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Plasticity and restoration of vision after visual system damage: An update

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Abstract. The traditional view that visual system damage is permanent has given way to a more optimistic view. Visual loss does not remain unchanged but it can recover spontaneously to some extent. Even when the period of spontaneous recovery has ended there is still additional potential for plasticity and regeneration, even months or years after the lesion. There are two fundamental approaches to harvest this plasticity potential: (i) to rescue dying cells or induce axonal regeneration of visual system neurons through biological (pharmacological) means and (ii) to capture the residual vision capacities and improve their functions by behavioural training. Visual training can be used to activate residual visual neurons either in the blind sectors of the visual field through alternative pathways or it can be used to activate partially damaged regions in the border zone near the lesion site. Another example of post-lesion neuroplasticity is the ability of the intact visual field sectors to (spontaneously) take over functions and this is seen, for example, in macular degeneration and even in developmental disorders, such as amblyopia who benefit from training even many years beyond the critical period. Just as plasticity after brain damage is well recognized in other functional systems (motor, somatosensory), plasticity of the visual system is now gradually being recognized as a useful mechanism whereby the brain compensates for its functional loss, either spontaneously or by repetitive visual stimulation.

1. Introduction

It was 10 years ago since the publication of the first special issue of the journal RESTORATIVE NEUROLOGY AND NEUROSCIENCE on the topic of "Visual System Restoration and Plasticity". It is now time to monitor the progress that has occurred since then and this motivated my initiative to assemble papers for the present special issue. During the last decade we have witnessed how the traditional view that visual system damage is permanent has given way to a more optimistic view. We now know that visual loss does not remain unchanged but that it can recover spontaneously to some extent. Even when recovery is complete, there is notable additional potential of plasticity and regeneration. This includes two fundamental approaches: (i) the rescue, regeneration and transplantation of visual system neurons through biological (pharmacological) means and (ii) the capacity to improve visual functions by behavioural stimulation through training. The papers included in this special issue can not cover all aspect of visual system plasticity, but they were selected to focus on specific aspects of plasticity being discussed these days and attest to the view that – just as in other functional systems (motor, somatosensory) – the visual system has a remarkable capacity for plasticity and this is gradually being recognized as a useful mechanism of brain repair. Though progress happens not at the desired speed, there is a continued and ongoing effort by different groups in the world to find new means to enhance restoration and regeneration of vision after neurological dysfunction.

2. Biological regeneration and rescue

One fundamental approach to restore vision is to "rebuild" the damaged structure itself by some biological or pharmacological manipulation. The attempt to un-

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derstand and manipulate regeneration of cut retinofugal axons is the subject of the paper by Rose et al. (2008). These authors assessed the potential for axonal regeneration both *in vitro* and *in vivo* in organotypic cell cultures of monkey retina and studied molecular mechanisms involved in the regeneration process. Injury to the mature optic nerve is thought to lead to irreversible impairment. Under normal circumstances the retinal ganglion cells (RGCs) fail to regenerate their cut axons but when a proper biochemical environment is offered, the axons are indeed able to regenerate. Rose et al show that aging monkey RGCs retain their ability to regenerate axons in organ culture and they show how axonal regeneration is associated with a specific proteomic profile. Indeed, when offered the right environment for growth, Rose et al. found vigorous regeneration of axons throughout all stages of life though fewer regenerating axons were found with increasing age. Several proteins are now identified to play a prominent role in regeneration of RGC axons including laminin and GAP-43, calmodulin, fatty acid binding protein, alpha-crystallin, IFN-gamma, cyclin-dependent kinase inhibitor (p21), beta-hemoglobin, 60s-ribosomal protein, GAP-DH and ADP-ribosylation factor (ARF). These studies provide important clues to further our understanding of axon regeneration in the damaged visual system and demonstrate that axonal regeneration is regulated molecularly in a well coordinated way.

Gaillard and Domballe (2008) used another approach to restore visual structure. They implanted fetal issue allografts in the damaged adult visual cortex and described the physiological properties of the grafts and the role of the re-establishment of neuronal connections to the host brain.

Besides traumatic, vascular or degenerative diseases of the central visual system there is a special case to be made for optic neuropathy caused by infection with the syphilis virus. This disease also produces visual field impairments but they are reversible if treated adequately. Prokosch and Thanos (2008) review the current state of the art in this newly emerging field of syphilitic optic neuropathy and based on a literature review and some own cases they recommend that patients should not only be treated with penicillin but also with adjunctive cortisone to achieve best possible improvement of visual acuity.

Despite the progress in the biological sciences, it is unlikely that some pharmacological treatment will be available any time soon to enhance axon regeneration or restore visual functions. However, different behavioral (functional) training paradigms are available and these are the subject of all other papers in this special issue

3. Training visual functions after brain damage

3.1. Training of the "blind" visual field sector

One training approach to enhance visual functions after damage involves the stimulation of the "blind" field with "blindsight" paradigms. Stoerig (2008) discusses how surviving pathways that send visual information to higher cortical regions can be engaged. Specifically, there are several retinofugal pathways that remain undamaged, by-passing the primary visual cortex to innervate higher cortical regions in cats, monkeys, and humans. These pathways support a variety of visual functions an can be improved with practice. Stoerig suggests that they may also play an important role in the effects of training on recovery, though she finds, as others did, that the extent of functional improvement is rather variable.

Along similar lines of reasoning the paper by Chokron et al. (2008) discusses how blindsight can be used for purposes of rehabilitation after visual field defects. They discuss how monkeys and humans have spared implicit visual functioning which mediate nonconscious vision ('blindsight') and describe experiments in their laboratories where training is aimed at stimulating blindsight to achieve restoration of conscious vision in the "blind" field in hemianopia. Nine patients with unilateral occipital damage were trained for 6 months using different forced-choice visual tasks (pointing to visual targets, letter recognition, visual comparison between the two hemifields, target localization, and letter identification). All 9 patients experienced improvement in at least some of the behavioural tasks and a significant enlargement of the visual field was noted in 8 patients. The authors interpret their findings as showing that "implicit" (unconscious) residual vision can be exploited to restore explicit (conscious) visual detections in the blind visual field.

3.2. Training of areas of residual vision in the border zone

Another fundamental approach of vision restoration is followed in my own laboratory in collaboration with many of my students and former colleagues. Here, the goal is to enhance visual functions in hemianopia by repetitively presenting training stimuli primarily to "areas of residual vision" (ARVs) typically located in the border zone of the damage. This training is termed "vision restoration training" (VRT) (Müller et al., 2007). Within this field of study, we have recently addressed

several specific issues such as outcome prediction and everyday life relevance of visual field improvements.

Specifically, Poggel et al. (2008) studied the issue of outcome prediction by using a multifactorial analysis to discover possible variables that predict outcome after visual training in hemianopic patients. This issue is important because VRT is not equally effective in all patients and we need to learn more about which factors contribute to outcome. Visual field size enlargement was quantified in 19 hemianopic patients and then correlated with different patient variables and visual field characteristics. As in prior studies, the size of the ARVs was found to be the strongest predictor for visual field recovery. Other variables such as age of the patient, time since lesion, number of absolute perimetric defects, eccentricity of the visual field border, and average reaction time to perimetric stimuli pre-training had a much smaller – if any – influence on outcome. Poggel et al. identified a small set of variables that are readily available from clinical charts to determine the likelihood that improvements can be expected from vision restoration training.

While it clearly is desirable to achieve visual field improvements, from a clinical point of view it is most important to know if such improvements are also relevant for every day life activities. This is addressed by Gall et al. (2008) who investigated vision- and health-related quality of life before and after Vision Restoration Training (VRT) in hemianopic patients. They studied a clinical sample ($n = 85$) with the Health-Survey SF-36 and the vision-related QoL 39-item questionnaire of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Not all patients benefited from the training and the results were as follows: 6% showed worse detection performance, 42% showed an improvement $<$5%, 24% an increase of 5–10% and 28% of the patients of $>$10%. Both vision- and health-related QoL measures improved after VRT in 8 out of 12 NEI-VFQ and 3 out of 8 SF-36 subscales. They conclude that the NEI-VFQ is a valuable measure of self-reported visual impairment in patients with visual field defects and that VRT improves vision-related QoL which is correlated with the extent of visual field enlargements.

Various authors have been critical about the efficacy of VRT and the argument has been raised that visual field improvements are an artefact of eye movements. Of particular interest is one study by Reinhard et al. (2005) using the Scanning Laser Ophthalmoscope (SLO) which could not find evidence for benefits of VRT. The paper by Kasten et al. (2008) addresses this topic by describing a case study of a 46-year old hemianopic patient to find out possible reasons for the failure of the SLO study. They studied simulated some of the SLO parameteres using computer-based perimetry and found that the SLO-like "inverse" stimulus detection paradigm (black target on red background) was a more difficult task for hemianopic patients than standard perimetric protocols confirming prior observations (Sabel et al. 2004). The findings suggests that the stimulus features are essential to determine if VRT-induced visual field enlargements can be detected which, in turn, implies that VRT effects do not generalize to all aspects of visual functions. Thus, training with simple, white dots does not improve all visual functions such as inverse stimulus detection.

Also Bergsma and Van der Wildt (2008) were interested in the detailed description of perceptual properties of the restored visual field after training hemianopia patients with simple white light stimuli. In these restored regions they then measured different elementary visual properties: visual acuity, temporal processing using critical flicker frequency (CFF) analysis and color perception. They found that – despite the simple nature of the training –, acuity, CFF and color vision could be demonstrated in the restored areas. In fact, performance of the elementary properties in the regained fields appeared "almost normal" when compared to control subjects or the patient's own ipsilesional visual field. They conclude that the restored visual field sectors are actually used for processing of visual stimuli beyond those used during training.

Werth (2008) reviews the visual capacities in children with occipital lesions, hemispherectomy or hydranencephaly and raises the issue whether the child's visual system is more or less vulnerable than that of adults, whether the child's capacity to recover from cerebral blindness is greater and which brain structures may be involved in mediating recovery. He summarizes that visual-field training after damage to the geniculostriate system improves lost visual functions in more than half of the children and in many children the enlargement of the visual field exceeded the enlargement as reported in hemianopic adults after visual-field training.

While most papers in this special issue focus on the restoration of functions in blind or partially blind regions of the visual field, there is a case to be made for the brains ability to compensate loss by engaging the remaining, "intact regions" of the visual field.

3.3. Training the intact sectors of the visual field

Macular degeneration (AMD) is an example where the intact visual field is engaged in the plasticity re-

sponse. In AMD the central region of the retina degenerates, leaving only the peripheral retinal regions intact. As Schumacher et al. (2008) show, there is some reorganization of visual processing in macular degeneration which related to the induction of eccentric viewing. Many AMD patients compensate the progressive loss of central visual acuity by adopting a "preferred retinal location" (PRL), i.e., they spontaneously learn to use more peripheral areas of the retina to fixate objects. Used fMRI activation Schumacher et al. scouted for signs of cortical reorganization in calcarine sulcus and found that visual stimulation of the PRLs indeed showed increased brain activity in areas of the cortex that normally represents central vision. These findings are compatible with the hypothesis of a cortical reorganization that may result from a spontaneous behavioural "adaptation" after loss of the central sectors of the retina.

4. Training vision in patients with retinal damage or amblyopia

Most training studies on vision restoration to date have been carried out with patients that have either damage of the brain itself (such as after stroke) or injury to the optic nerve. Little attention has been paid to the question if training is also helpful in patients with retinal lesions. One would predict that it should be impossible to improve functions that are lost after retinal damage. Despite this pessimistic expectation, Gudlin et al. (2008) now used computer-based vision restoration training to check if this could improve also vision in glaucoma patients. In a small pilot study five patients with primary open angle glaucoma (POAG) carried out VRT at home for three months which led to significant detection performance increases as assessed by high resolution super-threshold perimetry and by standard white/white perimetry. Performance in blue/yellow perimetry did not change. Gudline et al. concluded that visual field defects caused by retinal lesion may also benefit from systematic vision training and that this may be mediated by cortical plasticity.

Amblyopia, in turn, does not involve direct trauma to the retina, optic nerve or brain but it is caused by abnormal binocular visual experience during a 'critical period' early in life. This misalignment of the eyes prevents normal development of binocular vision and this disorder is generally considered to be untreatable unless treated very early during the critical period with patching the seeing eye. Polat (2008) addresses the restoration potential of underdeveloped cortical functions well *after* the first decade of life in adulthood and discusses how specific deficiencies in amblyopia can be improved not only in children but also in adults. He proposes that normal mechanisms of "perceptual learning" may contribute to the restoration potential even way beyond the critical period.

Also Mitchell (2008) focuses on the plasticity potential in adult amblyopia. He summarizes the current state of the art of animal models of deprivation amblyopia and points toward a special role for binocular visual input in the normal development of spatial vision and in occlusion (patching) therapy. By analyzing various early experiential manipulations on the development of visual acuity he finds that short periods of continuous and concordant binocular input can counteract long daily periods of monocular deprivation, thus allowing the development of normal visual acuity. He discusses animal studies in which amblyopia was induced by early monocular deprivation and where effects of patching therapy (reducing the input to the seeing eye) are usually only temporary, declining relatively fast after the patch is removed. However, critical amounts of binocular visual input each day helps the binocular vision to remain more permanent even after the patch is removed. He proposes that current patching protocol should include daily periods of specific stereoscopic vision training to achieve the best possible clinical management of amblyopia.

5. Non-specific visual training to enhance normal vision

So far, all papers addressed specific training approaches in patients with visual impairments. Another fundamental approach not having received much attention is the repeated "forced-use" of the visual system in normal subjects by using more non-specific visual training methods to induce "normal" plasticity of the uninjured brain. Achtman, Green and Bavelier (2008) discuss how playing action video games with specific game components may be used as a tool to enhance a range of visual skills. They suggest that visual system plasticity can thus be enhanced and the authors present perspectives of how to make use of such games in the rehabilitation of patients with different CNS disorders.

6. Conclusion

Ten years after the first special RNN issue in the field of visual system plasticity has been published some progress has been made and it appears that improvement of visual functions after damage is the rule and not the exception. Visual training can enhance visual functions not just in early development but also in adulthood and even old age, i.e. well beyond the critical period. Different approaches are promising in this regard. One venue is to restore the biological substrate through axon regeneration (only in animal models so far). Another is to train visual functions by repetitively presenting visual tasks to either the intact regions of the visual field, partially damaged areas and even presumably "totally" damaged areas of the visual field which still receive input from surviving pathways.

Neuronal reorganization is a likely mechanism for such clinical improvements, but it remains to be determined what the precise mechanisms are after brain damage and after retinal damage. Clearly, one can not expect "complete" recovery of vision (except for some rare cases) and there exists still lots of room for improvement of current techniques. However, there is growing evidence from independent laboratories that visual functions can be improved in patients with visual field defects to a clinically meaningful extent. We should be optimistic that the future will bring us more progress in understanding the mechanisms of neuroplasticity in the visual system and hope that vision restoration can be enhanced further by training regimen or other technologies yet to come.

References

Achtman, R. L., Green, C. S. & Bavelier, D. (2008). Video games as a tool to train visual skills. *Restor Neurol Neurosci, 26,* 435-446.

Bergsma, D. P. & Van der Wildt, G. J. (2008). Properties of the regained visual field after visual detection training of hemianopsia patients. *Restor Neurol Neurosci, 26,* 365-375.

Chokron, S., Perez, C., Obadia, M., Gaudry, I., Laloum, L. & Gout, O. (2008). From blindsight to sight: cognitive rehabilitation of visual field defects. *Restor Neurol Neurosci, 26,* 305-320.

Gaillard, F. & Domballe, L. (2008). Fetal issue allografts in the damaged adult visual cortex: physiology and connectivity. *Restor Neurol Neurosci, 26,* 267-277.

Gall, C., Mueller, I., Gudlin, J., Lindig, A., Schlueter, D., Jobke, S., et al. (2008). Vision- and health-related quality of life before and after vision restoration training in cerebrally damaged patients. *Restor Neurol Neurosci, 26,* 341-353.

Gudlin, J., Mueller, I., Thanos, S. & Sabel, B. A. (2008). Computer based vision restoration therapy in glaucoma patients – a small open pilot study. *Restor Neurol Neurosci, 26,* 403-412.

Kasten, E., Guenther, T. & Sabel, B. A. (2008). Inverse stimuli in perimetric performance reveal larger visual field defects: implications for vision restoration. *Restor Neurol Neurosci, 26,* 355-364.

Mitchell, D. E. (2008). A special role for binocular visual input during development and as a component of occlusion therapy for treatment of amblyopia. *Restor Neurol Neurosci, 26,* 425-434.

Mueller, I., Mast, H. & Sabel, B. A. (2007). Recovery of visual function after brain injury: a large-sample study using Vision Restoration Therapy, *Restor Neurol Neurosci, 25,* 563-572.

Poggel, D. A., Mueller, I., Kasten, E. & Sabel, B. A. (2008). Multifactorial predictors and outcome variables of vision restoration training in patients with post-geniculate visual field loss. *Restor Neurol Neurosci, 26,* 321-339.

Polat, U. (2008). Restoration of underdeveloped cortical functions: evidence from treatment of adult amblyopia. *Restor Neurol Neurosci, 26,* 413-424.

Prokosch, V. & Thanos, S. (2008). Emerging syphilitic optic neuropathy: critical review and recommendations. *Restor Neurol Neurosci, 26,* 279-289.

Reinhard, J., Schreiber, A., Schiefer, U., Kasten, E., Sabel, B. A., Kenkel, S., et al. (2005). Does visual restitution training change absolute homonymous visual field defect? A fundus-controlled study. *Brit J Ophthal, 89,* 30-35.

Rose, K., Schröer, U., Volk, G. F., Schlatt, S., König, S., Feigenspan, A., et al. (2008). Axonal regeneration in the organotypically cultured monkey retina: Biological aspects, dependence on substrates and age-related proteomic profiling *Restor Neurol Neurosci, 26,* 249–266.

Sabel, B. A., Kenkel, S. & Kasten, E. (2004). Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires. *Restor Neurol Neurosci, 22,* 399-420.

Schumacher, E. H., Jacko, J. A., Primo, S. A., Main, K. L., Moloney, K. P., Kinzel, E. N., et al. (2008). Reorganization of visual processing is related to eccentric viewing in patients with macular degeneration. *Restor Neurol Neurosci, 26,* 391-402.

Stoerig, P. (2008). Functional rehabilitation of partial cortical blindness? *Restor Neurol Neurosci, 26,* 291-303.

Werth, R. (2008). Cerebral blindness and plasticity of the visual system in children. A review of visual capacities in patients with occipital lesions, hemispherectomy or hydranencephaly. *Restor Neurol Neurosci, 26,* 377-389.