Vision Restoration Therapy in neuro-rehabilitation: Game-changer or time-waster?

Introduction

Vision is integral to efficient functioning in everyday life. We use it to orientate ourselves in our surroundings, identify objects, communicate with the written word and engage in social interaction.[1] Because visual function is distributed over large areas of the cerebral cortex, visual field defects are very common after cerebral insults such as stroke and traumatic brain injury.[2] Between 20% and 57% of patients with stroke report visual field impairment[3,4].

Estimates vary widely as the presence of visual field defects is highly dependent on length of time after stroke.[4] Literature suggests that visual field defects tend to improve in the first few months after the cerebral insult when there is resolution of oedema, diaschisis and improvement of neuro-transmission near and remote to the lesion. About 10% experience full spontaneous recovery in the first 2 weeks; recovery is minimal after three to six months.[5,6] The most common visual field defect is homonymous hemianopia, a deficit of the visual hemi-field contralateral to a post-chiasmal lesion of the visual pathway.[7] It counts for approximately two-thirds of all post-stroke visual field defects.[5,8,9] The extent of loss within the visual field may vary, and other types of visual field impairment include inferior and superior quadrantanopia, constricted visual fields, scotomas and altitudinal defects.[5]

Visual field impairment significantly impacts on functional ability and quality of life.[10,11] Patients with visual field defects suffer more falls, lower mood and higher levels of institutionalisation[12-16]. Reading ability is impaired because reading performance depends primarily on the size of the intact para-foveal visual field (extent of macular sparing);[17] and with most visual field defects extending to the vertical meridian, patients have difficulty identifying half of a word and finding the next line of text, and this results in hemianopic

alexia.[18] Visual impairment and disordered visual search mean more frequent collisions into obstacles or into people in crowded areas, tripping and getting lost in crowded or unfamiliar places.[15,19] Many patients with a visual field defect are unfit to drive, since standards for driving in the United Kingdom (UK) require at least 160° of vision.[20] Importantly, visual field defects can indirectly affect long-term outcomes by impairing patients' abilities to participate in rehabilitation. This then results in poorer long-term recovery, loss of independence, social isolation and depression.[21]

Vision Rehabilitation for Visual Field Defects

Vision rehabilitation is an emerging sub-speciality, with research in the field primarily published in the past four decades.[22] It is a therapeutic approach to any condition, disease or injury that causes visual impairment leading to functional limitation or disability. It helps affected individuals attain maximum function, a sense of well-being, a personally satisfying level of independence and optimum quality of life.[23] Vision rehabilitation begins with a careful evaluation of the visual system, which guides the development of an individualised rehabilitation plan. There are three main approaches to vision rehabilitation:

1. Substitution uses environmental adaptations and optical devices;
2. Compensation enhances unaffected parts of the visual system to make up for the affected;
3. Restitution attempts to restore lost function.[24]

Substitutive methods for rehabilitating visual field defects mainly involve the use of prisms; compensatory strategies use scanning training; and the most studied restorative approach is Vision Restoration Therapy (VRT) by NovaVision.[2,25] Typical neurological lesions found suitable for VRT include traumatic brain injury, stroke, cerebral aneurysm, brain haemorrhage, brain tumour and encephalitis.[26] In recent years, there has been growing

interest in the role of VRT for visual field defects in neuro-rehabilitation following a paradigm shift from the traditional thinking of a 'hard-wired' visual system to the concept of brain neuroplasticity. However, VRT has attracted both enthusiasts and critics, with responses ranging from "those that were blind can now see"[27] to "disappointing" and "ineffective"[28]. This essay therefore explores the developments in VRT and evaluates its efficacy and potential role in neuro-rehabilitation.

Vision Restoration Therapy: Promises and benefits

VRT is a computer-based training programme where therapy is directed to the border region between the intact and the damaged visual field over weeks and months to expand the visual field.[2] Hundreds of visual stimuli is presented to this border region every day, to which patients respond by pressing an appropriate key.[29] This therapy is based on the premise that there is considerable neuroplasticity in the injured visual system and receptive field reorganisation can be achieved through targeted and repetitive photo-stimulation.[2,29] It was postulated that vision loss did not involve an abrupt change between the seeing and non-seeing neural cells; rather, it is a gradual decline in function migrating from active cells in the seeing side to damaged cells on the non-seeing side. VRT therefore targets the 'transitional zone' where neural cells are thought to be partially functional.[29]

Recent research on the regenerating capabilities and plasticity of neural tissue support the possibility of restoring function to damaged neural cells.[30,31] Sabel *et al* put forward the 'residual vision activation theory' which explains how visual functions can be reactivated and restored.[32] The theory states that the cerebral visual injury is usually not complete and some structures are typically spared. This includes areas of partial damage at the visual field border, islands of surviving tissue inside the blind field, extra-striate pathways unaffected by the damage, and downstream, higher-level neuronal networks. These residual structures are

unable to be fully functional due to the presence of fewer neurons, disturbance in temporal processing and lack of sufficient attentional resources due to the dominant intact hemisphere caused by excitation/inhibition imbalance. As a result of this, the residual structures can no longer contribute much to everyday vision, which in turn further impairs synaptic strength. However, these residual structures can be reactivated by engaging them in repetitive stimulation, via visual experience, visual training or non-invasive electrical brain current stimulation. These will strengthen synaptic transmission and synchronization of partially damaged structures (within-systems plasticity) as well as downstream neuronal networks (network plasticity). The extent of the resulting visual improvement and restoration however will still depend upon the amount of residual tissue and its activation state.[32]

Proponents of VRT have reported modest enhancements in visual fields[29] and improvements in detecting and localising stimuli in blind areas[31]. In a randomised controlled study on patients with pre- and post-chiasmatic lesions, Kasten *et al* found mean visual field expansion in the post-chiasmatic group by 4.9° (± 1.7) compared to 0.9° (± 0.8) in controls, and demonstrated improvements in a neuro-visual paper and pencil task (the ZVT test).[32] This result has been supported by larger retrospective studies of VRT in patients with cerebral ischemia, haemorrhage, head trauma, brain tumour and anterior ischemic optic neuropathy. Findings confirm expansions of up to 5° of the central visual field, which represent a 10-13% increase in the number of detected stimuli.[33-35] Improvements of ≥3% were noted in 76% of patients in one study; but response of treatment was difficult to predict: age, time from lesion and type of visual field defect were not shown to be good predictors of response.[33]

A small follow-up study by Kasten *et al* investigated the stability of visual field expansions and found no significant decline in the number of correctly detected stimuli after a training-free interval (mean 23.5 months after end of therapy). However, cluster analysis revealed

three types of patients, with increased (Type I), decreased (Type II) and stable (Type III) performance. The authors therefore proposed an explanation that many patients learnt to use their regained visual capacities not only during VRT but also in everyday life, while some patients do not, which resulted in a decrease in their visual function after the end of training.[36]

Functional improvements after VRT have also been documented by a few studies that used structured questionnaires[35] and self-reported visual functional scales[37]. A retrospective study on patients with brain damage who received VRT reported benefits including a general sense of improved vision (in 48% of respondents), increased visual confidence and mobility (75%), less collisions with people or objects (32%), resumption of old hobbies (29%) and better reading (44%).[35] Subjective improvements in reading performance were backed by further studies using more objective measures. Reinhard *et al* found an increase in reading speed of a newspaper article from 103 ± 45 words per minute (wpm) before training to 113 ± 50 wpm after training. Reading speed while reading a book paragraph increased from 110 ± 37 wpm to 114 ± 39 wpm after training.[38] A prospective study by Gall *et al* observed improvements in detection of light stimuli in the para-foveal areas which, as previously mentioned in the discussion on hemianopic alexia, are most relevant for reading performance.[39]

Vision Restoration Therapy: Uncertainties

The efficacy of VRT however remains controversial. Debate largely stemmed from the results of the Tübingen-Magdeburg study of 17 patients where visual field expansion found with conventional perimetry and supra-threshold perimetry could not be confirmed by scanning laser ophthalmoscopy (SLO), which found no explicit shift in visual field defect borders.[38] The scanning laser ophthalmoscope is an instrument that presents visual stimuli to the retina while the fundus is observed and videotaped. It is the ‘gold standard’ of controlled

perimetry, with its well-recognised advantage being the ability to control for possible shifts in fixation. Invalid trials due to inadequate fixation (such as saccades) can then be disregarded.[28]

The results of the Tübingen-Magdeburg study therefore challenged the belief that VRT works by activating visual neurons and led to suggestions that apparent improvements in visual fields may be due to changes in fixation[40], and functional improvements due to a placebo effect[28]. Plant[28] and Horton[40] both argued that it is well established that patients with homonymous hemianopia develop adaptive eye movement strategies that involve frequent involuntary saccades (fast eye movements) towards their non-seeing side in an effort to maintain surveillance of blind regions in their visual fields, and so fixation is difficult to control in such patients. Saccadic eye movements may therefore have contributed to improvements observed in the performance on conventional perimetric tasks. They further argued that the method of monitoring fixation during VRT, which rely upon the patient reporting a change in colour of the fixation target, may not be fully sensitive to such eye movements. This is because detection of colour transition does not require foveal vision. Furthermore, this method is usually to prevent patients' eyes from wandering or shifting gaze for seconds of time and may not be effective if the patient is making frequent exploratory saccades throughout the testing period.[28,40]

Sabel *et al* defended the discrepancy between SLO and conventional perimetry findings with the explanation that SLO tasks was far more difficult and probably beyond the abilities of a damaged visual system.[41] They also disputed claims that visual field enlargements are artefacts induced by eye movements. It was pointed out that if patients had unstable fixation or eye movements, it would be expected for border shifts to be consistent across the entire border of the seeing and non-seeing field. However, this was not the case and border shifts often occur in some regions of the visual field and not in others.[26] It was also noted that the

Tübingen-Magdeburg study did not identify any shifts of fixation in patients undergoing VRT – although it remains possible that monitoring patients differently using SLO may have altered stimulation of eye movements by VRT.[26] However, previous studies have shown fixation reliability to improve over the course of VRT[29,35,42,43], and this is supported by subsequent studies which monitored eye movements more objectively.[44,45] In a study of 15 patients whose eye movements were monitored with an eye tracker, VRT was shown to have no effect on the direction or amplitude of horizontal eye movements during visual field testing, and saccades showed no preference toward or away from the blind hemi-field.[44] In a small series of seven patients with fundus-controlled microperimetry, which allows for accurate assessment of visual fields independent of eye movements, there was an average improvement in stimulus detection rate of 12.5%.[45]

Ultimately, the mechanisms by which VRT exerts its effects remain incompletely understood. Interestingly, recent trials combining VRT with transcranial direct current stimulation (tDCS), which modulates cortical excitability, had encouraging results with suggestions that brain electrical stimulation may enhance inherent mechanisms of plasticity that are associated with VRT.[46-48] Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies on small numbers of patients[49-51] have found changes in visual areas after VRT, which invoked suggestions of cortical reorganisation.[2] However it is unclear whether these results represent expansion of receptive fields in the primary visual cortex.[52]

It should be mentioned that most of the published VRT studies to date (and cited above) have been conducted by a group of researchers led by Kasten and Sabel, scientists at the University of Magdeburg who are also affliated to NovaVision.[26] The Tübingen-Magdeburg study was their collaboration with scientists in Tübingen, a centre renowned for leadership in the field

of perimetry. Interestingly, there was some disagreement between the two collaborators in the interpretation of their joint findings.[28]

Other doubts and concerns have also been raised with regards to VRT. Horton queried the logical possibility of an artificial stimulus applied one hour a day during VRT being more effective than the rich repertoire of natural light patterns that stimulate the retina every day. With VRT reported to be effective in both pre- and post-chiasmal lesions, he also found it difficult to conceive of a physiological mechanism that might explain how the same treatment could work at such different levels of the visual system.[40] Finally, VRT is a costly intervention. Most clinical centres in the United Sates (US) charge each patient approximately US$6000.[26] It also takes up a significant amount of patient time and effort. Could these therefore be justified by the purported benefits of VRT?

Conclusion

The US Food and Drug Administration (FDA) cleared the commercialisation of VRT in 2003 and the first patients were treated with VRT in the US in 2004.[26] However, a Cochrane review of interventions for visual field defects in patients with stroke and the UK national stroke rehabilitation guidelines did not recommend the use of VRT on the basis of insufficient and inconsistent evidence.[25,53] Therefore, despite the growth in research on restorative interventions for visual field defects, further research is still needed to determine the precise mechanisms of action of VRT, develop more sensitive objective measures of therapy outcome, and identify predictors of outcome. Higher quality studies with larger sample sizes and a control group are needed to properly assess the efficacy of VRT.

To conclude, VRT has the potential to be an effective intervention in neuro-rehabilitation for patients with visual field defects. It has however a long road ahead and further research and understanding is required before it can be considered a valid treatment option.

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