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THE INFLUENCE OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON SACCADIC EYE MOVEMENT

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ABSTRACT

Introduction: Saccadic eye movements are fundamental for interactions with the visual environment. In recent years, there has been interest in verifying whether the use of transcranial direct current stimulation (tDCS) may influence saccadic eye movement. **Methods:** The aim of this review was to gather data from the scientific literature on the influence of tDCS on saccadic eye movement in adults. In combined with this, it is sought to analyze its relationship with healthy, pathological human aging, performance in ADLs, postural control and cognitive aspects. **Results:** We found 8 recently published articles that used tDCS as a way to influence the performance of the execution of the saccades. **Discussion:** It seems that the next steps to be followed need to meet protocols with longer duration of time, with different therapies of ocular training for reflex and active components, with long-term follow-up, with the exploration of new cortical regions as a target and with evaluation of the influence of these treatments on functional activities such as gait and activities of daily living.

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INTRODUCTION

Saccadics (saccades) eye movements are fundamental for interactions with the visual environment. From these movements it is possible to focus on targets of interest, which helps internal orientation as a response to external changes (Avila et al., 2015; Chen 2016). As a concept, saccades are rapid and brief movements of the eyes, mediated by reflex and voluntary central control (Avila et al., 2015; Hopp, 2003; Pélisson, 2010). Investigated for many years through the analysis of as implementation in several populations (Chen, 2016; Coiner et al., 2019), saccadic eve movement has been the target of research involving the application of transcranial electrical currents in brain areas corresponding to its oculomotor command. In order to verify how much saccadic oculotricity can be influenced by noninvasive neuromodulation, the most studied components are "prosaccades", "anti-saccades", "latency", "gain" (Kanai et al., 2012; Chen, 2016; Tseng et al., 2018; Reteig et al .2018; Chen, 2018; Max, 2020), and "saccadic adaptation" (Panouillères, 2015; Avila et al., 2015).

The eye movements towards a visual tip are called "pro-saccades", while the eye movements that move away from this tip are called "anti-saccades" (Chen, 2016). The visual and oculomotor care system is able to learn probabilistic information from the environment and later predict where a target of interest may be located. From this predictive capacity it is possible to perform a parametric adjustment as a response to changes in the direction and a target, in a learning called "saccadic adaptation" (Miller, 1988; Liu et al., 2011; Avila, 2015). "Latency" refers to the time (measured in milliseconds) between the presentation of a visual stimulus and the beginning of an eye response and the "gain", is the speed of eye movement (Chen, 2016). For a good performance of the saccadic function, with the correct direction of the eyes to an object of interest in the environment, for the contribution to a good acuity and visual perception, it is necessary that this movement be accurate and capable of anticipating future saccades, mainly through reflex activity (Hopp, 2004; Pèlisson et al, 2010). However, from the motor point of view, the execution of a reflexive response of eye movement is not always advantageous, due to the high probability of parametric errors. Thus, the ability to respond effectively to changes in the visual environment also depends on voluntary oculomotor control (Dowiasch et al., 2015).

With aging, there may be impairment of the functioning of saccadic eye movements, with voluntary control of these movements being the most affected (Dowiasch et al., 2015; Peltsch et al., 2011). It is important to point out that this decline in older adults may be an early sign of transition from healthy to pathological aging, for example, with mild cognitive impairment and Alzheimer's disease (Peltsch et al., 2011), Parkinson's disease (PD), and in situations such as Traumatic Brain Injury (TBI) and Stroke (Rizzo et al., .,2017; Gunning, 2017). One of the possible explanations for age-related declines in brain function, including voluntary saccadic eye movement control, is related to cerebrovascular changes. In general, neural excitation increases the local rate of cerebral oxidative metabolism, with increased blood supply to certain areas. But with aging, structural changes occur in the cerebral blood vessels that can compromise both the contribution of regional cerebral blood flow and the rate of cerebral oxidative metabolism in relation to neural excitation (D'esposito, 2003). In neurological pathologies, changes in saccadic movement are described in the functions "anti-saccade" and in "latency", with the presence of hypometry, in PD patients (Anderson, 2013; Lemos et al., 2016; Gunning, 2017). In post-stroke people, the dysfunction is related to an increase in the rate of anticipatory and early saccades. On the other hand, in post-TBI patients, there is a high rate of anti-saccade errors (Rizzo et al., 2017; Gunning, 2017).

Specifically in Parkinsonians, this saccadic dysfunction is constantly related to postural instability, with the "freezing of gait" (Terao et al., ., 2013) and with difficulties in performing anticipatory postural adjustments for ADI's (Ewenczyk et al., 2017). In post-stroke and TBI patients, the increase in the rate of anticipatory saccades and antisaccade errors can hinder activities involving, for example, tasks of upper limb reach (Meadmore et al., ., 2017). The relationship between aging and some neurological pathologies with the decline in control of saccadic eye movement (Peltsch et al., 2011; Chen, 2016) is documented in the literature. The deficits described are well evidenced when eye movement requires a high level of voluntary control and when inhibition of eye movement reflexes is necessary (Bos, 2013; Abel, 2013). Therefore, it is essential to understand that these declines have negative implications for the performance of time-related tasks that depend on effective visual orientation, such as driving a motor vehicle or crossing a busy intersection ((Doroudgar et al., 2017; Bédard et al, 2006; Zito et al., 2015). There is a scarcity of studies investigating methods to neutralize oculomotor deficits in older adults with and without neurological-based pathologies. This insufficiency, added to some recent findings, pave the way for the use of neuromodulatory techniques as a therapeutic strategy with potential to improve the control of saccadic eye movement, optimizing the remaining neural resources and, consequently, functional aspects (Chen, 2016). Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that involves the application of low intensity electrical currents (1 and 2 mA) by means of electrodes fixed in the skull, with the objective of altering the excitability of the underlying cortical neurons (Nitsche and Paulus, 2000; Kanai et al, 2012; Panouillères, 2015; Avila et al., 2015). Through 2 electrode channels, anodic stimulation (positively charged) usually promotes excitability of the underlying neurons, making them more likely to fire while cathodic stimulation (negatively charged) usually promotes hyperpolarization of neurons, thereby suppressing their excitability and making them less likely to fire (Chen,2016; Lefaucheur et al,2017, Max et al., 2020). From a physiological point of view, tDCS can induce lasting changes in neuronal excitability, brain activity, functional connectivity (Nitsche and Paulus, 2000; Lefaucheur et al ,2017) and cerebral blood flow (Chen, 2018). In light of these recent findings, it is proposed that this neuromodulatory technique may be a therapeutic strategy with potential to improve the control of saccadic eye movement (Avila et al., 2015; Chen, 2016; Chen, 2018; Max et al., 2020). Regarding stimulated brain areas, tDCS is believed to be a therapeutic strategy to treat saccadic eye movement dysfunction (Chen, 2016), influencing the improvement of its components such as "pro-saccades", "antisaccades", "latency" and "gain", through the stimulation of regions such as the Cerebellum, Dorsolateral Prefrontal Cortex (DLPFC) and Frontal Ocular Field (FOF) (Kanai *et al.*, 2012; Panouillères, 2015; Avila *et al.*, 2015; Chen, 2016; Max *et al.*, 2020). The FOF is the main stimulated area, since it is one of the main cortical regions involved in the control of eye movements and selective attention (Serences, 2007). Recent findings on the influence of electrical stimulation on brain activity and brain activity in saccades seem promising and may contribute in the future to studies aimed at people with neurological pathologies (Chen, 2018). Therefore, the aim of this systematic review is to gather data from the scientific literature on the influence of transcranial direct current stimulation (tDCS) on saccadic eye movement in adults. In combined with this, it seeks to analyze its relationship with healthy, pathological human aging, performance in ADLs, postural control and cognitive aspects.

METHODS

This study followed the recommendations proposed by *preferred reporting items for Systematic Reviews and Meta-Analyses* PRISMA (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). A review of articles published in the last 05 years (2015-2020) was performed that used tDCS protocols to influence motor components of eye movements, especially saccadic movement.

Research strategies: The search of the studies was carried out in the Pubmed, Cochrane and Science Direct databases. The keywords used were "tDCS and eye movement" and "tDCS and saccades". The choice of keywords aimed to partially restrict the search for the correct direction to the theme, since previous searches using the term "vision" reached a large area of research and knowledge.

Eligibility criteria: The eligibility criteria included review articles on the subject and clinical trials that used tDCS to influence the function of any of the components of saccadic eye movement in adults.

Study selection titles and abstracts of the papers identified by the search strategy were evaluated by the main author of this study. The selection process was structured in four stages: 1) The duplicate titles were process

The excluded; 2) Articles that did not evaluate the parameters of saccadic movement were eliminated with standardized clinical test; 3) Articles that did not use tDCS as a way to influence the performance of any of the components of saccadic eye movement were deleted; 4) The work that did not provide sufficient information in their respective abstracts was extinguished.

RESULTS

The results of this search totaled 634 publications. Figure 1 shows the flowchart of the search strategy used.

DISCUSSION

By collecting data from the literature on the influence of tDCS on saccadic eye movement in adults and analyzing its relationship with healthy and pathological human aging, performance in ADLs, postural control and cognitive aspects, this study brought interesting results. In general, the findings show that most studies sought to verify in which components of saccadic eye movement the use of tDCS was able to provide changes, especially in healthy populations. As a precursor to the tDCS approach to influence saccadic oculomotor performance, Kanai *et al.*, (2012) promoted a research

oculomotor performance, Kanal *et al.*, (2012) promoted a research with healthy individuals in which it was researched whether anodic tDCS would be able to modulate the excitability of the frontal eye fields (FOF), which is one of the main areas involved in the control of eye movements. It was observed that through this stimulation there was an improvement in performance in "pro-saccade" and "antisaccade" tasks, with reduction of saccadic "latency". These findings may be a light for the therapy of saccardious dysfunctions in several populations.



Figure 1. Flowchart of the search strategy used

The parameters modified by the neuromodulation of the FOF in this study are some of the dysfunctional parameters in PD patients, who present among other oculomotor alterations, hypometric saccades, with increased rate of "anti-saccadic" errors, in addition to increased "latency" and reduced "gain" (Terao et al., 2013; Crotty, 2019). As a complement to this reasoning, some evidence shows that FOF impairment or inactivation prolongs "latency" in "pro-saccade" and "anti-saccade" (Kanai et al., 2012; Gaymard et al., 1999). For example, studies using Transcranial Magnetic Stimulation (TMS) have shown that saccade latency in the "pro-saccade" task increases after 10 min of repetitive 1 Hz EMT (REMT) or "Theta Burst" stimulation on FOF (Nyffeler et al., 2006), highlighting how it is possible to interfere in this central control through noninvasive neuromodulation protocols. The findings of Kanai et al., (2012) were replicated by Tseng et al., (2018). With the application of an anodic or cathodic tDCS protocol on the right FOF of adults, while they performed interleaved tasks "pro-saccade" and "anti-saccade", were observed that anodic tDCS facilitated the "pro-saccades" for the contralateral side to anodic stimulation. The convergent results in these studies, together with knowledge about the central control of eye movement, offer an important contribution to future research that intends to modulate the function of reflex and voluntary eye movement from cortical stimulaiton. The FOF is essentially involved in all eye movements, from preparation to initiation of intentional saccades and in eye movements of search, maintenance of fixation and combined between eyes and head (Coiner et al., 2019). This knowledge about the importance of FOF in eye movement motivated Chen's literature review (2016), focused on the analysis of active control for "anti-saccades" that aging can negatively affect.

Thus, Chen (2016) brought important information and proposed that studies with the use of tDCS can generate therapeutic alternatives to improve the control of voluntary saccadic eye movement in the elderly. On the pathophysiology of this dysfunction, it seems that the deficits are sustained by the deterioration of the frontal lobe with aging and by local vascular factors and its connections with the parietal lobe. Due to tDCS's ability to increase regional cerebral blood flow, brain activity and connectivity between regions (Lefaucheur et 2018), it is possible that this noninvasive neuromodulation al. technique optimizes the remaining neural resources and improves the efficiency of neural networks. This is the basis for an effective therapeutic strategy with the potential to neutralize voluntary saccadic control deficits along with other cognitive deficits (Chen, 2016). Oculomotor dysfunction is commonly observed in neurology with hypokinetic and hyperkinetic movements detected during bedside ocular motility examination (Jung, 2019).

Functionally, eye movements facilitate a number of behaviours to perform ADLs, ranging from a simple visual screening while reading a book, to driving a car on unknown roads. These behaviors require

integration of several sensory, attentional and cognitive processes, such as memory and planning (Luna, 2008). In the search for new targets for tDCS and nonsense of verifying the correlation between oculomotricity and attentional aspects, Chen (2018) investigated whether the control of saccadic eye movement for "anti-saccade" and "pro-saccade" could be improved using a tDCS protocol in the DLPFC of the elderly and, if this improvement could reflect on attention gains. The responses were positive, and this is the first study to report evidence that anodic tDCS in DLPFC can provide effective therapy to improve deficits in control of saccadic eye movement in older adults. The DLPFC is considered crucial for decision-making processes that coordinate eye movements (Pierrot et al., 2003). The behavioral effects of lesions in the human DLPFC and neuroimaging studies indicate their involvement in the inhibition of saccades (Jamadar, 2013). Another important contribution of the DLPFC to the oculomotor function, which reinforces its importance in the control of this movement and cognitive aspects, is corresponding to the prediction of eye movements (Coiner et al., 2019).

The interest in the study of saccadic movement has focused on different areas that go beyond its analysis for oculomotor control. This is justified by the fact that it is increasingly clear that the cortical centers involved with oculomotricity occupy several areas of the brain, such as the Frontal Ocular Field (FOF), Supplementary Eye Field (SEF), Parietal Ocular Field (POF) and Dorsolateral Prefrontal Cortex (DLPFC), also with the aid of structures such as Cerebelus, Base Ganglios and Brainstem (Takagi, 1998; Kojima, 2010; Shemesh, 2019; Coiner et al, 2019). The studies of Kanai et al., (2012), Tseng et al., (2018), and Chen (2018) brought important responses, especially with regard to the influence of regions such as FOF and DLPFC for voluntary oculomotor control and reflex control with anticipatory and acoustic components, respectively. The excitatory activity of the FOF and DLPFC triggers functions related to selective attention, memory and oculomotricity, important bases for human behavior, especially motor behavior (Kanai et al., 2012; Tseng et al, 2018; Chen, 2018). Based on these results and the motor and cognitive deficits already known in PD and Alzheimer's, the deteriorated cortical function and the potential described by physiology for the use of tDCS, it is plausible to believe that care protocols with the union of this neuromodulatory technique with rehabilitation approaches can be effective. Due to the large number of structures involved in oculomotricity, coiner et al., (2019) is described as the "Eye Movement Network", with the initial objective of expanding and documenting knowledge about the regions involved with oculomotor control. The description of this neural network helps to understand the findings of Ávila (2015) and Panouillères (2015), which from motor learning mechanisms with the involvement of the cerebellum improved saccadic function, which was initially described as originating from the Frontal Ocular Field. The Cerebellum is an important brain region, with motor and non-motor functions. Currently, the main non-motor functions related to the cerebellum concern behaviors and global learning (Schmahmann, 2019). In order to evaluate the influence of tDCS on saccadic adaptation, which is an engine learning mechanism for saccades, Avila et al., (2015) and Panouillères (2015), they apply in a series of adult individuals to anodic tDCS, targeting the cerebellum. The results of these two studies suggest that cerebellar excitability is critical for saccadic adaptation, as there was an improvement in oculomotor performance for saccadic adaptation after the proposed protocol. Saccadic adaptation occurs due to learning mechanisms, such as trial and error, through parametric motor adjustments and muscle coordination, known functions performed by the cerebellum (Schmahmann, 2019). Thus, it is acceptable that tDCS can be used as a neuromodulatory technique to alter cerebellar oculomotor function (Avila et al., 2015; Panouillères, 2015). With a behavioral analysis objective Max et al., (2020) applied an anodic tDCS protocol in the DLPFC of individuals with binge eating, proposing the performance of a "anti-saccadical" task modified with food, with the objective of inhibiting this compulsion.

Table 1. Description of the population, objectives, protocols used and the results of the studies added in the review

Authors	Population	Goal	ETCC Protocol	Findings
(Kanai et. al,2012)	Sixteen young individuals (6 men and 10 women). They were all right-handed and had normal or corrected visual acuity.	Examine whether tDCS can modulate the excitability of FOF. Towards this objective, it was examined how etcc acting on the FOF modulates the "pro-saccades" and "anti-saccades".	Bilateral, anodic and cathodic tDCS on the left and right FOF. The electrodes were of 3x3 size and provided a current intensity of 1mA for 10 min.	Anodic tDCS reduces latency from contralateral "pró saccades"; Cathodic tDCS increases the "latency" of "anti- saccade" ipsilateral; Anodic tDCS reduces contralateral saccadic errors; Amplitude and variability are not affected by tDCS.
(Panoiullères, 2015)	79 participants (44 women), with a mean age of 25.1 years. All subjects had normal vision or corrected for normal vision.	Investigate the consequences of modulation of excitability of the middle line of the cerebellum in saccadical adaptation.	Anodic or cathodic tDCS with the active electrode centered on the inion and the reference electrode on the upper face of the right trapezoid muscle. The intensity was 2mA for 20 min. tDCS Sham was applied using the same procedure as above, except that the stimulation lasted only 30 s.	Human cerebelar vérmis plays a crucial role in saccadic adaptation which is influenced by the proposed tDCS protocol.
(Avila et. al, 2015)	13 healthy individuals with a mean age of 22.4 years, right-handed, (6 women), without a history of neurological or psychiatric conditions. They did not use medicines and drugs, with normal vision.	Use anodic tDCS as a tool to modulate cerebellar oculmotor control and provide a functional view of learning during saccadic adaptation.	Group 1: Anodic tDCS applied in right cerebellum 3 cm to the right of the inion with the reference electrode (cathode) on the left buccinator muscle, with intensity of 1.5 mA for 15 min. Group 2: sham condition with the current off after 30s of its start.	tDCS on the cerebellum significantly influenced saccadic adaptation, with reduction of the "gain", compared to simulated stimulation.
(Chen, 2016)	Review Article	Review changes in age-related saccadic control, focusing on the "anti-saccadic" task. Review the neuroanatomy of voluntary saccadic oculomotor control. Explore the potential of tDCS to counteract aging deficits.	-	tDCS may be a therapeutic strategy to improve the control of voluntary saccadic eye movement in the elderly
(Chen, 2018)	The final sample included 16 men (age range 65-71 years) in the first experiment and 10 men (age group 65-74 years) in the second experiment. All were right-handed, except one (ambidextrous). All reported having normal or corrected vision, with no history of, and not taking any medication for neurological or psychiatric problems	Investigate whether saccadic movement in older adults can be improved with the application of tDCS on DLPFC	Anodic tDCS in left or right DLPFC, with the reference electrode (cathode) positioned in the contralateral supraorbital area, with intensity of 1.5 mA for 10 min. During sham protocol, the device was switched off 30 seconds after the start.	Anodic tDCS in DLPFC can provide effective therapy to improve saccadic eye movement control deficits in older adults. The results indicate improvements in oculomotor control after online activity in relation to TDCS Sham
(Reteig et al, 2018)	26 participants (14 women), with a mean age of 25.9 years were included in the analyses.	Replicate results of Kanai et al., 2012, with application of anodic tDCS in FOF	Anodic or cathodic tDCS in FOF, with intensity of 1mA for 15min. The reference electrode was over the contralateral supraorbital region Anodic tDCS did not decrease the latency of contralateral "pro-saccades".	tDCS has not reliably affected the latency or accuracy of saccadic movement. It was concluded that the efficacy of tDCS in FOF remains uncertain
(Tseng et. al, 2018)	Young adults between the age of 20 and 30 years. 20 participants in the anode condition, 15 in the cathode condition and 18 in the control experiment. All participants had normal or corrected vision.	Check the influence of anodic or cathodic tDCS on FOF during "pro-saccade" and "anti-saccade" tasks.	Anodic or cathodic tDCS in FOF for 10min at an intensity of 1.5mA. In the simulated condition, tDCS was switched off after 30s.	The anodic tDCS on the right FOF facilitated "pro-saccades", while the cathodic tDCS facilitated "anti-saccades"
(Max et. al, 2020)	16 patients were randomized within the tDCS group with intensity of 1mA and 15 participants in the group with intensity of 2mA to receive sham first (simulated treatment) and then real tDCS or vice versa	Check whether tDCS associated with an "anti-saccadical" task generates learning effects in a sample with people with binge eating disorder	Anodic tDCS in right DLPFC with reference electrode in left deltoid with intensity of 1 mA or 2 mA, depending on the assigned group, for 20 min. For simulated stimulation, the current was applied only for 46 s	The reduction of binge eating over time in the condition of 2 mA was evidenced

The findings suggest that the association of these techniques may be useful for this treatment in the future, in an adjunct way. This finding reinforces the close structural and functional relationship of frontal lobe regions such as FOF and DLPCF, besides corroborating studies that show the existence of brain connectivity through the neural network of ocular movement (Coiner *et al.*, 2020). In an important counterpoint, Reteig et. (2018), in an attempt to replicate the findings of Kanai *et al.*, (2012), found no significant differences in latency and speed of saccadic movement for "pro-saccades" and "anti-saccades" after a tDCS protocol. The authors conclude that it is not yet clear whether eye movements or other aspects of spatial attention may be affected through tDCS of the frontal eye fields and further research is suggested, with new targets, populations and protocols with tDCS.

In a reflection on new cortical targets for research in this area, the Parietal Eye Field (POF) is shown to be one of the regions still little studied. It is believed that cop plays an important role in visuospatial care and integration, being crucial for the generation of reflective saccades (Leigh, 2015). In this sense, Lemos et al., (2016), suggests that the increase in POF activity may somehow compensate for deficits caused by PD in which there is underactivity of the FOF. The studies found in this review show a growing interest in eye movement, with emphasis on the relationship of saccadic eye movement with motor and non-motor aspects and pathological states. The therapeutic approaches reported in this review focused on adults and the elderly and evaluated saccadic ocular performance in "prosaccadic", "anti-saccadic", "saccadical adaptation" tasks, in addition to evaluating components such as "latency" and "gain", from the stimulation of brain regions such as FOF, DLPFC and cerebellum. The results are still discrete, with reduced populations, however, with promising potential, since it was noted that in general tDCS can influence parameters of performance of saccadic eve movement from the excitatory stimulation of the aforementioned regions. It is important to highlight some gaps from the findings. Most studies are based on short-term results, with performance analysis in a single session or with a reduced number of sessions, compared to most neuromodulation protocols proposed in large reviews (Lefaucheur et al., ., 2018). Another important aspect concerns the proposed training. Protocols based on computer programs were used, from preprogramming, with no simulation closer to reality, in environments that require greater problem solving and active motor control. Furthermore, the results were not evaluated in functional aspects such as gait performance or in ADLs. Finally, no article analyzed in this review sought to evaluate and treat saccadic eye movement dysfunctions in populations with neurological pathologies, such as PD, Alzheimer's, stroke or TBI.

Conclusion

The studies added in this review make evident the complexity of human oculomotricity, which is under the influence of several cortical and subcortical regions, where each of them performs functions for the planning and execution of eye movements. It is acceptable that brain regions such as FOF, DLPFC and Cerebellum may be affected by noninvasive neuromodulation techniques such as TMS and tDCS, causing temporary changes in the functionality of specific components such as "pro-saccades", "anti-saccades", "latency" and "saccadic adaptation". The results described in this review apply to the adult and elderly population, without neurological impairment, and also promote an initial reasoning about the possibility of applying this technique in these brain regions in people with neurological diseases. Due to the pathophysiology of saccadic dysfunction, it is possible to verify that the deficits in this movement in aged brains are similar to the same deficits in people with neurological diseases directly related to aging, such as PD and Alzheimer's. The most important limitation of this review is related to the scarcity of studies and the lack of analysis of overall functional performance in the individuals studied. It was not possible to verify whether the results found were maintained in the long term and whether the modification of performance in "pro-saccade", "anti-saccade", "saccadic adaptation" and "latency" was able to change functional aspects such

as gait pattern, balance and performance in ADLs. The follow-up of research with the use of tDCS in adults and the elderly from the evaluation and treatment of saccadical dysfunction should be encouraged. It is also necessary to develop protocols to evaluate whether in people with neurological pathologies, in which oculomotor deficits are reality, the use of tDCS and protocols with eye movement training can restore or compensate for lost function. It seems that the next steps to be followed need to meet protocols with longer duration of time, with different therapies of ocular training for reflex and active components, with long-term follow-up, with the exploration of new cortical regions as a target and with evaluation of the influence of these treatments on functional activities such as gait and ADL's.

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