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Editorial
Residual vision and plasticity after visual system damage

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Abstract

This is an introduction to a special issue of the journal Restorative Neurology and Neuroscience which contains a series of papers presented at a satellite symposium held in conjunction with the European Forum of Neuroscience, Berlin, July 1–2, 1998, entitled "Visual System Damage: Residual Vision and Plasticity". The symposium highlighted research findings both from animals and humans which sustained brain injury in early development and in adulthood. The findings demonstrate the degree of residual vision the injured brain possesses and summarize the effects of drugs and training on the plasticity of the visual system. As this conference demonstrated, the visual system is able to respond in many ways in an adaptive manner to lesions inflicted early in life and in adulthood. These changes may bring about spontaneous recovery of visual functions as long as the brain contains a sufficient capacity of residual vision. Both in children and in adults, systematic visual training can help patients to regain some visual functions which have previously been considered to be irrevocably lost. By carefully assessing residual vision it is proposed that the potential for plasticity of the visual system can be utilized to achieve clinical improvement using appropriate training paradigms.

Keywords: Plasticity, rehabilitation, brain injury, regeneration, training, vision, compensation, restoration

1. Introduction

This special issue of the journal Restorative Neurology and Neuroscience contains a series of papers which were presented at a satellite symposium held in conjunction with the European Forum of Neuroscience, Berlin, July 1–2, 1998, entitled "Visual System Damage: Residual Vision and Plasticity". In order to achieve a coherent and balanced presentation of the subject matter, several additional authors which did not participate at the meeting were invited to contribute to this special issue. Their contribution to the field of visual system plasticity has also been notable and without these contributions this special issue would not have adequately represented the field.

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This volume is the first to focus on visual system plasticity. To the best of my knowledge, there is currently no other book or special journal issue which incorporates both preclinical and clinical research of visual system plasticity after brain injury with comparable breath.

Beyond the period of early development, the visual system was considered as hard-wired, with numerous specialized feature detectors being responsible for certain sub-functions analyzing visual scenes. The way we conceive of how the visual system functions is thus a typical representation of how the central nervous system (CNS) is considered to function in general: In the beginning of neuroscience the CNS was believed to be somewhat fixed, unable to actively respond to insult other than by degeneration. Ramon y Cajal's doctrine that the CNS "is fixed and immutable; everything may die, nothing may regenerate" (cited in [4]) was, until just recently, the generally accepted dictum. But during re-

Fig. 1. Group photo of the participants of the symposium held in conjunction with the European Forum of Neuroscience, Berlin, July 1–2, 1998, entitled "Visual System Damage: Residual Vision and Plasticity". Upper row, from left to right: Ulf Eysel, Douglas Frost, Georg Kerkhoff, Bertram Payne, Ulrich Schiefer, Erich Kasten, Giorgio Innocenti, unidentified student, Maurice Ptito. Lower row: Bernd Meyer, Lut Arkens, Mark Wessinger, Reinhard Werth, Bernhard Sabel, Yuzo Chino

cent years a gradual paradigm shift has taken place towards recognizing that behavioral recovery from CNS damage is possible, even well into adulthood [14]. The field of neuroplasticity research, having emerged during the last two decades is, without doubt, one of the most exciting endeavors in the neurosciences with clear practical benefits for neurology and neurosurgery.

Examples of plasticity have been found in many functional systems of the brain, particularly the somatosensory and the motor system. In the visual domain, however, plasticity has only been studied by a few laboratories, most of which focussed on early developmental periods, when neuronal plasticity is most vigorous and therefore most easily studied. The term "plasticity" is generally used to describe the nervous system's ability to adapt to change. The more subtle form of it is the adaptation of the organism to environmental changes, i.e. learning. The more dramatic form of plasticity is the adaptation which is seen after brain lesions.

For various reasons I have studied the visual system as a model of recovery for more than a decade in collaboration with many students and colleagues. This special issue is dedicated to my teachers, who have strongly influenced my thinking and to whom I am very grateful (Donald Stein, Gerald Schneider and Ernst Pöppel, see below).

Because the visual system is considered to be so remarkably specific in its neuronal organization, recovery of vision is a particularly striking example of plasticity. Though the mechanisms of recovery of vision – also referred to as restoration of vision – are currently not fully understood, much has been learned in the last few years. This special issue gives an overview of what is currently known about residual vision and plasticity, covering a wide range of scientific disciplines, both preclinical and clinical. To be able to easily view each contribution of this special issue in the overall context of all other contributions, a brief summary is now provided.

2. Residual vision and plasticity in animals

2.1. Developing animals

Traditionally, research on visual system plasticity has been carried out in animals during their early developmental stages. It is during development that the response of the visual system to lesions is particularly obvious. Developmental lesion studies are often inspired by the wish to determine the neurobiological mechanisms of normal development, the desire to understand how growing axons find their appropriate target and how the wiring of the brain is laid down with such a great degree of specificity. Lesion studies have played a special role in this context, and it is clear that such studies have direct relevance to our understanding of recovery from brain injury, even in adulthood as discussed in the very first book on recovery of function and plasticity edited by Donald Stein in 1974 [14]. There are many parallels be-

tween normal development and lesion-induced changes (such as changing neuronal connectivity), and much has been learned since Schneider's [13] seminal work on axonal re-routing following early tectal lesions in hamsters.

In his article, Payne [10] describes how visual cortex lesions early in a cat's life unmask a high degree of latent flexibility (plasticity) in axonal connectivity. He describes how the lesion disrupts the normal organization of the brain, but that the effects are minimized by orderly expansions of reorganizing axonal pathways. Retinofugal pathways expand their projection fields in different midbrain, thalamic and cortical areas, forming new terminal fields which are retained well into adult life. Payne considers these modifications to be useful, as they support relatively normal signal processing in the visual system and help spare certain visually guided behaviors, by maintaining pattern vision and object localization. He proposes that the individual is thus optimized to survive in the visual world despite the absence of primary visual cortex.

After early lesions axons devoid of their proper visual target may also innervate non-visual areas, a topic which is discussed by Frost [5]. Using newborn hamsters, Frost created lesions of visual structures and combined them with damage of pathways to the primary auditory or somatosensory thalamic nuclei. This combination of lesions leads to the formation of permanent retinal projections to non-visual areas of the brain which allows the study of how retinofugal axons behave when innervating non-visual, deafferented structures. Surprisingly, they behave just as they do in visual "home" territory, with comparable morphology and function. Re-routed retinofugal axons innervating non-visual structures are retinotopically organized and form functional synapses. As a result of this aberrant innervation from the retina, neurons in the auditory or somatosensory cortices, which are not driven by visual stimuli in the normal brain, become visually responsive and have receptive field properties that resemble neurons in visual cortex. Furthermore, the surgically-induced retino-thalamo-cortical pathways to non-visual cortex can mediate visually guided behaviors. This suggests that the functionality of a system is determined by its inputs, opening up the possibility that if inputs can be restored (as with regeneration, for instance), there is a good chance that the innervated structure will permit the processing of information from the afferent input, even if the axons originate from an entirely different functional system.

This raises the possibility that activation of an afferent input may determine functionality or, in other words, experience can modify the maturation and organization (or reorganization) of a neuronal system.

Recent efforts were aimed at determining the role of neurotrophins in developmental plasticity. Galuske, Kim, and Singer [6] studied this issue in the visual cortex of kittens, where they focussed on the activity-dependent competition between different sets of axons for growth related molecules, the neurotrophins. They investigated the role of the neurotrophins by administering nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) and studying the experience-dependent rearrangement of thalamocortical connections after monocular deprivation in the developing cat. Neurotrophins were infused intracortically during the time of monocular deprivation, and cortical neuronal responses were then assessed with optical imaging of intrinsic signals and single unit recording techniques.

While control and NGF treated cats with monocular deprivation showed the expected shift of ocular dominance towards the normal eye, in BDNF infused hemispheres ocular dominance had shifted towards the deprived eye in a 2.5–3.5 mm zone from the infusion site where neurons lost their orientation selectivity. These experiments suggest that neurotrophins, particularly BDNF, but not NGF, play a critical role in cortical plasticity, though Galuske, Kim and Singer assume that their contribution is more complex than simply being a substrate of an activity dependent competition.

Along similar lines of reasoning, Maffei and his colleagues [1] also propose a role for neurotrophins in regulating cortical developmental plasticity. They summarize early data on the action of NGF in visual cortical development and plasticity in the rat and the actions of other neurotrophins in the visual cortex of other mammals. Particularly, they consider the different roles neurotrophins play in regulating visual cortical development and plasticity by acting on different neural targets, such as LGN afferents, intracortical circuitry and subcortical afferents.

Thus, when viewed together, the studies by Payne and Frost suggest that after early lesions the abnormal size or trajectory of retinofugal fibers are functionally meaningful, indicating that plasticity of the visual system in early development may strongly contribute to recovery of visual functions during early development as well. The establishment of normal and abnormal connectivity depends, in turn, on specific molecular events which, as Singer, Maffei and their colleagues propose, involve specific neurotrophins, molecules that play a particularly important role in developmental plasticity.

The clinical implications for the field of pediatric neurology are clear: lost visual functions after early lesions are not always permanent because the nervous system of the child can more extensively adapt and recover lost vision (see also [15]).

2.2. Adult animals

In contrast to the more classic approach of studying visual system plasticity in developing organisms, in recent years adult plasticity has received increasing scientific attention. There are many examples of plasticity after lesions in adulthood, but the fact that even the normal, un-injured brain shows a remarkable plasticity is a plausible argument in favor of the proposal that plasticity after lesions is an extension of normal brain function.

Wörgötter and his colleagues [17] studied the normal cat's receptive fields in the visual thalamus and cortex during different EEG states. Though these studies do not direct-

ly bear on the issue of post-lesion plasticity, they demonstrate the modifiability of receptive fields on a fast time scale that could also be used as first steps for a longer lasting reorganization after lesions.

Wörgötter et al. noted neuronal activity patterns to display a pronounced dynamic behavior. Particularly, spatial (size) and temporal (firing characteristics) aspects of visual receptive fields changed not only by means of the actual visual stimulation but also as a consequence of the synchronization state of the neuronal network. They described *temporal* firing characteristics of cells in the visual thalamus by analyzing inter-spike interval distributions. Wörgötter et al. propose that the change of this temporal firing influences the *spatial* shape (size) of receptive fields and of their subunits in the visual cortex. Using a biophysical model, they argued that the observed receptive field changes in the normal brain could serve to adjust the temporal and spatial resolution within the primary visual pathway depending on whether the system is in an attentive or a non-attentive state. Although this study does not directly bear on the issue of post-lesion plasticity, it does highlight the tremendous plasticity even the normal brain possesses. By inference, similar plasticity has long been known in the injured brain; That normal and abnormal plasticity are closely related is not a great leap of faith. If there is such a tremendous plasticity already in the normal brain, then post-lesion plasticity is no longer a surprising curiosity that can be ignored.

Eysel has been the first to describe visual system plasticity following lesions in the adult mammal with electrophysiological procedures and has published numerous articles in this field. Now Eysel and his colleagues [3] discuss the earlier work in the context of their own new findings, comparing the cortical electrophysiological responses to homonymous lesions of the central retina with effects of visual cortex lesions. Eysel found that both, in cortical regions representing the border of a retinal scotoma and at the border of small focal cortical lesions, single neuron activity is suppressed immediately after the lesion. However, the initial suppression coincides in time with an increased glutamatergic NMDA response and a reduction of $GABA_A$ and $GABA_B$ responses in a narrow peri-lesion ring of hyperexcitability adjacent to the region of functional loss during the first days to weeks after a cortical lesion. Similarly, in the areas surrounding retinal scotomas in area 17 an increased neuronal excitability and higher glutamate levels are found while inside the scotoma glutamate and GAD levels are reduced. In addition, Eysel and his colleagues noted shifts in topography of retinal representation and increased receptive field sizes as signs of lesion-induced neuronal reorganization after long survival times irrespective of whether the lesion was made in retina or visual cortex. It is proposed that the combined reduction of GABAergic inhibition and increase of glutamatergic excitation leads to increased spontaneous activity and visual excitability that is accompanied by facilitated LTP, thus initiating local cortical reorganization after visual system damage in the areas surrounding the lesion.

These observations are interesting and important as they suggest parallels between post-lesion plasticity and normal learning, an idea supported also by Chino [2]. He describes how mature visual cortex reorganizes its functional connections in response to retinal injuries and addresses a number of unresolved issues which include the questions if visual system reorganization is experience-dependent, if the origin of reorganization is cortical or subcortical, and if reorganization involves axonal sprouting and/or perceptual fill-in phenomena. His preliminary data show indeed that a large-scale reorganization of cortical maps following retinal injuries requires increased synaptic strengths at key cortical sites which may be enhanced by long-term, repeated use. As the work by Eysel and Chino shows, the mechanisms of normal learning and those of cortical, post-lesion plasticity share many similarities.

If we assume that, firstly, post-lesion plasticity and normal learning share many common features, and, secondly, that normal mechanisms of learning are still operative in the surviving brain tissue the question arises if the injured brain is able "learn" to deal with a new situation of cells having been lost and environmental demands of the visual world forcing the organism to adapt. This translates to the question to what extent brain injured animals are able to recover from their injury in adulthood.

In my own paper [11] lesion studies of the visual system in animals (mammals) are reviewed and, based on the currently available evidence, the neurobiological mechanisms of recovery of vision are discussed.

Following lesions in different areas of the visual system, recovery of vision is often observed in the course of weeks or months after the lesion, but, despite its clinical relevance, this issue has not been studied extensively. As experiments in my laboratory with adult rats having sustained partial optic nerve crush (ONC) show, as long as a small number of retinal ganglion cells survive the injury (in the order of 10–20 %), adult rats can recover some of their visual functions. Molecular, anatomical and physiological correlates of this recovery are described which indicate that the plasticity response of the visual system includes alterations both in the area of primary injury as well as in down-stream structures such as the tectum, the lateral geniculate nucleus and visual cortex. Restitution of vision is therefore a multifactorial event of within-systems plasticity, involving neurobiological alterations along the entire retinofugal axis. I have proposed that the mechanisms responsible for recovery of vision in animals may be similar to those in patients during spontaneous recovery or after prolonged visual restitution training.

3. Residual vision and plasticity in humans

Visual system plasticity is not just limited to animals, but there are many signs that it occurs in humans as well. However, as Schiefer et al. [12] have pointed out, when assessing recovery of vision or effects of visual training in humans, there are numerous methodological details to which investi-

gators have to pay attention in order to avoid artifacts. Measuring visual functions often requires a quantification of the visual field. As Schiefer and his colleagues point out, follow-up measurements of homonymous visual field defects require appropriate perimetric procedures: because postgeniculate lesions usually produce absolute scotomata, supraliminal strategies with comparatively high stimulus densities are proposed to be the method of choice over threshold measurements. In addition, a centripetal stimulus condensation and multimodal assessment of visual subfunctions is suggested (using static, kinetic or color test points, random dot patterns or optokinetic stimulation) which activate different functional channels or regions of the visual pathways. Automation and continuous fixation control are important tools to assure a sufficient quality of follow-up measurements.

From this discussion it appears that residual visual functions can only adequately be addressed by careful investigations. Routine ophthalmological examination are apparently not sufficient to reveal the detail required to detect residual, visual capacities. Yet, as studies in both children and adults illustrate, there are many residual, visual functions in patients which, when assessed carefully, can provide numerous clues as to the tremendous undetected potential of the human brain. Only by analyzing this residual potential will it be possible to design optimal strategies for treatment.

3.1. Residual vision and plasticity in children

Innocenti et al. [7] describe the nature and limits of cortical developmental plasticity after an early lesion in a single case of a child. They report the case of a little girl, M.S., who suffered severe, bilateral destruction of her primary visual cortex around the time of her premature birth. They noted that she recovered different visual functions between the ages of 4.5 and 5.5 years, such as figure-ground segregation. One conceivable mechanism is that recovery was due to a compensatory activation of remaining visual areas that could have acquired response properties of the primary visual cortex. However, functional magnetic resonance imaging revealed abnormalities in the pattern of stimulus-induced changes of interhemispheric EEG-coherence. Innocenti and his colleagues take this as evidence that callosal connections, and possibly other cortico-cortical connections, must have re-organized abnormally. Since cross-hemispheric connections are believed to be involved in perceptual binding and figure-background segregation, their reorganization could be an important element in the functional recovery after early lesions and determine the degree of residual perceptual impairments.

In another chapter of the present volume Werth and Moerenschlager [15] also investigated children with visual field impairment. They trained cerebrally blind children with a visual field training and studied the outcome in these children. Twenty-two children aged 1 to 15 years who had their blindness for at least one year were trained and compared to an age-matched control group. Functional visual fields and luminance difference threshold were carried out with an arc perimeter. Some visual functions developed within a training period of three months in 15 of 22 children who received such training whereas there was no comparable recovery in the control group. These findings in children support the concept that systematic visual training can facilitate recovery of visual functions in brain damaged children, and the suggestion is made that spared tissue in the striate and extrastriate visual cortex, and perhaps underlying white matter, may provide the anatomical substrate for the visual field restoration. That the child's nervous system has a great potential for plasticity confirms what has long been known from animal studies, but does the adult human brain also possess potential for residual vision and plasticity?

3.2. Residual vision and plasticity in adults

The issue of residual visual capacities has been studied by Wessinger, Fendrich and Gazzaniga [16] who have used stabilized visual field mapping techniques to investigate residual visual capacities in seven hemianopic subjects. In four of them isolated islands of detection were found as evident by the patients' ability to perform saccadic and verbal localization, wavelength discrimination, form discrimination, and motion detection of visual stimuli. Because performance was characterized by low-confidence ratings, they are very similar to the known blindsight responses, and just as in the classic blindsight cases, the subjects displayed significant between- and within-subject variability. Because magnetic resonance imaging revealed variable occipital cortex sparing, Wessinger et al. conclude that at least some instances of blindsight are mediated by remnants of the primary visual pathway.

Residual visual capacities thus exist in the visual cortex which, when properly assessed, can be characterized in detail. Given that the injured visual cortex does possess such areas of residual vision, the next logical and clinically important question arises to what extent residual vision can be improved in the human brain by visual field training. Such investigations have first been carried out in Germany in the late seventies, but unfortunately this line of research was discontinued until it was picked up again by other investigators, including ourselves, in the last few years.

Kerkhoff [9] reviews his experience and that of others with visual compensation training. He first analyzes the kind of visual field disorders in a population of 313 patients and found that 50–90 % of all patients had severe reading problems and visual exploration deficits and related this to practical impairments of vision. Kerkhoff considers different restorative and compensatory treatment approaches in patients with postchiasmatic injury and reports that partial restitution of visual function is achieved in the majority of patients treated with "pure" restoration training including saccadic localization or light detection in the scotoma. However, in his experience training-induced visual field improvements are limited to 5–12° in 90 % of these patients. Kerkhoff also describes compensatory strategies so that patient can better use their intact visual field sector to scan visual scenes. This is achieved by training patients to carry out small or large-

scale saccadic eye movements to the scotoma in order to improve reading ability. Significant reading improvements are achieved in 95 % of all patients with visual field disorders, documenting the practical benefit of compensatory training in every day life. Interestingly, Kerkhoff reports that even compensation training, though not aimed at strengthening areas of residual vision, produced a significant visual field increase of 5–7° of visual angle in 30–50 % of the patients.

Visual restitution training is the focus of the contribution by Kasten et al. [8] who have developed a diagnostic methods to first carefully examine residual vision in transition zones near the blind visual field sector and then to use this information to carry out training of such areas of residual vision. These transition zones are similar to, but not identical with, the blindsight responses found in spared islands of vision described by Wessinger and his colleagues [16].

Animal studies have already revealed a high degree of plasticity in the visual system and systematic visual training in animals results in visual field expansions as well. Kasten et al. summarize a series of studies with patients suffering from either pre-chiasmatic or post-chiasmatic injury who have carried out visual restitution training. In addition to providing an overview of all previous experiments, two clinical trials are reported from their own laboratory in which visual training was carried out by computer-based training for a 6 month period in the patient's home. The computer program presented visual stimuli in such a way that areas of residual vision were preferentially stimulated. It was found that even long after spontaneous recovery was complete (the patient's lesion was, on the average, 7 years old), computer-based visual training resulted in significant visual field enlargements, evident as an average border shift of about 5 degrees of visual angle which can not simply be explained by eye movements or eccentric fixation. It was concluded that the visual system possesses a remarkable plasticity which can be used for clinical goals. It is proposed that computer-based visual field training can now be used for routine clinical application.

4. Conclusions

The injured visual system has a much greater degree of residual vision than generally appreciated. An improved understanding of these residual potentials and their stimulation by appropriate procedures, such as training, has already advanced our clinical knowledge of how to help patients with visual system disorders. Further research in finding new methods for unfolding this residual potential is clearly warranted. Only through an improved understanding of the underlying mechanisms of residual vision and plasticity can we ultimately find the most efficient way to restore lost vision.

5. Dedication

This special issue of Restorative Neurology and Neuroscience is dedicated to my teachers, Drs. Donald Stein (Emory University, Atlanta, GA, USA), Gerald E. Schneider (Massachusetts Institute of Technology, Cambridge, MA, USA) and Ernst Pöppel (University of Munich, Germany). Their scientific guidance and enthusiasm, understanding and support have, in many direct or indirect ways, laid the foundation of my scientific interest in residual vision and plasticity. Donald Stein has introduced me to neuroscience and to the field of brain plasticity and recovery of function. With Gerald Schneider I have studied early lesions in the hamster visual system, thus awakening my interests in visual system plasticity. Being exposed to the interdisciplinary environment of Ernst Pöppel and his colleagues has helped me to realize that there is a real possibility to apply knowledge gain from animal research towards clinical problems. The vision of these outstanding scientists led me to study the new paradigm that the visual system has a great degree of plasticity, and they encouraged me not to be afraid to explore uncharted territory and to think beyond generally accepted paradigms.

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