

Uncovering the connectivity of the brain in relation to novel vision rehabilitation strategies

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With advances in assistive technology, the development of retinal prostheses, and the use of stem cells for retinal and corneal repair, the paradigm of vision rehabilitation is evolving. Now more than ever, clinicians need novel strategies for rehabilitative treatment, assessing outcomes, and determining overall rehabilitative success. The capacity of the adult brain for reorganization following damage and training is likely underestimated, and uncovering the neurophysiology underlying neuroplastic change can reveal opportunities for evaluating, predicting, and even influencing rehabilitative outcomes.

Various forms of noninvasive brain stimulation have been combined with visual rehabilitative training approaches as a means of improving overall therapeutic success. For example, patients with hemianopia who underwent computer-based rehabilitative training showed improved performance in stimulus detection as well as increased visual field size when training was combined with transcranial direct current stimulation applied over the occipital cortex.¹ Alternating current stimulation is another method of noninvasive stimulation that, when delivered transorbitally for 10 days to patients with optic nerve damage, was associated with increased alpha power measured with EEG as well as improvements in detection accuracy in high-resolution perimetry (HRP), detection performance in static perimetry, and visual acuity.² Although these 2 studies used very different stimulation protocols, both demonstrated how combined therapeutic approaches could influence the improvement of visual task performance in patients with acquired vision loss.

Yet restoring more complex visual perceptual function will require the successful reintegration of visual stimuli into coordinated neural networks, highlighting the need for a greater understanding of the functional connectivity of the brain and its response to therapy such as noninvasive brain stimulation. In this issue of *Neurology*®, Bola et al.³ provide insight into the functional connectivity of the brain in patients with prechiasmal damage. After recording EEG activity in 15 patients and 13 normal controls, they applied Granger causality analysis (GCA) to reveal effective brain connectivity based on observed correlations over time.⁴

They then randomized the patients to treatment with repetitive transorbital alternating current stimulation (rtACS) or sham treatment. While current aims of the study did not include determining the efficacy of rtACS, the patients did undergo perceptual testing before and after stimulation.

Analysis of separate EEG bands revealed that patients had lower power in the high-frequency alpha (alpha II) band in the occipital region. The authors calculated coherence, or functional connectivity, from pairs of channels within areas (short-range coherence) and from occipital channels paired with frontal channels (long-range coherence), and patients demonstrated decreased short- and long-range coherence in the alpha II band. In addition, their spatial patterns of network activity showed less clustering.

At baseline, greater local low-frequency alpha (alpha I) coherence within the occipital region was related to greater size of intact visual field measured by HRP, faster processing speeds measured by HRP, and better detection in the fovea measured by static perimetry. Post-rtACS, an increase in occipital alpha II coherence was associated with increased detection accuracy with HRP, and an increase in long-range alpha II coherence correlated with faster processing speed measured by HRP.

The results support the authors' conclusion that a prechiasmal lesion within the visual pathway affects not only the local area but also the functional connectivity and synchronization of neuronal networks within the brain. Indeed, previous studies using MRI-based functional connectivity density analyses have also revealed differences in whole-brain functional connectivity patterns in patients with early- and late-onset ocular blindness compared to normally sighted controls.⁵

Alpha activity is considered an index of reduced cortical activity during wakefulness generated by the thalamus⁶ and plays a role in visual attention as well as the modulation of selective attention.⁷ In the present study, stronger alpha band connectivity was related to better performance on some visual perception tasks, suggesting that alpha activity may be a marker for sensory processing. Specifically, changes in local and long-range alpha II coherence correlated with improvements,

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so measuring activation within these sub-bands might have some predictive value in determining rehabilitative success. The association between alpha sub-bands and training outcomes has been explored previously in psychomotor studies. For example, better outcomes in musical performance after biofeedback training were associated with certain characteristics of individual alpha sub-bands.⁸

The study by Bola et al. found no correlations between EEG activity and some outcomes, such as near/far acuity, kinetic perimetry, or the National Eye Institute Visual Function Questionnaire. These negative findings make the immediate clinical meaning of these results difficult to assess. However, analysis of functional connectivity may have some predictive value in patient selection, allowing clinicians to identify those patients who may have maximal response to therapy, and this information would be of great clinical importance and utility. It would also be useful to compare brain functional network connectivity with other clinical measures of ocular structural integrity, such as retinal nerve fiber layer analysis using optical coherence tomography. Future studies in these patients could also explore correlations between the functional connectivity of sub alpha bands detected by EEG and more focal patterns of activation revealed by fMRI. However, to do so would require a more robust model of causal analysis than GCA, given the inherent limitations associated with making time-dependent observations from the blood-oxygen-level-dependent signal, which shows hemodynamic lag in fMRI-based studies.^{4,9}

As advances in vision restoration rapidly evolve, vision rehabilitation must appropriately keep pace and draw inference and insight from revelations into the neurophysiologic correlates of the brain's response to damage and subsequent therapy. More studies such as this are needed to help determine the possible application of

functional connectivity analysis to patient selection and predicting rehabilitative success. Such knowledge would transform the way multidisciplinary rehabilitation teams create treatment plans and assess results and would ultimately lead to better patient outcomes.

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