Mini-Review

The potential application of transcranial magnetic stimulation in ophthalmology: a brief perspective

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Abstract: Transcranial magnetic stimulation (TMS), while employed in both cognitive investigations and evaluated as a potential therapeutic technique for several conditions, is not widely used in ophthalmology. As a technique, one of the advantages of TMS is that it can create a "virtual lesion", or temporary disruption of the functioning of a brain area, to facilitate investigation of the processes that the disrupted area may be involved in. In ophthalmology, higher association cortex is associated with visual cognition and control of eye movements, processes which could further be investigated using TMS experiments. This paper aims to provide a perspective of how TMS could be more broadly applied in ophthalmology.

Keywords: transcranial magnetic stimulation (TMS); neuro-ophthalmology; eye movements; visual cognition; amblyopia

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Introduction

Transcranial magnetic stimulation (TMS) employs the use of brief magnetic pulses which allow for direct noninvasive interference with functioning of the brain cortex (1,2). Stimulation results in interference with the functioning of a specific brain area to which it is delivered, therefore, in conscious healthy volunteers, creates a temporary "virtual lesion" effect (1,3). TMS experiments thus provide causal information about the role of an area due to behavioral changes in a specific task or process after stimulation of a specific area (3). This paper describes a brief perspective regarding the potential future use of TMS in ophthalmology.

TMS protocols

Choosing the correct TMS protocol is crucial before starting a TMS experiment. The simulation protocols include single pulse, double pulse, low or high frequency repetitive TMS (rTMS), and theta burst stimulation (TBS) (2,4). In more detail, single-pulse TMS, as the name suggests, employs one pulse per stimulation. The benefits of a single pulse TMS protocol can be seen in the mapping of motor cortical outputs by measurement of TMS motor evoked potentials (MEPs). This has allowed evaluation of empathy effects on the motor system (MEPs induced by a single-pulse of TMS while viewing painful image/video stimuli) (5,6) as well as in investigation of motor conduction (7). Paired-pulse stimulation has a number of forms, one of which is the use of two single pulses to one cortical area (often the motor cortex) to investigate modulatory effects, and another is the use of two different coils so that single pulses can be delivered to two different brain regions (8). This second case allows the investigation of *cortico-cortical* interactions.

There are two commonly used rTMS protocols, with 'high-frequency' stimulation typically using frequencies more than 1 Hz (most often 10 Hz) and 'low-frequency' rTMS using 1Hz or lower stimulation rates (2,9). These are typically used to produce 'on-line' and 'off-line' disruption of a cortical area, respectively. An example of rTMS use is in visual cognition experiments, such as delivering rTMS over posterior parietal cortex (PPC) to investigate the contribution of this area to visual search performance wherein a subject searches for a target amongst several distractors (10,11). It is important to note that rTMS might induce facilitation due to activation of inhibited neural pathways or inhibition of maladaptive responses (12), although the neurophysiological mechanisms of exactly how this occurs remain unclear.

TBS is a 'high frequency' rTMS protocol, involving 3 pulses, 50 Hz stimulation bursts delivered at a rate of 5 Hz. TBS protocols include intermittent (2 s of stimulation repeated every 10 s) (iTBS), intermediate (5 s of stimulation repeated every 15 s) (imTBS), and continuous (40 s of uninterrupted TBS) stimulation (cTBS) (13). These types of stimulation typically, in turn, produce facilitation, no change, or disruption of the area stimulated.

TMS application in ophthalmology

TMS is important in that it allows investigation of the effects of stimulation of the central nervous system. However, it is not yet broadly used in ophthalmology where there is potential for it to become a useful tool in ophthalmology cases that are related to central nervous system function. Examples include: spatial analysis experiments, in testing theories of eye movements, and in treating amblyopia.

Visual perception

TMS has been found to be able to interfere with spatial perception in numerous experiments, and data obtained show it could be used as a tool to evaluate visual hemifield asymmetries. This can be performed by analyzing the perception in left versus right visual fields. For example, TMS over PPC produces a "neglect-like" effect using tasks such as the conjunction visual search paradigm, where effects are particularly seen for peripheral target locations (14). Using such a task, the effect of TMS on performance with distant visual presentation (when compared with near visual presentation) was profound and this was found across both visual fields and, with PPC stimulation, a significant left versus right visual field difference was seen (the "neglect-like" effect). Data from this experiment give an example of investigating the role of a higher brain cortical region PPC (rPPC) in processing information from extrastriate cortex (15). PPC has been suggested to be important in generating a response weighted transformation into the appropriate body coordinate system, a process which is important to allow action in space. Further investigation of this sort of visual processing, and the brain areas associated with it, in more specifically ophthalmological conditions has the potential to offer new insights, both in terms of brain function mechanisms and possible therapeutic interventions.

Eye movements

Processing related to eye movement generation involves several cortical areas, including the frontal eye fields (FEF) in the frontal lobe and the PPC in the parietal lobe, functions of which can be investigated using TMS (11,16). An example of such an investigation looked at the control of the eyes and essentially whether they each have a single 'control center', in which case the coordination of the eyes would have to be learned, or whether a unique command is sent to each eye causing them to behave like a single organ (10). Unlike the 'control center' idea, the suggestion where the eyes behave like a single organ is associated with innate binocular coordination. The former of these ideas was proposed by Helmholtz as early as 1868, while the latter was suggested by Hering (17). Using single pulse TMS delivered over the PPC, Vernet *et al.* (18) found that such stimulation increased the misalignment of the eyes before saccades and caused binocular coordination to deteriorate during saccades, consistent with the PPC both maintaining eye alignment during fixation and being involved in binocular coordination during saccades. These findings were argued to fit with Hering's suggestion of equal innervation for the eyes (10).

Amblyopia

In the condition of reduced visual acuity in the absence of any demonstrable abnormality in the eye, one possible cause is amblyopia. Amblyopia might be caused by long-standing visual suppression and an imbalance in cortical activation. One possible use of TMS might be in stimulating to alter this inhibition within the human cortex by modulating abnormal inter-hemispheric patterns of suppression. Interestingly, application of TMS to the amblyopic visual cortex has been found to temporarily improve contrast sensitivity (19), with contrast sensitivity being a parameter that can be affected by many aspects of vision and can be a more sensitive measure of visual acuity. These findings lead to the suggestion that TMS may potentially be useful in reducing pathological suppression. Along similar lines, cTBS has been shown to be effective in improving amblyopic eye contrast sensitivity for high spatial frequencies (20).

Optic neuritis

Optic neuritis is often caused by multiple sclerosis (MS), which is characterized by autoimmune inflammation, demyelination, and degeneration. This demyelination can affect nerve conduction and it is often followed by Uhthoff's phenomenon, a temperature induced change in central motor conduction. These changes in motor conduction could be tested with TMS, making use of the fact that stimulation of motor cortex causes induced action potentials to descend, resulting in a "twitch" of the innervated muscle. Any delay or slowing in motor conduction could be recorded after temperature modification (for instance, due to a cold bath) (7). For motor conduction stimulation, it is important to threshold the level of TMS intensity according to individual subject motor thresholds (usually obtained using electromyographic recordings). This type of experiment must be done with caution as deterioration of visual acuity can occur with an increase of temperature in patients with optic neuritis, so study protocols must be particularly thoroughly reviewed before conducting this experiment in MS patients with, or suspected of having, optic neuritis.

Conclusions

TMS can be employed to investigate human visuospatial perception and eye movements, with one example being to test eye movement theories. TMS also has potential in treating amblyopia although more research is needed to investigate the efficacy with which it could be employed. It could also be employed where measurement of changes of the types associated with conditions such as MS occur. Overall, there is significant potential for expansion of the use of TMS into areas related to ophthalmology.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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