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Rehabilitation of damage to the visual brain

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Abstract

Homonymous visual field loss is a common consequence of stroke and traumatic brain injury. It is associated with an adverse functional prognosis and has implications on day-to-day activities such as driving, reading, and safe navigation. Early recovery is expected in around half of cases, and may be associated with a return in V1 activity. In stable disease, recovery is unlikely beyond three and certainly six months. Rehabilitative approaches generally target three main areas, encompassing a range of techniques with variable success: visual aids aim to expand or relocate the affected visual field; eye movement training builds upon compensatory strategies to improve explorative saccades; visual field restitution aims to improve visual processing within the damaged field itself. All these approaches seem to offer modest improvements with repeated practice, with none clearly superior to the rest. However, a number of areas are demonstrating particular promise currently, including simple web-based training initiatives, and work on neuroimaging and learning. The research interest in this area is encouraging, and it is to be hoped that future trials can better untangle and control for the number of complicated confounds, so that we will be in a much better position to evaluate and select the most appropriate therapy for patients.

Keywords

Homonymous hemianopia; rehabilitation; eye movements; neuroplasticity; stroke

1. Introduction

It is widely recognised that stroke is the most frequent cause of homonymous visual field defects (HVFD), with an estimation that between 40-86% of isolated HVFD are caused by posterior circulation ischaemia (Smith 1962, Fujino 1986, Trobe 1973, Zhang 2006a). Other common aetiologies include traumatic brain injury, tumour (each <15%), and less frequently brain surgery and demyelination (Zhang et al., 2006a), with causative lesions most commonly in the occipital lobes (45%) and optic radiations (32.2%).

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In the UK alone there are approximately 150,000 new cases of stroke a year, with between 8-26% left with persistent hemianopia (Gilhotra 2002, Gray 1989), which may be closer to 30% acutely (Haerer 1973). Figures vary quite extensively, however, with variable population demographics, measurement techniques, and reporting biases.

Stroke is also considered to be the most common cause of disability in adults (Hankey 1999), and is likely to increase in the future with an aging population. Importantly, HVFDs in such patients are associated with an adverse functional prognosis, including likelihood of discharge home (Schlegel et al. 2003), mobility, and survival (Haerer 1973, Gray 1989). Functionally, HVFD may impair day-to-day activities including driving, reading and obstacle avoidance, which can cause reduced participation in social activities and quality of life (Trauzettel-Klosinski 2011). At the other end of the spectrum, it is also worth noting that HVFDs often go unreported, perhaps overlooked or under-prioritised by clinicians, or because patients learn to compensate for their deficit (Zhang 2006a, Gilhotra 2002).

2. Natural History

2.1. Early recovery

There has been some debate about how quickly recovery of HVFD takes place after brain injury, with reports varying from two weeks (Gray 1989) to one year (Trauzettel-Klosinski 2005). Zhang et al. (2006b) reviewed the medical records of 254 consecutive patients with HH over a 15-year period, and performed a regression analysis to determine probability of improvement (reduction in VFD more than 10° horizontally or 15° vertically) as a function of time after injury. Although this was not a prospective study and follow-up varied between patients, they suggested that at one month there was a 50-60% chance of recovery, which fell to around 20% at 6 months. They continued to see a similar improvement beyond 6 months, although changes were attributed to improvement in the underlying disease or cognitive ability to undergo testing. No cases with stable underlying brain disease such as stroke continued to improve beyond 6 months, with most occurring within 3 months.

These results are consistent with prospective stroke studies (Tiel and Kolmel 1991, Gray 1989) including Celebisoy et al. (2011) who used automated perimetry to document recovery in 32 patients with occipital lobe infarct at 6 months. They found improvement in the peripheral zones of the lower quadrants, with worst prognosis associated with striate cortex involvement and greater lesion size.

More recently, two studies have utilised brain imaging to monitor the neural changes over this 'recovery period'. Raposo et al. (2011) observed 8 patients with posterior cerebral artery stroke using fMRI at three time points: within 30 days of stroke, then at one and three months later. Visual stimuli targeted motion and colour separately to each hemifield. When compared to control stimuli, colour in the blind field only activated V4 by the third time-point (contralesionally), at which time there was also activation of ipsilesional V1 compared to rest. In contrast, both moving and static checkerboards seemed to activate contralesional V5 at the first two time-points, then ipsilesional V5 at three months. Behaviourally, half of subjects at the start could already identify direction of motion from a choice of four, whilst only two correctly identified colour over chance. Over time, this improved for all patients

such that average success was around 75% for colour, and 85% for motion. The reason for a lack of true motion effect (moving vs. static stimulation) on fMRI is unclear, and does not correspond with the behavioural findings. The authors suggest it may be due to the small stimulus size, however the overall findings are interesting and encourage further work to be undertaken. Polonara et al. (2011) only investigated recovery in one individual, but also employed DTI. They also found that recovery in the acute phase (although slightly earlier, at one month post-stroke) is associated with a return in V1 activation, together with a restoration of tract integrity in the ipsilesional optic radiations.

2.2. Residual function and spontaneous functional adaptation

In the chronic phase after injury, it appears that HVFDs become more static, and it is this stage which is most difficult to treat. Numerous studies have suggested that during this chronic phase, patients may adopt compensatory eye movement strategies to assist with their deficit (Pambakian 2000, Zihl 1995). Whilst healthy controls fixate mostly at the centre of a patterned image, hemianopes paradoxically concentrate on the blind hemifield, thus shifting it into view (Ishiai et al. 1987). This has been shown in a number of different tasks such as viewing images of real scenes (Pambakian et al., 2000), and whilst assembling wooden models (Martin et al. 2007) – although in the latter this was not seen in every participant.

Hemianopes may also adopt strategies for refixating between targets (Meienberg et al., 1981), for example performing a number of increasing hypometric saccades (stairstep) before finding the target or overshooting by a few degrees together with a short, corrective saccade to foveate the target. These mechanisms, however, are not ideal as an increased number of refixations, together with somewhat disorganised scanning leads to longer search times and possible omission of relevant objects (Zihl 1995). More recent research suggests that which gaze strategies are employed vary according to lesion site, and as a function of task demand (Hardiess et al., 2010).

3. Blindsight

As well as compensation to simply shift the field of view to the unaffected side, some work has suggested that saccadic eye movements (Barbur et al., 1988) and obstacle avoidance (Striemer et al., 2009) can be influenced by unseen stimulation within the blind hemifield.

‘Blindsight’ refers to the observation that certain stimuli within the blind hemifield can undergo processing and influence behaviour despite the individual often being completely unaware of their presence (Weiskrantz 1974, 1987). It suggests that even within the chronic phase when standard perimetry demonstrates a HVFD, certain aspects of visual abilities including motion, colour, and contrast detection are retained, with the degree of subjective awareness varying considerably across different manipulations (see Weiskrantz 2004 for review). This was initially attributed to surviving ‘islands’ of V1 (Fendrich et al., 1992), however there is now substantial evidence to the contrary (Stoerig et al., 1998). Indeed, stimuli with specific spatio-temporal properties are particularly effective at eliciting blindsight, with this ability perhaps even present in the majority of patients with V1 damage (Sahraie et al., 2008).

Two main pathways are reputed to subserve blindsight, with evidence existing for both. One involves subcortical projections from the retina to superior colliculus and pulvinar, which then project to other visual cortical areas bypassing the damaged V1. The other projects directly from surviving LGN neurons to extrastriate cortex.

Several studies demonstrate activation of the superior colliculus during VHFD stimulation (Barbur 1998, Barbur 1993, Sahraie 1997). Similarly, primate studies involving selective destruction of V1 and superior colliculus show manual and saccadic localisation become severely disturbed (Feinberg et al., 1978). In contrast, more recent work shows a clear causal role for LGN pathways. Non-human primates can detect targets presented within a scotoma caused by V1 damage, associated with contralateral extrastriate fMRI response (Schmid et al., 2010). Chemical inactivation of the LGN then abolishes virtually all activity, which returns once inactivation is reversed.

Although these results lend support for alternate pathways mediating blindsight, they do not explain whether activation comes from intact residual pathways, or some innate ability of the human cortex to reorganise following injury. This remains a controversial discussion, with important implications on treatment.

4. Plasticity in the visual system?

Despite certain limitations, diffusion-weighted MRI offers a unique method to explore noninvasively the organization of white matter in the living human brain. Two important studies have employed this technique with probabilistic tractography following V1 damage. Leh et al. (2006) looked at four patients with previous hemispherectomy for intractable epilepsy. They subdivided patients into those with and without indirect blindsight, and suggested that those with blindsight showed unique contralateral connections from superior colliculus to visual, parietal, and prefrontal areas as well as to the posterior part of the internal capsule, which were not present in the alternate group or healthy controls.

Bridge et al. (2010) used similar techniques in a well-described blindsight patient, GY. They showed that normal pathways bypassing V1 from LGN to extrastriate cortex remain intact. They also demonstrated two new connections absent in healthy controls, from contralesional LGN to ipsilesional extrastriate cortex, and extrastriate cortico-cortical connections bilaterally. Both studies should be interpreted with the caveat that the original brain damage occurred early in life, when it is suggested that plasticity is more viable. However, recovery of motor function after stroke is often attributed to cerebral reorganisation (Ward 2003), and other examples of plasticity following visual pathway damage in adulthood have been reported (e.g. Dilks 2007, Henriksson 2006, Raninen 2006).

5. Rehabilitative Approaches

Irrespective of the presence or absence of unconscious processing, hemianopic patients remain significantly impaired in day-to-day life. Here we detail the rehabilitative approaches designed to offer both practical improvements to the sighted field, as well as techniques designed to improve vision with training. There are currently three main approaches, incorporating a number of techniques of varying popularity and evidence. These include the

use of visual aids, a number of eye movement training techniques, and attempts to restore the deficit itself, so-called visual field restitution (VRT).

5.1. Optical Aids

A number of optical devices can be used to improve perception of the visual scene by expanding or relocating the visual field. This is most commonly achieved through use of prisms, which are fitted onto spectacles on the side of the field loss, and reflect images onto the functional side of the retina. Other devices used in the past include mirrors that can be partially reflecting, or dichroic, causing a disparity in colour between the reflected and transmitted images (Cohen 1993).

Prisms can be fitted binocularly or monocularly, with the former providing only visual field relocation and not expansion, and the latter providing field expansion only when gaze is directed into the prism. This can be a problem if the prism is restricted to the hemianopic field, but can be resolved by stretching the prism out across the whole lens. Another problem can be central diplopia, which is often disorientating to the patient.

To preserve vision and prevent central diplopia, monocular prisms can be fitted separately to the upper and lower parts of the lens. Peli (2000) tested this technique using a 40 dioptre prism in 12 patients with HVFD. In all but one patient they found a field expansion of 20°, with subjective improvement in nine. A further multi-centre evaluation of peripheral prism glasses was carried out by Bowers et al. (2008). They found that 47% patients still wore the prism glasses more than 8 hours a day after 12 months, finding subjective benefit in obstacle avoidance.

5.2. Eye Movement Training

5.2.1. Visual Search—The idea that explorative eye movements can be enhanced to provide an improvement in visual perception and obstacle avoidance has been around for decades, although it has received somewhat of a resurgence in the last few years. The general principle is based upon the earlier description that visual search in these patients is often unsystematic and time-consuming, thus reducing the ability to appreciate the visual scene as a whole (Zihl 1995). Explorative training tries to manipulate the compensatory strategies seen in patients, to an advantageous outcome.

In earlier work, subjects were trained to make large saccadic eye movements to targets in the blind field using sizeable Tübingen perimeters. Findings were encouraging and suggested that a period of training such as 8-23 half hour sessions were enough to generate altered search strategies (Zihl 1995). Even 'blindsight'-guided training, using 100ms targets, appeared to show an improvement in the ability to detect and localise stimuli (Zihl 1980). It was, however, difficult to see how this would translate into real-world effects.

Pambakian et al. (2004) adapted the technique by offering a portable, low cost method for training visual search. They recorded more functional outcomes including completion of activities of daily living (ADL), and a visual disorder questionnaire. 76% of patients had a significant improvement in visual search response times, which persisted for one month post-training and was not attributable to practice. Three patients became slower for both

blind and sighted fields, although this appeared to be a trade-off for a dramatic improvement in error rate. Functionally, there was a small overall improvement in ADL times and self-reported performance in crossing the road and finding objects. Another more recent technique that can be carried out at home via a computer-based ramp-step search paradigm also appears promising, with a significant improvement in search reaction times after only one training period (Jacquin-Courtois et al., 2012).

Nelles et al. (2001) provided patients with 4 weeks of two daily 30-minute sessions practicing visual search, and showed similar improvements lasting 8 months after training. They went on to use functional imaging to investigate whether there was any change in brain activation (Nelles et al., 2009 and 2010), in the same way that motor training in the healthy adult is associated with a change in BOLD signal (Kami et al., 1995). Unfortunately, training was started only 8 weeks post-stroke, thus introducing the significant confound of natural progression, as well as the fact that patients were undergoing general post-stroke rehabilitation at the time! Nevertheless, they found an increase in contralesional extrastriate activity during hemifield stimulation in the scans taken 4 weeks after training was complete, which was not present in controls. They also showed increased ipsilesional extrastriate activation during visually-guided saccades. It is interesting that the most notable changes occurred some time after training was complete. This could certainly represent a gradual evolution of the learning effect (Karni et al., 1995). It would, however, be important to rule out other factors to clarify these results.

There are very few randomised controlled trials within this area, with one comparing digit-search to flicker training on explorative saccadic behaviour (Roth et al., 2009). They concluded that search training was superior on various measures including reaction times and number of fixations in the blind versus sighted hemifield. This was a positive step as patients were recruited in the chronic phase and were randomly allocated to treatment groups. However, it did not address the role of attention on training effect, which is an important point to consider.

Lane et al. (2010) compared a standard exploratory training paradigm to attentional training, although in the former they did not provide instructions for how participants should move their eyes (generally this is specified in other studies). In an attempt to make both tasks as similar as possible, attentional training also involved 'search' for targets within 1° of fixation. Results were mixed and dependent upon which search test was used to measure outcome. In a 'find the number' test within the trained field-of-view, there was significant improvement in reaction times after exploratory training, but none after attentional training. In the visuomotor test, both showed improvement, even if attentional training had already been given. For the most difficult 'projected search' test (outside the trained field), both tasks caused improvement, but there was no additional gain when exploratory training followed attentional training. These results highlight the importance of attention in training, although further work needs to be done to fully understand its contribution to rehabilitation trials to date.

5.2.2. Alexia & Reading—Both Lane and Roth (2010, 2009) amongst others have also shown that visual search training does not translate to improved reading speed. Indeed,

search strategies do not address the small, step-wise eye scanning or specific part of the visual field that is required to read left-to-right text (Zihl 1995, see Schuett 2008 for review). Hemianopic alexia is an important consequence of hemianopia and can be particularly debilitating. It is also receiving particular attention at the moment.

In research substantiating the above views, Schuett et al. (2012) performed the first cross-over rehabilitation study to look for transfer of training-related improvements between reading and visual exploration training. Reading training required patients to read a presented word out loud, before rapidly shifting gaze to beginning or end of the word, depending upon their affected field-of-view. When accuracy reached 90%, difficulty was ramped up, continuing for around 45 minutes. They found that reading training led to significant improvements in reading performance but had no effect on visual exploration; likewise, while visual exploration training significantly improved visual exploration performance, it had no effect on reading. Neither training alone appeared sufficient to improve both abilities.

It therefore appears that at the moment at least, distinct training strategies should be employed. Indeed there is increasing evidence for success with targeted reading training. Spitznaya et al. (2008) trained patients to read scrolling text for four weeks, as a way of inducing small-field optokinetic nystagmus. They found a significant improvement in static reading speeds compared to controls, as well as a direction-specific effect on saccadic amplitude for rightward but not leftward reading. In a modern 'web-app' approach that also presents patients with laterally scrolling text, Leff and colleagues demonstrate improvements in reading speed that correlate with duration of treatment (Ong et al., 2012). Although in its early stages, they hope to offer this 'app' to patients as a more practical approach to rehabilitation.

5.3. Visual Field Restitution (VRT)

5.3.1. Border-field VRT—Visual field restitution (VRT) is the general term given to improving visual processing within the damaged field itself. It is an area that has proved controversial at times, but still continues to receive much support. In reality VRT encompasses a number of different approaches to visual field recovery, although VRT as a term is generally synonymous with the work of Sabel, Kasten and colleagues (NovaVision). We will refer to this area as 'border-field VRT'.

Initial work on VRT came from Zihl and von Cramon in the 1980s, which sought to replicate work on non-human primates (Zihl and von Cramon, 1982 and 1985). Later on, Sabel and Kasten provided patients with a computer-based therapy, carried out for an hour a day over 6 months (Kasten, 1995). Investigators designed an algorithm to enable specific targeting of the 'transition zone', an area representing the border region between intact and damaged visual-fields. They proposed that these zones were functional representations of partially spared neuronal structures in areas of the brain that were only partially injured (Kasten et al., 1998). With repetitive stimulation, they showed that 95% of patients gained visual field expansion of around 5°, measured by high-resolution perimetry. This assessment technique was described, together with the training program, in a separate publication from the authors (Kasten and Sabel, 1997).

One criticism of the work was that saccadic eye movements were not fully controlled for, nor appropriately taken into account. As already discussed, patients develop compensatory mechanisms to increase saccades into the blind hemifield. This concern was quite categorically upheld in a follow-up study using a scanning laser ophthalmoscope (Reinhard et al., 2005), considered one of the most effective ways to control eye movement as experimenters visualize fixation on the fundus throughout the task, and discard trials whenever saccades are made (Plant 2005). Another obvious criticism was that the measurement technique was almost identical to that used in training (Horton 2005). This is an important issue for all rehabilitative trials, and remains relevant in more recent publications (Romano et al., 2008). To determine a true effect on visual field loss, a standardized and independent measure must be employed. In the follow-up study of 17 patients, no improvements in field size were found using microperimetry, despite 6 months of similar VRT (Reinhard 2005), nor were they found using Tuebingen automated perimetry (Schreiber et al., 2006).

One unfortunate sequela of these discussions was to further polarize the rehabilitative camps for recovery versus eye-movement training. Work on border-field VRT continues to be published, with an increasing number of patients involved in trials across Europe and the United States. Despite limitations, the principal is an interesting one that may lead to further developments in the future. Perhaps more understandable in terms of its biological target, are rehabilitative methods incorporating intact visual pathways discussed earlier.

5.3.2. Blindsight VRT and perceptual learning—Although not often considered a unique subgroup in visual rehabilitation, there is a growing literature on perceptual learning in HVFD. Perceptual learning refers to the improvement in psychophysical performance that comes with practice. For instance, anyone undergoing repeated visual field testing would expect to see a degree of improvement in sensitivity. In one respect, this is to be considered a confounding factor when assessing VRT (Horton 2005). Conversely it is argued that repetitive training can help the damaged visual system relearn how to process visual information (Das and Huxlin, 2010).

A large component of this work comes from so-called ‘blindsight VRT’ led by Sahraie and colleagues. There are, however, a number of other studies that have employed blindsight-stimulating techniques, without necessarily labelling them as such (e.g. Raninen 2006, Henriksson 2007). The principal is for repetitive presentation of salient stimuli, custom-designed to undergo blindsight via particular spatial and temporal properties. By using this technique in 12 patients over a three-month training period, Sahraie et al. (2006) demonstrated improvements in sensitivity, detection and awareness deep within visual field defects. They suggest that positive feedback further accelerates this effect (Sahraie et al., 2010).

One of the positive aspects of this research is that it targeted patients with chronic (>6 months old) brain injury and amongst other techniques, used standardized Humphrey perimetry to measure outcome. However, other outcome measures included recording awareness (which generally improved) of the same high contrast, high salience stimuli that were used in the training task. One concern about this group’s work is that it, as indeed

blindsight itself may be, is tuned to stimuli of specific spatial and temporal properties that may not be translatable to different stimulus types, or untrained parts of the visual field. Also, the very nature of blindsight is that it can occur without conscious perception. Overall, the approach appears promising, and represents one of the first methods to generate improvement deep within the scotoma. Whether one can expect a functionally useful improvement in conscious vision will need to be determined.

Huxlin and colleagues (2009) used perceptual learning to train patients to discriminate global direction of moving dots in a random dot kinetogram (RDK) via a staircase learning procedure. After training for several thousand trials, patients become able to correctly discriminate direction for coherent dots, and also attain normal direction integration thresholds. Interestingly, whilst not specifically trained for, there is also an improvement in contrast thresholds for direction, measured using drifting sine-wave gratings. This is important because it shows that perceptual relearning of motion direction is possible and can be translated to stimuli distinct to those used in training (Das and Huxlin, 2010). All these studies, however, demand very long training periods with retinotopic-specific learning taking considerably longer than might be expected for perceptual learning in healthy subjects. It is therefore important to understand the mechanisms behind these findings, and a number of recent neuroimaging studies have offered some early insight into these.

6. Functional imaging of rehabilitation

Henriksson et al. (2006) investigated the effects of training on changes in fMRI and MEG activation. Training involved a difficult detection task of flickering discs and recognition of flickering letters twice a week over 2 years. They found that after training, stimulation of the blind hemifield with a large reversing checkerboard activated contralesional V5, as well as V3a, and to a lesser extent V3, dorsal V2, and a border region between V1 and V2d. Although only MEG and not fMRI were measured before training, no initial MEG response was found. Behaviourally, two patients improved on flicker detection and subjective reports of real-world navigation, but made no gains on static perimetry (Raninen et al., 2007), highlighting again the specific nature of improvements.

As discussed earlier, Nelles et al. used fMRI to study the effects of eye movement training. In the study looking at hemifield stimulation (Nelles et al. 2010), they also used a reversing checkerboard to invoke visual activation, this time recording changes pre- and post- training. They found that even at baseline, there was significant activation bilaterally in extrastriate areas, strongest in the contralesional hemisphere, which increased further 4 weeks after training was complete. This is interesting but highlights the discrepancies still present, as other studies have suggested stimulation of the blind hemifield (without training) activates ipsilesional extrastriate cortex (Goebel et al., 2001).

In a retinotopy fMRI study pre- and post-VRT, Raemaekers et al. (2011) find early visual cortex receptive field changes, but suggest that they can only account for small, local visual field increases, and are insufficient to account for the larger visual field improvements seen in some of their patients. Even in the healthy state, to what extent perceptual learning relies

on local changes in receptive fields of neurons in early visual cortex remains strongly disputed (Bao et al., 2010).

Overall the evidence is mixed, but proponents suggest there is growing support for some sort of plasticity-driven process employing either ipsi- or bilateral intact visual cortex. We have already discussed the possibility of altered cortico-cortico, thalamocortical, or subcortical pathways in certain patients with blindsight (Leh 2006, Bridge 2008). It may be possible therefore for similar pathways to become recruited during training. Whilst far from clear, this avenue is certainly generating enthusiasm for future research (see e.g. Stoerig, 2008).

7. Conclusion

There are a number of rehabilitative techniques currently available, most of which offer specific and non-transferrable improvements in vision. No treatments to date claim to be able to fully restore vision to the damaged hemifield, although this remains the goal for restitution and plasticity-based research groups. The approach in other laboratories remains more pragmatic, focusing on the most effective ways to compensate for the deficit rather than looking for recovery. At this stage, it appears that separate, specific therapies would need to be employed to maximise improvements in vision. As most therapies require repetitive training over a prolonged period, this would be extremely time-consuming for patients and would be very difficult for them to adhere to. Ideally we would see a more integrated, single therapy that could provide the best outcome in terms of visual search, field size and patient experience. It is also important, as well as improving the quality of future studies through larger sample size and better control for attention, placebo-effect, and disparate outcome measures, to look closer at the mechanisms involved in recovery and plasticity after visual cortex damage. This may allow better focus for future research, and creation of more effective options for rehabilitation.

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