The quest to restore vision long after brain damage in adulthood

Activating residual functions improves visual fields

It has long been thought that blindness after brain lesions is permanent. Patients who suffer visual field defects as in hemianopia following visual cortex lesions or the more diffuse visual field loss found after optic neuropathy have had no real options to be treated. Some clinicians trained patients to better explore the missing areas of their visual field by compensatory (scanning) eye movements into the blind field. Though this approach results in enlargements of search fields and reduced reaction times to locate targets on the side of the visual field defect, actual improvements of perceptual dysfunction could not be achieved by this approach.

However, visual field stimulation strategies have been developed that are aimed at increasing the sensitivity of residual functions at the border of the blind regions or inside of it. Such vision restoration stimulation can achieve improvements in detection ability, which is also seen as enlargements of the visual field. These studies have unveiled previously unrecognized potentials of residual visual functions; they can be activated to achieve visual improvements.

Areas of residual vision
The predominant strategy here is to activate residual visual capacities within ‘areas of residual vision’ (ARV) located at the border of the scotoma or inside of it or even deep in the blind field. These ARV can be observed easily in standard visual field examinations such as static threshold perimetry. ARV are regions of reduced detection thresholds (relative defects) or areas where patients respond less reliably or more slowly to stimulus presentations. Thus, ARV have been there all along, but in the world of perimetry they were termed ‘relative defects’. But just as a glass of water may be seen as half empty or half full, the term ARV is less pessimistic, pointing rather to the therapeutic value of these visual field regions. The relative defects were rather traditionally viewed as just a less severely affected sector of the deficit or areas of ‘ambiguity’ caused by variable patient performance or eye movement artefacts, with no real need for further study.

It is now becoming clear that ARV are functional representations of regions of the visual pathway, which are only partially injured and this might explain why perception in ARV is variable (i.e., more prone to sensitivity changes during the course of the day, such as attention loss or fatigue, and other influences that alter their functional activation state). Vision is not a static affair, determined by the optical apparatus only. It also engages many brain mechanisms of perception and attention, which seem less ‘physiological’ and more ‘psychological’.

For instance, light detection performance within ARV may increase with higher levels of alertness and attention and decrease with fatigue. In fact, patients feel that their performance varies during the day and assessment in the clinic or the laboratory typically shows some variable performance that is typically seen in the size or defect depth of the relative defect, which can be measured with threshold perimetry.

It has become clear that ARV can be activated to achieve therapeutic progress. In fact by regular activation residual functions can improve permanently. In recent years there has been some progress in this field and now activation of residual functions can be achieved in two different ways:

In short...
Blindness after brain lesions has long been considered permanent damage with no real options for treatment. As vision restoration research shows, it is possible to increase the sensitivity of residual functions at the visual field border or inside of the blind regions, with improvements in detection ability. The predominant strategy is to activate residual capacities within areas of residual vision (ARV) that can be observed easily in standard visual field examinations. Recently it has become clear that ARV are functional representations of regions of the visual pathway that are only partially injured and might explain why perception in ARV is variable and modifiable. Further to this work, there has been research in the area of non-invasive electrical brain stimulation. These strategies not only improve visual fields but also quality of life. Functional improvements in vision can be achieved through a variety of methods and future research should focus on the opportunity of vision restoration.
by vision restoration training that entails visual stimulus presentation repeatedly to these ARV, or (2) by non-invasive electrical stimulation, a research field that is now emerging. Figure 1 shows visual field charts of a patient with nearly complete monocular blindness with some residual vision in the lower left quadrant. After treatment with non-invasive electrical brain stimulation (electrode placement around the eye) significant improvements of vision were observed within this quadrant, emerging from the fields of residual vision.

**Stimulation approaches**

Both approaches, behavioural training and non-invasive electrical stimulation, are similar in that repetitive stimulation may lead to functional visual improvements. However, visual field training uses small visual stimuli to which the patient responds by pressing a key (just like in perimetry) in daily training sessions for 6 months. The recently developed non-invasive transorbital alternating current stimulation (tACS) achieves repetitive stimulation by electric current with comparable effects only after 10 days. The stimulation protocols of visual field training uses rather unspecific stimuli. For example, in vision restoration training small white dots are used on black background. The tACS approach, in contrast, uses no visual stimuli at all but trains of electrical current in particular frequencies that stimulate brain plasticity. It is interesting to note that the number of stimulations to achieve clinical effects in both procedures are roughly in a similar range: Whereas training requires about 10 000 visual stimulus presentation per day for 3–6 months (i.e., a total of approximately 90 000–180 000), the tACS protocol requires the delivery of about 10 000 pulses per day, which can be done in about 30 min, for a total of 10 days (i.e., 100 000 stimulations). Though both lead to similar clinical improvements, visual training is a rather laborious affair to the patient, a hurdle in scaling up its use. In contrast, current stimulation, which is not focused only on the ARV but stimulates the entire visual system, is a more accelerated method. It cuts down therapy time from 6 months to about 10 days. This means less effort is required of both the patient and medical personnel, facilitating adoption in clinical practice.

**Functional improvements**

Whatever method one chooses to activate residual function, functional improvements can be seen. For example, repeated stimulation of ARV with light stimuli (e.g., by visual field training) lead to functional gains observed in both standard and high resolution perimetric measurements and the improvements occur mostly (80%) in ARV, and only 20% in the areas of absolute blindness. However, about a third of the patients do not respond to the therapy, especially if their ARV size is rather small. Based on these observations we propose that the fundamental mechanism of vision restoration is permanently increased neuronal activity in ARV. We hypothesize that injured neurons mediate residual vision at a sub-threshold capacity and stimulating these neurons and their up-stream neuronal networks (by inducing brain plasticity) improves the function of the visual pathway.

This basic hypothesis was recently confirmed by computer-simulation studies using data-mining methods. Here, areas of visual field improvements were primarily found in regions with considerable residual vision and recovery depended to a large extent on local topographic interactions. The probability of a given spot to recover (‘vision restoration hot spots’) depended not only on its residual activity (defect depth) but also on the residual activity in the immediate surround.

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**Figure 1:** Visual field of a patient P3 (see Figure 2) suffering optic nerve damage. This visual field chart was obtained at a computer monitor and displays areas of the absolute defect (black), partial visual function (areas of residual vision, ARV, shown in grey) and intact areas (white). Defect depth was determined by repeated presentation of super-threshold stimuli. As this graph shows, the patient showed a significant recovery of the visual field predominantly in the lower left quadrant after 10 days of non-invasive alternating current stimulation of the brain (stimulating electrodes are placed around the eye).
but observed not only increased light stimulus detection but also improved visual acuity, critical flicker fusion frequency and colour vision in the regained visual field areas of the visual field. This is similar to our own studies where a transfer of training to other visual capacities (such as colour vision) was noted. If the concept of ‘residual visual activation’ is correct, one would expect that functional changes go along with cortical activation pattern changes. The particular role of ARV was confirmed by Marshall et al. who measured the blood oxygenation level (BOLD) in six patients with chronic homonymous hemianopia in ARV (here, border zone between intact and defect visual field) and at an intact seeing position before and after one month of visual field training. They observed an alteration of brain activity, which was associated with an attentional shift from the intact visual field towards the area of residual visual function at the border zone to the blind field. This suggests that attention plays a central role in vision restoration. In fact, in a behavioural study where visual training was combined with a localized attention task (induced by cues) permanently improved visual functions were specifically observed in those attended locations.

While some critics are at issue with the fundamental proposal that vision restoration is possible at all, the concept of post-lesion plasticity in the adult visual system is now generally accepted. While short-term improvements similar to those observed during spontaneous performance fluctuations might be scientifically interesting, it is of far greater interest to continue collecting evidence of vision restoration and to find clinically useful means to achieve long-lasting functional changes with as little effort to patients and personnel as possible. So far, many months of training were required to achieve enlargements of visual field with clinical benefits. Studies are now underway to develop new methods to speed up restoration. We are currently evaluating the tACS method to achieve visual field improvements in as little as 10 days of therapy. Initial findings are encouraging and suggest that such a goal may actually be achievable (Figure 2). Properly controlled clinical trials with positive and clinically meaningful outcome are necessary to make this method ready for routine clinical use. These trials are currently underway.

Whatever method one chooses to achieve vision restoration it appears clear that functional improvements in vision can be achieved in a variety of indications. These not only include diseases caused by brain-dysfunction such as...
as hemianopia/scotomata and optic neuropathy, but also amblyopia\textsuperscript{16} and retinal disorders such as glaucoma.\textsuperscript{17} In hemianopia it was already shown that vision restoration can not only be demonstrated by clinical parameters (such as detection performance in perimetry), but it also positively influences some activities of everyday visual functions.\textsuperscript{18} It is important to note that after VRT and tACS treatment patients still have to cope with a somewhat smaller visual field defect but many patients consider the vision improvements as subjectively meaningful.

Fortunately, the traditional view of an ‘inflexible’ visual system has given way to a more optimistic view: visual field loss must not be permanent. Rather, the brain has a remarkable potential for plasticity and self-repair, even in the adult visual system. If still sceptical, consider this quote by Torsten N. Wiesel (Nobel Laureate, Rockefeller University) made during a lecture at the symposium ‘Restoration of vision after brain damage’ at the ‘VISION 2005’ meeting in London on 6 April 2005, Royal National Institute of the Blind (RNIB):

“Restoration of vision after damage is an issue I am very interested in and I think that there is progress; to find different means of restoring visual functions is very interesting and encouraging... (My experiments on receptive field enlargements) are hard evidence that it is possible to restore (visual) function through time. In this case we did not make any special effort by stimulating the eyes... trying to restore visual functions... but this kind of experiment gives you hope that there is more to learn from this kind of experiment and also from the clinical work that it should be possible to restore patients’ vision in spite of an initially apparent lack of vision.”

Summary

The visual system, thought to be irreparably damaged after brain injury, has a remarkable plasticity potential that can be stimulated to improve residual functions. In this respect the visual system does not differ from any of the other functional domains (such as language, memory, attention, motor performance etc.) which all have plasticity potential after training or electrical stimulation. Just like these systems, the visual system of the brain is not only able to adapt to the damage by spontaneous recovery and self-repair, but it is quite receptive to rehabilitation, be it vision training or non-invasive electrical stimulation. Future research should focus on this opportunity of vision restoration. It gives patients a chance to restore some of their lost visual functions and raises the hope that even more effective therapies may be found to reduce vision loss that was thought to be permanent.

References

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