visual fields are irreversible for patients with chronic cortical blindness. However, recent studies showed that perceptual sensitivity in the impaired visual fields, to some extent, could be recovered by novel rehabilitative methods.

TES was able to speed up vision restoration for patients with cortical blindness. First, in the absence of tES, repetitive stimulation of the border zone adjacent to the blind field was a promising strategy to restore patients' visual fields partially. Extensive Vision Restoration Therapy (VRT) training, dozens of sessions of training adopted usually, could expand patients' visual fields during the chronic phase (more than six months following brain damage) after occipital stroke [142]. Through VRT, visual fields from the sighted-blind boarder deep into the scotoma were recovered to some extent [38, 40, 143]. Secondly, serial tDCS applied over visual cortex of the damaged hemisphere could ameliorate the impaired visual fields rapidly [144]. Then, when tDCS was administrated during VRT training, the impaired visual fields in patients with cortical blindness could be enlarged [145–148], and the recovery of vision rehabilitation was accelerated [149], compared with the sham condition. Moreover, patients obtained greater functional benefits of daily life after receiving tDCS-coupled VRT training [147, 148].

In addition to enhancing the visual fields of people with cortical blindness, tES was also effective in boosting VPL in other perceptual tasks. The tES-boosted effects on non-visual field tasks were first found in a tRNS study, in which tRNS was released during executing a motion direction integration task [110]. The results showed that though repetitive practice was performed for patients who underwent training concurrent with sham stimulation, no substantial change in performance of the trained task was found. By contrast, patients who were stimulated by high-frequency tRNS showed a gradually better performance with practice, demonstrating that high-frequency tRNS can make patients learn to complete the trained task better [110]. But the results of tDCS-boosted VPL were inconsistent. In a repeated measures study across multiple daily sessions wherein tDCS was administrated, this study found that patients who were stimulated by anodal tDCS had more improvements in the performance of a motion direction detection task in the intact visual hemifield compared with the sham condition [150]. Considering that repetitive behavioral assessments can cause perceptual

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 administered 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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