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Restoration of vision I: Neurobiological mechanisms of restoration and plasticity after brain damage – a review

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Abstract

Lesions in the central nervous system often lead to loss of vision due to visual system involvement. In the course of weeks or months, some vision can recover in rats, cats, monkeys, and humans, though it is mostly incomplete. This paper reviews the current knowledge of the underlying neurobiological mechanism of recovery of vision, particularly those observed in adult rats with partial optic nerve crush (ONC).

Immediately after ONC, rats are almost completely blind, evident by their inability to perform visual tasks such as brightness and pattern discrimination and they fail to orient towards small, moving targets. Within about two weeks, however, rats significantly recover some of their lost visual functions despite the fact that only about 10 % of the retinal ganglion cells (RGCs) maintain a viable connection with their brain targets. Molecular, anatomical and physiological studies have identified some of the neurobiological determinants of this visual restitution. Immediately following ONC there is a massive soma swelling of about 80 % of the RGCs with subsequent cell death due to apoptosis and necrosis. The remaining 20 % survive with or without axonal connection to their target and undergo marked changes: (i) about half of these RGCs experience a moderate, reversible soma swelling, (ii) there is a loss of anterograde axonal transport in the optic nerve which partially recovers after several weeks, and (iii) many of the surviving RGCs undergo alterations in gene expression, particularly that of the NR1 receptor and the immediate early gene, c-jun. While these changes may be part of an adaptive program of the cells to cope with the trauma, cell survival in the retina does not correlate well with subsequent recovery of vision. We have therefore also studied plasticity in the down stream denervated brain structures which are innervated by retinofugal pathways, particularly the superior colliculus. Here we found (i) recovery of metabolic activity and (ii) changes in gene expression, such as an up-regulation of the enhancer of split (R esp-1) gene.

When viewed together with studies on recovery of vision and neuronal reorganization done in other laboratories it is clear that recovery of vision involves simultaneous plasticity in the damaged structure itself and, transsynaptically, in down-stream structures such as the tectum, the lateral geniculate nucleus and visual cortex. Considering both pre-clinical and clinical evidence, I propose the biological substrate underlying restoration of vision as follows: surviving neurons within areas of partial damage – which corresponds clinically to "transition zones" located between intact and deficient visual field sectors – act in concert with down-stream areas, which themselves undergo dramatic reorganization to cope with a condition of reduced, but residual input. Restitution of vision is therefore a multifactorial event of within-systems plasticity, involving neurobiological alterations along the entire retinofugal axis. It is likely that these mechanisms are also responsible for visual improvements that are seen both in animals and patients after prolonged visual restitution training.

Keywords: Recovery, rehabilitation, vision, plasticity, blindness, restitution

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1. Introduction

This manuscript reviews the current knowledge of the mechanisms of recovery of vision following brain injury in adulthood. Because spontaneous recovery of function after brain injury occurs even in the absence of axon regeneration, regeneration will not be considered in this review. Also, studies of early lesions are not extensively referred to because here, unlike in the adult brain, residual vision and recovery may largely be explained by expanding terminal fields ("rewiring") of surviving systems in the brain [100,101], an issue which has been discussed by others. This paper addresses several issues: (i) how much structure needs to survive for recovery of at least some visual functions to be possible, (ii) what are the mechanisms involved in recovery of vision and (iii) can recovery be manipulated experimentally by drugs or training. While the present review focuses on studies conducted in the authors laboratory, wherever appropriate, reference is made to work by others. The goal of the paper is not to provide an exhaustive review of the field but rather to give an interdisciplinary overview including a description of molecular, physiological, anatomical and behavioral studies conducted in my laboratory.

1.1. The emerging concept of recovery of function

Since the beginning of modern neuroscience the central nervous system (CNS) was believed to be hard-wired, 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 [45]) was a frequently invoked dictum, but during recent years a gradual paradigm shift has taken place towards recognizing that behavioral recovery from CNS damage is possible. The concept of post-lesion brain plasticity is now the subject of numerous studies and has been discussed in several volumes [44,45,47,49]. It is, without doubt, one of the most exciting endeavors in neuroscience with clear practical benefits for medicine. Yet, even though it is often observed clinically, little is known about the mechanisms of recovery of function, though many different theories have been considered [81].

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. Because the visual system is considered to be so remarkably specific in its neuronal organization, I always viewed recovery of vision as a particularly striking example of recovery. Though the mechanism of recovery of vision – also referred to as restoration of vision – is currently not fully understood, much has been learned in the last few years. Before discussing these findings in detail, let us first consider some pertinent aspects of traumatic brain injury in general and consider how they might apply to the issue of restoration of vision.

1.2. Diffuse axon injury

Traumatic brain injury (TBI) and stroke are the most frequent causes of brain damage. In about 30–40 % of the patients there is visual system involvement which is not surprising given that about 50 % of the cortical mantle is involved in visual processing. To simulate TBI in the brain, experimental models are used such as fluid percussion injury [31], producing diffuse axon injury (DAI) throughout the brain, which is characterized by axon stretch, compression, or destruction [53,54]. It is important to note that DAI is not assumed to completely destroy white matter structures. It is rather a diffuse axon loss within white matter, but, most relevant here, with survival of a certain proportion of the fibers. It is this diffuse injury and not the *complete* loss of axon tracts which are thought to underlie much of the neurological and neuropsychological deficits after TBI [53–55]. Damage of the visual system white matter presumably follows similar principles; the visual system is affected by DAI just as other brain areas are [34], and the damage is often non-complete (partial).

Because recovery of the visual system is generally considered to be impossible, the identification and precise description of residual visual functions have not been identified as a relevant subject except perhaps for a small group of scientists engaged in "blindsight" research (see [148]). It was not until the demonstration of "transition zones" in patients with visual field defects that the issue of residual visual functions has become an issue of great clinical implications in my laboratory [70,71]. Transition zones are areas of partial visual functions located between the intact and the damaged field defect [159], and we have proposed that they are functional representations of partially surviving neuronal tissue [68]. Because these areas of partial injury are those which improve when stimulated by regular visual training [69,70,159], partially surviving neurons within the damaged area must play a special role in post-lesion plasticity.

To simulate the process of restoration of the visual system in animal models it is therefore imperative to create a partial visual system injury in which many cells die but some survive (Fig. 1). It is not reasonable to assume that disconnected axons contribute to recovery of vision in any significant way. Rather, surviving neurons within the area of primary injury which have somehow managed to survive the injury and remain connected with their targets are critical elements for recovery.

Gennarelli [53] has already proposed the existence of cells with internal axon damage – as opposed to clear axotomy – after DAI, and it is these cells, in concert with some axons which remain unaffected by the lesion, which are likely to provide the structural basis for recovery of vision. As Fig. 2 shows, three types of axons may exist after injury: axons that have been cut (axotomy), those with internal axon injury (non-disruptive damage) and unaffected, intact ones. Assuming that recovery of function can only occur when brain nuclei are properly connected, there are – at least theoretically – three ways whereby recovery of vision can be achieved: (i) by regrowth of axotomized axons (which we do not discuss here), (ii) by "repair" of axons which have suffered from internal injury or (iii) by somehow enhancing the function of intact neurons of the visual system, within the injury zone or

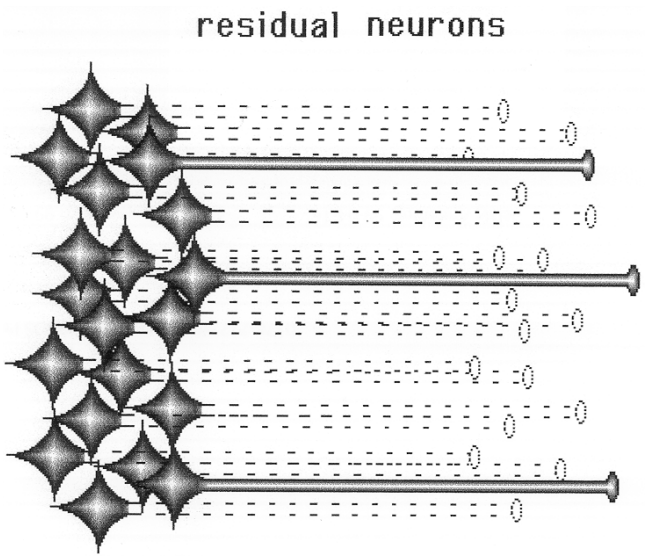
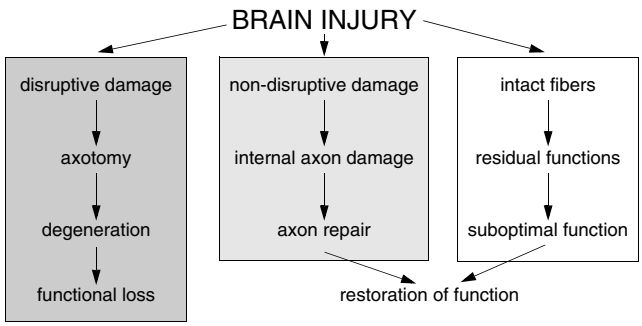


Fig. 1. Partial neuronal injury: This graph represents the structural situation after optic nerve crush. The crush leads to a loss of a large number of fibers (axotomy) in the nerve with retrograde cell loss and the survival of a small percentage of retinal ganglion cells in the order of 10–20 % (solid cells). Of these cells surviving the injury, some remain intact while others have an impaired axon transport which can recover over time.



modified after Gennarelli 1986

Fig. 2. The concept of diffuse axon injury: This flow chart shows the series of events following mechanical, traumatic brain injury. Mechanical injury leads to axon shear and stretch, resulting either in axotomy (left panel) or internal axon damage (middle panel). Note that some fibers may survive the damage uninjured (right panel). In the case of axotomy, structural and functional loss are the consequence. Here, only regeneration, i.e. regrowth of the injured axon, can lead to repair and functional restitution. In case of internal axon injury (or any other cellular change which impairs neuronal function), where the axons are still in continuity with their target, repair of axonal (or other neuronal) function is conceivable with no need for axon regeneration. The nature of neuronal impairment (due to internal axonal injury or other pathological events) and its restitution is not known at the present time, but this schematic provides a heuristic approach to better understand the state of neuronal systems after diffuse axon injury (DAI) and the principle neuronal elements involved in recovery (adapted from Gennarelli et al., [53])

outside of it in down-stream brain structures. Because under normal circumstances axonal regrowth ("regeneration") does not occur in the CNS, axon regeneration is probably not a mechanism that contributes to recovery of vision.

This raises the question of how one would best model such a condition. In principle, a suitable brain injury model should (i) be partial, such that within-systems recovery can be studied, and (ii) it should involve axonal injury of the non-disruptive type. I believe that the mild crush of the adult rat optic nerve (ONC) fulfills these criteria and is therefore in many ways well suited to study recovery of vision. Just like the defined stretch of the optic nerve in guinea pigs [55] ONC can simulate DAI and is well suited to delineate the neurobiological basis of recovery of function in general, and recovery of vision in particular.

Before discussing the results of ONC studies in detail, let us first consider the evidence whether recovery of vision is possible in animals at all. Particularly in view of the tremendous specificity that characterizes the visual system, recovery of vision is at least not an obvious possibility. Though recovery of vision has occasionally been observed both in animals [46,56,62,94,137] and humans [133,147,160], the subject has not been well studied systematically, despite its obvious clinical implications.

1.3. Residual vision after injury

There are thousands of research reports describing and analyzing the high degree of neuronal specificity the visual systems possesses [156], and the generally held assumption is that once visual functions are lost, not much can be done about it. The view that restoration of vision is impossible prevails to this day, despite the fact that for many decades reports of remarkable residual vision and recovery have occasionally been published.

In 1941 Klüver [74] demonstrated that monkeys with visual cortex removal still showed some visually guided behaviors after V1 lesions which led him to propose that areas other than V1 are involved in visual functions. As Schneider [119] has pointed out, the visual system contains pathways other than the geniculate-striate route, namely the retino-tectal projection, and many investigators have suspected that residual vision after striate lesions may well be mediated by such alternative pathways (see also the studies on blindsight as referenced by [100,148]). However, rats and cats with combined lesions of the tectum and the striate cortex still maintain their brightness discrimination abilities [46,56,62, 94,137]. This suggests that recovery of vision may, in part, be mediated by residual, un-injured sections of tissue; this notion is supported by electrophysiological recordings revealing a greater number of visually responsive cells in the tectum after striate lesions compared to normal monkeys [90, 152]. In fact, as studies in adult rats with optic nerve injury document, recovery is possible even when all visual pathways are damaged, as long as a small proportion of diffusely surviving fibers remain [107,112]. Before discussing these findings in detail, let us first establish to what extent the phenomenon of recovery of vision can be generalized to different animal species.

2. Recovery of vision

In humans with brain injury, recovery of visual functions is not uncommon [133,71], but the study of mechanisms of

recovery has been hampered by the lack of good animal models, although many animal species have been studied.

2.1. Recovery of vision in rats

Rat vision was originally assumed to be poor, but Lashley [78], who used the jumping stand to document remarkable pattern vision in pigmented rats, demonstrated otherwise. It was he who first reported also on recovery of vision in rats. In one study, Lashley [80] found that with only small remnants of tissue surviving, amounting to as few as 700 cells in the lateral geniculate nucleus of the thalamus (which is about one fiftieth of the normal number), rats are still able to discriminate visual figures. This shows, in a more general sense, that "normal" or near-normal visual discrimination can be carried out by a minute remnant of cerebral areas immediately adjacent to extensive cortical lesions.

Since Lashley's time, rat vision has received considerable attention and, particularly in the 1970s numerous studies were conducted to determine in the rat (and other animals) to what extent brightness and pattern discrimination is lost following lesions of various visual areas. Rats, just like other species (such as hamsters, hedgehogs, tree shrews, cats and monkeys), are initially impaired in their ability to solve visual problems due to visual cortex lesions, but over time some visual functions recover. While most studies at the time were conducted with the goal to determine which structures of the brain are critical for vision, many investigators noted improvement of vision over time, though they did not study it systematically. For example, it was repeatedly noticed that if a large brain lesion is made at one point in time (termed "single-stage lesion"), this has different (more severe) effects then when the same lesion is made in two steps (termed "two stage" lesion) which is often referred to as the "serial-lesion effect". In many studies, though, both single and two-stage lesions did not eliminate brightness and pattern discrimination permanently, but, depending on the amount of testing ("training") the animals receive and the amount of tissue sparing, vision recovered significantly (see discussion below). Unfortunately, the serial lesion literature is somewhat unclear in its conclusions concerning the issue of recovery of vision, as the interval between the first and the second lesion is often not training-free, confounding the issue of "spontaneous recovery" with that of "training".

To determine which brain areas are involved in recovery from visual cortex damage, Baumann and Spear [5] removed additional areas of the brain after animals had successfully recovered from the original lesion of visual cortex. Loss of the lateral portions of the suprasylvian gyrus left the animals unable to recover, suggesting that this area plays a special role in the recovery process. This is in agreement with the conclusion by others [46] who also suspected that a third brain area (pretectum or the suprasylvian gyrus) might be critical for recovery in such combined lesion cases.

Since Schneider's hypothesis of the two visual systems [119] and Payne's review [100,101] suggest that alternative visual pathways, such as the retinotectal route, may be involved in vision, the question arises if lesions of the alternative structures lead to permanent visual loss as well. In this context a study by Stein and Weinberg [131] is of interest who subjected adult rats to single-stage or two-stage lesions and tested their brightness discrimination ability. Whereas animals with single stage lesions did not recover their brightness discrimination abilities, those with two-stage lesions were less impaired in their visual performance, being able to solve brightness discrimination tasks, though they did retain some impairments. An inspection of the brain sections reveals sparing of some small remnant of SC in these rats. As in the Spear and Barbas [125] study, reorganization of the visual system after the first lesion may have been sufficiently extensive such that a second lesion did not produce visual impairments. Also, in both studies the rats actually received training during the interoperative interval.

Unfortunately, in many other serial lesion studies it can also not be decided if the simple passage of time (spontaneous recovery) after the first lesion or the visual training during the interoperative interval accounts for recovery of vision. Yet, because even extensive recovery times (up to 3 months) after bilateral, total visual cortex removal do not necessarily bring about recovery [125] it may be inferred that visual training, rather than the mere passage of time, accounts for the return of visual functions. Whatever the cause of the improvement of vision may be, the point is that despite the lack of large, critical visual areas, some visual functions can recover.

2.2. Recovery of vision in cats

The evidence of recovery of visual functions in cats has been explored for many decades. Wiesel and Hubel [149] have already shown some limited recovery in kittens with early visual deprivation in which the sutured, deprived eye was reopened even when this was done beyond a critical period. Even in adult cats, recovery of brightness discrimination was described [137], after bilateral cortex or superior colliculus removal or simultaneous removal of both structures (in which case additional training was required, see below). Only when also pretectum or suprasylvian gyrus were also damaged as well, recovery was precluded [46].

Since these early experiments a wealth of studies have been published, using either electrophysiological measures of cortical reorganization or behavioral measures of recovery of vision. Examples of such studies are: (i) receptive field reorganization after retinal [15,57] or cortical lesions [35] which depend in their extent on visual experience [88]; (ii) recovery from monocular deprivation during or after the early critical period when the competing, intact eye is occluded or removed [58, 85,123,89,139,127]; (iii) restoration of visual functions after additional brain lesions which lift inhibition by competing fibers to the deafferented zone [19,30,144] or after loss of the intact, fixating eye in amblyopia [136] and (iv) complete or incomplete spontaneous recovery of visually elicited behaviors after lesions in cortex [40,28,29,144,5,6] or optic tract [65,66]

2.3. Recovery of vision in monkeys

In the macaque monkey primary visual cortex and visual association areas together occupy about 50 % of the total cortical mantle [138] and specific lesions within visual pathways usually lead to stable deficits. However, there have been a few reports showing recovery of some visual functions in monkeys indicating that an initial loss of vision must not always be permanent.

In one study, Zee and colleagues [157] subjected monkeys to bilateral occipital lobectomies, rendering the animals incapable of smooth pursuit eye movements one month after the surgery. In the subsequent month, however, smooth pursuit performance recovered to normal levels. This is in agreement with findings by Mohler and Wurtz [90] who noted recovery in a visual detection paradigm within 3 weeks following either cortical or tectal injury, but no recovery occured when both lesions were combined. Also, lesions in area MT produce pursuit eye movement deficits from which the monkeys recover within the relatively short period of about one week [93,32] which has been attributed to their relatively small size compared to the larger striate ablations such as those employed by Mohler and Wurtz [90]. Surprisingly, unilateral lesions produce more permanent deficits from which the animals do not recover [120]. Segraves et al. [120] offer the following explanation for this apparent paradox: "First, the monkey with unilateral striate lesions presumably relies upon the intact striate cortex for input to the smooth pursuit system. However, a monkey with a bilateral striate lesion is left with only subcortical and residual extrastriate visual mechanisms, and so may use them more fully. The effect could be analogous to the tendency of monkeys with unilateral rhizotomies to avoid use of the deafferented limb until the intact one is mechanically restrained" (p. 3056). It is also conceivable that the intact hemisphere has an inhibitory effect on contralateral, subcortical areas (such as the superior colliculus). Such cross-hemispheric inhibition was demonstrated by Sprague [128] who showed in cats that lesions in the intact hemisphere may restore some of the lost functions in the residual subcortical visual structures located ipsilateral to the first visual cortex lesion (sometimes referred to as the "Sprague-effect").

2.4. Role of surviving tissue in recovery of vision

As the discussion above illustrates, there have been many scattered reports on recovery of vision, but these experiments did not delineate the mechanisms of visual restitution.

Before claiming any within systems plasticity of surviving fibers we first need to acknowledge the possibility that parallel processing of information in the visual system essentially permits alternative structures to take over the function of the damaged pathways. For example, if the retino-geniculo-striate pathway is injured, the retino-tectal pathway might mediate residual visual capacities, particularly in "blindsight" and after early lesions (for references, see [100]). Therefore, recovery may be mediated by some uninjured, alternative pathway and what appears to be true recovery could, in reality, be merely an increased use of an alternative, intact route, a kind of re-routing of information flow. Indeed, areas surrounding the injured visual cortex [150] or spared tissue remnants of injured superior colliculus [131] have been proposed as possible substrates of recovery of vision.

The fundamental problem with prior studies becomes apparent if one considers that in most studies only one visual structure was damaged, usually either the retino-geniculo-striate or the retino-tectal pathway. It was Pasik and Pasik [99] who combined lesions of different visual areas simultaneously and still found visual sparing (in luminous flux) despite loss of different brain areas unless the suprachiasmatic nucleus also was involved, leaving the brain without any visual structure whatsoever. Also, Wood et al. [150] noted less recovery in cats with combined visual cortex and suprasylvian gyrus lesions.

The effort of previous research, perhaps inspired by Lashleys original reports, were directed at the question of which and how much visual tissue needs to be eliminated to prevent recovery to occur. Of course, it is trivial to state that a complete loss of visual structures precludes recovery of vision (no eye – no vision), but it is not so trivial to determine how many retinofugal fibers are minimally required for recovery of vision because traditional lesion approaches struggle with the problem that once one or two visual areas are destroyed, tissue remnants may have survived in such structures or yet a third or fourth structure may contribute. This creates a level of complexity that makes it virtually impossible to associate specific cellular events, such as cell number and cell morphology, with functional measures.

To circumvent this complexity, over about one decade, together with a number of collaborators, I have worked out a new model of visual system injury and plasticity, namely that of the optic nerve crush (ONC) in adult rats. Here, the entire visual system is damaged in a diffuse way, without sparing of any visual pathway.

3. Recovery after partial injury of the visual system

3.1. Optic nerve crush as a lesion model

The partial crush is done with a cross-action forceps, producing lesions which are both definable, reproducible and easy to apply (Fig. 3). Though monkeys and cats are generally the preferred subjects for vision research, we have used the adult pigmented rat to study recovery of vision for practical reasons. Though the rat, compared to higher mammals, has a relatively simple visual system organization and rats are generally not considered to be "visual" animals (as rats are thought to depend in their everyday life mostly on their sense of touch with their vibrissae and on the sense of smell), the rat visual system shares many of the morphological and functional features of higher mammals. Indeed, the contrast sensitivity function of the rat, an inverted U-shaped curve, is comparable to that of cats and primates, including humans [73].

Fig. 3. Crush device used to perform optic nerve injury: This reverse, cross-action forceps produces a mild crush if the tips of the forceps are spaced 0.2 mm apart (in the "closed position") and if the lesion of the optic nerve is made at a 2–3 mm distance to the eye ball (adapted from [113]).

The paradigmatic advantage of the ONC is that any recovery of vision could not possibly profit from other, intact parallel fiber systems as there are no intact alternative pathways through which visual information can reach high brain structures. After ONC, only a definable, small number of cells and their processes survive the injury within the area of primary damage, thus providing a small remnant of residual structure (see Lashley's work, e.g., [80]). As we show below, the visual system, when damaged in such a manner, spares just enough axons and neurons to permit recovery of some visual functions. It is under these defined conditions that recovery of vision can best be studied. It is also possible to use NMDA to lesion the retina [110] as it is also highly susceptible to glutamate [84]. However, as the fundamental features of the NMDA-model are essentially the same as the ONC-model, the effects of this lesion approach will not be discussed in further detail here.

The partially injured visual system in general, and the optic nerve crush in particular, offers several advantages compared to other lesion models of recovery, some of which are scientific and others are practical. They are:

(a) Experimental optic nerve injury may be a useful model to simulate diffuse axonal injury (DAI) in the brain [55] which is considered to be a hallmark pathology of human traumatic brain injury;
(b) ONC allows the study of causal relationship(s) between structural changes and functional improvements following traumatic axonal injury;
(c) The optic nerve is central nervous system tissue and therefore comparable to other brain lesions in that the axons do not regenerate under ordinary circumstances;
(d) The anatomy of the rat visual system has been the subject of intense study in the past, and RGCs are well described both morphologically and electrophysiologically (for references see 112);
(e) The ONC can be created in a reproducible and graded manner by selecting different pressures at the tips of the forceps [112];
(f) Lesion severity correlates well with functional outcome and recovery of vision follows a defined time-course of about 2–3 weeks (see below);
(g) Unlike fiber tracts in the brain or spinal cord, the optic nerve is structurally and functionally well separated from other, non-visual structures, thus allowing specific and precise lesions of visual structures only, without concomitant injury to other functional systems (such as those involved in locomotion, learning, attention etc.);
(h) The extracranial part of the rat optic nerve is approachable by relatively simple surgery, avoiding unintended damage to other brain structures or the vascular system;
(i) The neurons of origin in the retina are clearly separated from their axons (optic nerve) and the target (superior colliculus and lateral geniculate). This allows the independent manipulation of these compartments;
(j) The vast majority (more than 90 %) of optic nerve axons in the rat cross to the contralateral hemisphere, providing an elegant opportunity to use the opposite eye as an internal control;
(k) The visual system is retinotopically organized and somata of RGCs are segregated in different layers, thereby providing excellent laminar properties for studies on cellular gene expression after injury;
(l) Unlike total transection, crush lesions leave the major blood supply to the retina intact. Our routine observation of the blood supply in the retina through the rat eye lens indicates that except for the 30 sec during crush, the blood supply resumes normally.

3.2. Recovery of vision after partial optic nerve injury

Using the ONC model we have made a systematic effort to characterize recovery of vision in adult laboratory rats using different behavioral tasks [110,112,113,116,117]. Fig. 4 displays the kinetics of recovery of vision as reported in several publications from our laboratory. By recalculat-ing published data and displaying them as percentage values of visual performance the time-course of recovery of vision can be compared among these studies. After injury to either the retina or the optic nerve, different visual parameters recover spontaneously over time, including brightness [112] and pattern discrimination performance [116,117] as well as orientation towards small moving targets [33,113]. Surprisingly, the slope of recovery is rather similar between these independent experiments even though these studies were carried out in different experimenters in the authors laboratory, using different behavioral tests and lesion paradigms. Yet, in all studies maximal visual performance is reached at about 2–3 weeks after the injury, without significant improvement in vision thereafter. This similarity in time-course of recovery among different studies suggests that comparable neurobiological mechanism(s) of recovery of vision must be operative. In fact, the 2–3 week time course is also frequently seen after partial lesions in other central nervous system structures [103], possibly extending the value of these observations to other CNS-lesion situations.

One could always argue that these experiments were not sufficiently sensitive to detect some residual deficits which may not have recovered. For example, a rat that may have

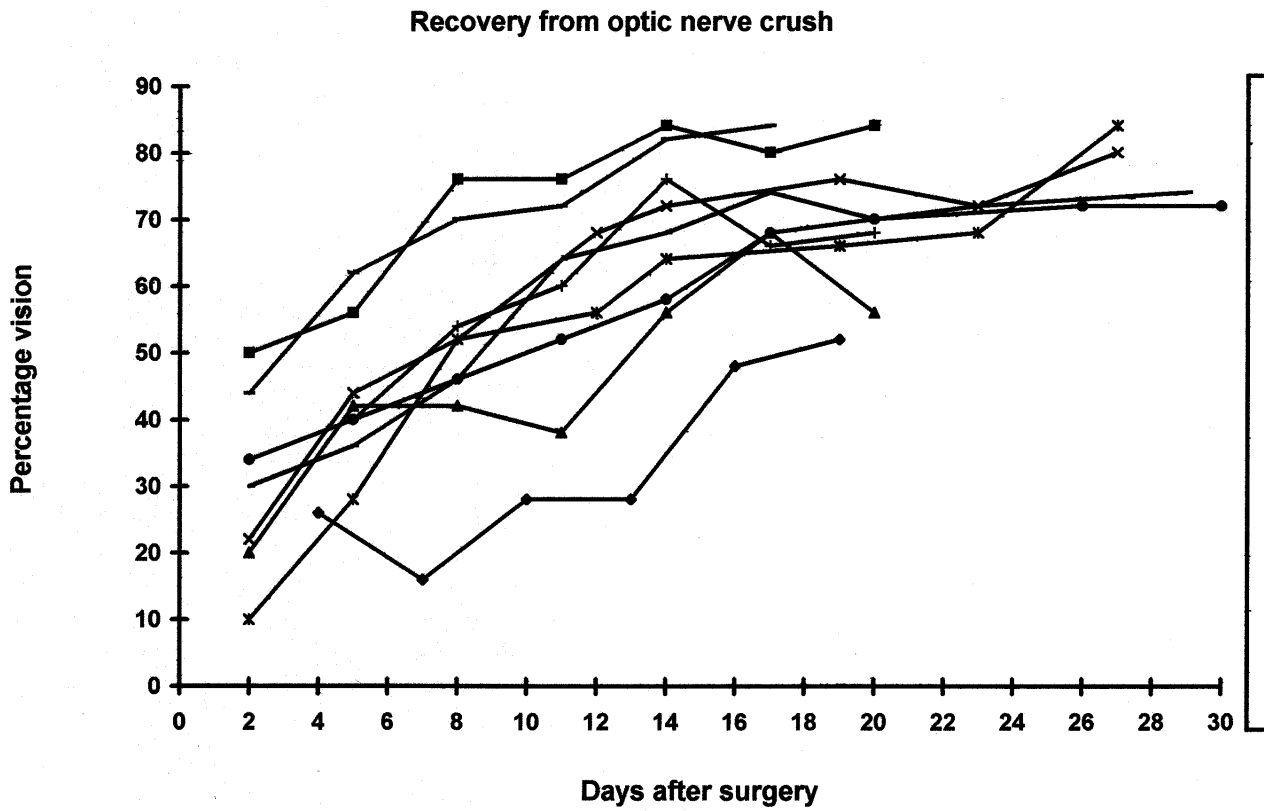


Fig. 4. Kinetics of recovery of function: A meta-analysis of behavioral studies after ONC. To allow for a direct comparison of the data among the studies, behavioral performance scores were standardized and expressed as "percent function" over time for all studies conducted thus far in the authors laboratory. In case of the two-choice discrimination maze, 50 % (e.g., chance) performance corresponds to 0 % visual function. In case of the orienting task, 0 % visual function refers to no orienting responses toward the small, moving target in any of the visual field sectors ipsilateral to the injured side. The numbers refer to the references in which the original data were reported. Treatment groups were not included in this graph. As this graph shows, the starting point of residual vision immediately after injury varies considerably among the studies, but the kinetics of recovery of vision is rather comparable, with maximum performance at about 2–3 weeks. The reference numbers are: A = [142]; B = [117]; C = [116]; D = [110, Fig. 2]; E = [110, Fig. 13]; F = [113]; G = [113]; H = [113]; I = [132];

recovered to discriminate brightness and pattern discrimination may still have residual deficits in high-load or complex tasks. Though this may be the case, the counter argument to this is that if any recovery occurs at all, whatever the parameter of vision may be, this would lead us to new insights into possible repair mechanisms.

3.3. The hypothesis of "minimal residual structure"

As we have seen there is no clear-cut correlation between the number of surviving cells and behavioral performance, yet, without intact optic nerve fibers neither plasticity in the retina nor plasticity in the target would be of any use. As in the studies mentioned above, we have also seen remarkable degrees of recovery with just a small remnant of tissue sparing. This raises the question, what amount of "minimal residual structure" (MRS) [107] within the optic tract is needed for recovery of vision to occur. Clearly, if not at least some minimum substrate for neurobiological information transfer along the optic nerve is provided, then plasticity in the target region would be of no functional use. It is obvious that the loss of structure can not fall below a certain critical threshold value and the question arises, just how many cells need to survive for visual functions to be able to recover.

Based on our experiments with optic nerve crush we concluded that only about 10 % of the retinal ganglion cells are sufficient for recovery of vision to occur. This view is compatible with the attempt by others to determine the minimum number of striate cells required to support pattern vision. Lashley [80] estimated that as little as one-sixtieth of the neocortex to be sufficient, and Chow [17] and Galambos et al. [50] found 2–3 % of the optic tract fibers to the LGN to be able to support "normal vision". Chow and Stewart's figure is about 28 % [18], much larger than the figure given by Hubel and Wiesel [64] who observed that with as little as 1 % of the cells remaining responsive, limited recovery of form deprivation can still occur.

Here, the studies by Pasik and Pasik [99] are of interest as well. They trained 14 macaques in a two-choice task (light vs. no light) after occipital cortex was removed bilaterally. Immediately after the injury, the animals were blind, bumping into objects and falling from platforms, though pupillary reactions and eye movements appeared intact. Three months after the injury the monkeys showed evidence of brightness discrimination as they were again able to reach for visual stimuli. Concomitant removal of ventrolateral portions of the temporal lobe, posterior portions of the parahippocampal gyrus, the

pulvinar, the superior colliculus or the medial tectum only resulted in temporary visual defects from which the animals recovered. Only when the lateral pretectal region was injured as well, which caused a bilateral, severe degeneration of the nucleus of the accessory optic tract, the monkeys were unable to relearn the brightness discrimination task.

In a sense the Pasik and Pasik study mentioned above supports the hypothesis of "minimal residual structure" [107] which states that as long as a small number of cells survive within the damaged structure, recovery of function is possible. In fact, Pasik and Pasik also considered small remnants of surviving tissue after the lesions as possible substrates of recovery, but a single case with a purported 100 % combined tectal/cortical lesion in a single monkey leads them to speculate that the nucleus of the accessory optic tract plays an essential role in the recovery. From today's view the relatively simple anatomical methods employed in the 1970s makes one wonder if more detailed tract tracing techniques available today may not have revealed some neuronal sparing in the cortical and/or tectal tissue.

Thus, not only does the visual system have capacities to recover from damage, but more generally speaking, just as Lashley stated, the extent of visual dysfunction depends on how much of the visual structure was removed (which was termed the principle of "mass action" by Lashley). While this somewhat holistic interpretation of visual system function is perhaps too simplistic, yet from today's point of view it emphasizes the tremendous potential that just a small amount of residual visual structures may possess.

The surprisingly small number of neurons required to obtain functional recovery is not a new phenomenon since similar observations were also made in other diseases, including Parkinson's disease and spinal cord injury (reviewed in [107]). Thus, a certain "minimal residual structure" (MRS), often on the order of 10 % (5–20 %), is required for visual functions to recover which emphasizes the role of spared neuronal tissue in brain plasticity and points to an unrecognized potential of residual neurons to contribute to recovery [107]. However, as the number of neurons in the primary area of damage does not correlate well with functional outcome the question arises, if perhaps down-stream structures, i.e. those which are deafferented by the lesion, may not contribute in a significant way to recovery of vision as well.

Even if vision is described in great detail using behavioral methods, to obtain a fundamental neurobiological understanding of visual restitution, processes on the molecular, cellular and systems level of analysis have to be considered.

3.4. Molecular correlates of cell survival and recovery

Over the last several years we have followed molecular events in the retina and in the tectum to characterize gene products which might be involved in cell survival and plasticity after injury. Specifically, we carefully examined the retrograde reaction of retinal ganglion cells in retinal whole mounts at various times after the injury and found retrograde cell loss to be on the order of 80 % (for details of the anatomical situation see below). Such massive cell death in the retina can not possibly leave the remaining, surviving cells unaffected. To determine if and how surviving cells react to this injury with alterations at the molecular level, we have conducted several studies using standard molecular biological techniques to find indicators of molecular plasticity [77].

3.4.1. Immediate early genes

The expression pattern of immediate early genes (IEG) in the degenerated retina, particularly the proto-oncogenes c-fos and c-jun, are of particular interest because they play a crucial role in the genomic response of neurons to injury. A relationship has been established between the expression of c-fos and c-jun, the transcriptional regulation of their target genes, and the cellular processes such as apoptosis, differentiation, senescence, and neuronal activity [114]. Therefore, we examined the expression of c-fos and, in addition, studied fos-b, c-jun, jun-b, jun-d, krox 24, srf, and pc4 mRNA after optic nerve crush in the rat retina by in situ hybridization [59].

Besides minor early increases in c-fos, ONC leads exclusively to the expression of c-jun in the retina while no expression of any of the other immediate early genes was detectable. Within the retinal ganglion cell layer c-jun expression was found at 2, 3, and 7 days post-injury. At later stages (i.e., 2 weeks and 4 weeks post-injury) c-jun expression was also observed in the inner and outer nuclear layers, but no longer in the RGC layer. To determine the role of c-jun expression in cell death or survival, we have performed antisense experiments *in vivo* to explore how the antagonism of the c-jun expression would affect cell survival [75]. Antisense, but not a missense, oligonucleotides against c-jun were injected intraocularly two and three days after ONC which led to dramatic increase of cell death of RGC. Immunocytochemistry demonstrated that also axotomized RGCs show c-jun expression, but unlike connected RGCs, these cells did not express a particular transcription factor, ATF-2, as documented by co-labeling experiments. Thus, the co-expression of c-Jun with high levels of ATF-2 may be an important factor for the maintenance of axonal connections of surviving RGC. In axotomized RGCs, in contrast, low levels of ATF-2 and the co-expression of c-jun may be related to cell death. In conclusion, cell survival may require high levels of ATF-2 and the simultaneous expression of c-jun [75]. This argues for a special role of c-jun as a survival factor in all those RGCs which remain connected with their target, a hypothesis previously proposed [60].

3.4.2. Glutamate and alternative NR1-splicing

Brain damage after trauma or stroke results from both, direct tissue damage and "secondary" cell death that occurs after some time delay. This is true not only for the brain but also for the retina. Many efforts have been made to determine the neurochemical mediators of secondary cell death and glutamate. Overstimulation of cells with ex-

citatory amino acids is a key factor mediating secondary cell loss after stroke [7,122] or trauma [41], and many studies on the "excitotoxic hypothesis" [82,95,96] have led to the discovery that specific glutamate antagonists, especially those acting at the N-methyl-D-aspartate (NMDA) glutamate receptor subtype such as MK-801 [20], can be neuroprotective both *in vitro* [16,98] and *in vivo* [86,87]; for review see [1].

It was Lucas and Newhouse who, in 1957, first discovered that systemic glutamate injections in the infant mouse results in the destruction of cells in the retina [84], and retinal neurons are now known to be highly sensitive to glutamate and its agonists [12,97,158]. Thus, glutamate deserves particular attention in the context of retinal cell death and plasticity. We have therefore studied the ability of NMDA to produce a dose-dependent loss of neurons in the adult rat retina with concomitant deficits in rat vision [110]. Intraocular NMDA-administrations led to a concentration-dependent loss of retinal ganglion cells and a less severe loss of displaced amacrine cells; as little as 20 nmoles of NMDA resulted in a 80 % RGCs loss and even at very high doses of 100 nmoles of NMDA about 13 % of the entire RGC population survives, i.e. this is an NMDA-resistant RGC population.

Why do some cells have a better chance of survival after NMDA administration or crush? To address this issue, we assessed the composition of several glutamate receptor subtypes by identifying mRNA expression and corresponding protein synthesis of NMDA receptor subunits in the retina [76]. The reasoning was that particular subtypes of NMDA receptors may be more or less susceptible to traumatic damage. We have therefore studied different splicing variants of the NMDA receptor [61, 161] and determined their role in secondary cell death using standard techniques of molecular biology [76].

As early as two days after ONC a selectively enhanced expression of the NR1-2b and 4b isoforms occurred in surviving RGCs, and the question arises why splicing of the NMDA-receptor would be altered after crush? It is known that optic nerve crush increases extracellular glutamate concentrations in the retina due to the degeneration of RGCs [154] which have a high glutamate content. Because glutamate and NMDA are highly potent toxins for RGCs and because RGC death after optic nerve crush can partially be blocked by low doses of the NMDA-antagonist MK-801 [153], it is probable that excitotoxicity contributes significantly to massive cell death after optic nerve trauma. The role of alternative splicing must be related to this glutamate toxicity, but only blockade of the splicing event with antisense oligonucleotides directed against specific splicing variants can provide some insight in the role of splicing. We found that intraocular antisense treatment directed against the NR1-2b splice variant of rats having previously sustained ONC significantly increased retrograde death of RGCs. This indicates that alternative splicing of the NR1 is an endogenous, adaptive mechanism that helps cells to better survive the trauma. By changing their NR1 splicing pattern, retinal ganglion cells become less vulnerable to excitotoxic damage because they are less susceptible to proton inhibition [76]. This can be viewed as a molecular plasticity event which helps the cells to survive and function better in an acidic post-traumatic environment [140]. The preferential expression of NR1-2b after axonal trauma may provide a means whereby RGCs express NMDA-receptor channels with a reduced cation permeability and agonist potency that are still functional at a more acidic extracellular pH. Thus, injury-induced alterations of NR1 receptor physiology are part of a protective/adaptive and not a pathogenic cellular response to an altered extra- and intracellular milieu after the lesion.

3.4.3. Gene expression changes in the deafferented target

Besides the retina, the deafferented target also undergoes some molecular alterations. We have started to characterize biological alterations of the deafferented target and conducted a subtractive differential display analysis of gene expression in the tectum. Among those genes which were altered, increased expression of the R-esp1 (enhancer of split) gene was the most notable [2]. Its expression temporarily increased in the SC of adult rats after optic nerve crush. The precise function of R-esp, however, is still unclear, but we have proposed that when R-esp1 is expressed, HES-1 DNA-binding capability is abolished due to formation of HES-1/R-esp1 heterodimers. HES is known to be the transcription factor that controls the phenotypic expression of PC12 cells to neuronal phenotype and thus belongs to the NGF signaling pathway. Our *in vitro*-studies confirmed that the overexpression of R-esp1 promotes PC12 cell survival even in the absence of nerve growth factor (NGF) and, conversely, antisense-mediated inhibition of R-esp1 expression reduces PC12 cell survival and suppresses neurite outgrowth even in the presence of NGF. This may be taken to indicate that R-esp1 plays an important role in the brain's response to injury *in vivo*.

In summary, the molecular plasticity studies indicate gene expression changes throughout the injured system (i.e. the retina and the deafferented target), the precise meaning of which have to be explored further. Molecular alterations as such are of little interest from a clinical perspective, however, unless these alterations are considered in the context of the visual system as a whole.

3.5. Anatomic consequences of partial optic nerve injury

To understand the mechanisms involved in restitution of vision a detailed understanding of the anatomical consequences is required. First and foremost we need to know how many and what kind of cells survive the injury. Although this appears to be a straightforward anatomical problem, as we shall see below the dynamic changes of basic cellular processes after injury (such as axonal transport) add an unexpected level of complexity to this seemingly straight forward question.

3.5.1. Retrograde cell death and cell soma reaction to injury

The most powerful techniques to determine the anatomical state of the injured visual system is probably the assessment of neuronal connectivity using anterograde and retrograde tracers. It is usually assumed in such tracing studies that axonal transport as such is not altered and that tracing techniques permit reliable determinations of the number of neurons which maintain a connection between the retina and the brain. Typically, tracing studies involve the application of a tracer substance such as horseradish peroxidase (HRP) or some fluorescent dyes [112]. These tracers are injected either into the eye (for determining anterograde axonal transport) or into a target of the retinofugal fibers (to label cells retrogradely), such as the superior colliculus (SC), which is the principal retinofugal target in the adult rat brain, receiving more than 90 % of all retinofugal axons.

To visualize surviving RGCs which remain connected with their target we have initially used such conventional tracing protocols in which retina and brain tissue are fixed and cells are subsequently counted with conventional microscopy [112]. However, because animals have to be sacrificed, such studies are only "snapshots" in time which do not allow one to follow morphological changes over time in the same rat. We have therefore recently developed the "*In Vivo* Confocal Neuroimaging" (ICON) technique [108] which permits, for the first time, the repeated observation of retinal ganglion cells in the living retina of anaesthetized rats. The ICON technique allows us to witness cell death in real time in living rats, revealing numerous unexpected, yet highly relevant, findings.

Using such retrograde tracing techniques, we first determined the number of RGCs that are morphologically connected with their target after graded crush injury. We then quantified the number, size and distribution of surviving RGCs either in retinal whole mounts or in the living rat retina. From these experiments the following neuroanatomical picture of cell death emerges:

The rat retina, which normally contains approximately 110,000 RGCs with intact retrograde axonal transport, experiences dramatic changes after ONC. Within two days after mild crush, only about 30,000 RGCs can be labeled retrogradely, after moderate crush 25,000, and after severe crush only 8,900 RGCs [112]. Although this loss of retrograde transport does not represent immediate death of cell somata, it is an early indication of soma death which occurs gradually sometime after axon transport ceases [108]. Nevertheless, retrograde transport is a functionally meaningful parameter because the percentage of cells with intact retrograde transport immediately after ONC roughly equals the percentage of vision loss at post-injury day 2, which is, in case of mild ONC, about 30 % (Fig. 5).

While 2 days after mild crush, rats had on average 30,000 RGCs per retina, when allowed to survive for 14 days, the number of retrogradely labeled RGCs decreased even further to about 12,000 (Fig. 5), which is a 11 % survival of the original cell number. This progressive cell loss, seen also with ICON [108], points toward the existence of a RGC population which is "at risk" and which has an impaired axon transport immediately after the injury. The delayed death of these cells may explain the very late cell body loss seen up to 4 weeks after ONC with ICON. Although there were some differences in the distribution of labeled RGCs between rats, in all lesion groups the RGC loss was evenly distributed throughout the retina, with no particular retinal sector being spared from cell death [112]. Thus, loss of axon transport appears to anticipate cell body death.

We also made the rather curious observation that many cells which did manage to survive the neurotrauma [108, 112] or intraocular NMDA-administration [110] have relatively large diameters. Initially we interpreted this to indicate that large diameter cells had selectively survived. Serendipitously, this later turned out to be a rather important issue. Namely, subsequent analysis with the ICON [108] revealed that the soma size actually grew larger over time in about half of the surviving RGCs (Rousseau and Sabel, unpublished observations). In fact, by plotting the precise dynamics of soma size increases we were able to predict, for each neuron, whether the cell would live or die after the injury: while a massive cell body increase of > 80 % above baseline anticipated certain death by post-operative day 20, either no increase or a moderate, slower soma increase in the first few days after crush predicted RGC survival with high accuracy. Interestingly, only half of the surviving cells experienced such a "ballooning" of their soma and, after about 4 weeks, the cells shrank slightly, but soma size remained elevated above baseline values as long as the animals lived (Fig. 6C). Most recently we have studied the issue if these cells which experience cell soma swelling play a special role in recovery of vision, or if this is simply a pathological event (Rousseau and Sabel, unpublished observations) and have correlated cell soma swelling and the recovery of this swelling with recovery of visual performance. Because the number of cells which managed to recover from some swelling correlated highly with recovery of visual performance ($r < 0.86$) we now think that recovery from soma swelling predicts (and probably causally relates to) recovery of visual functions.

Interestingly, Chow and Stewart [18], who conducted monocular deprivation experiments with kittens, noted that cell sizes in the lateral geniculate nucleus of the thalamus were reduced by 35 %, but this soma shrinkage could be prevented when the eye was re-opened and the kittens were forced to use it by visual training. In fact, in one cat (EC12) LGN cells which were previously deprived but later trained were, on average, actually 13 % bigger compared to the non-deprived side. Also, in the deprived eye which had been exposed to visual stimulation the number of large neurons was found to have increased. These data indirectly support our conclusion that there is compensatory, adaptive cell soma swelling in the damaged brain.

To understand the possible role of the moderate RGC size increase after ONC, in a subsequent experiment (Rousseau

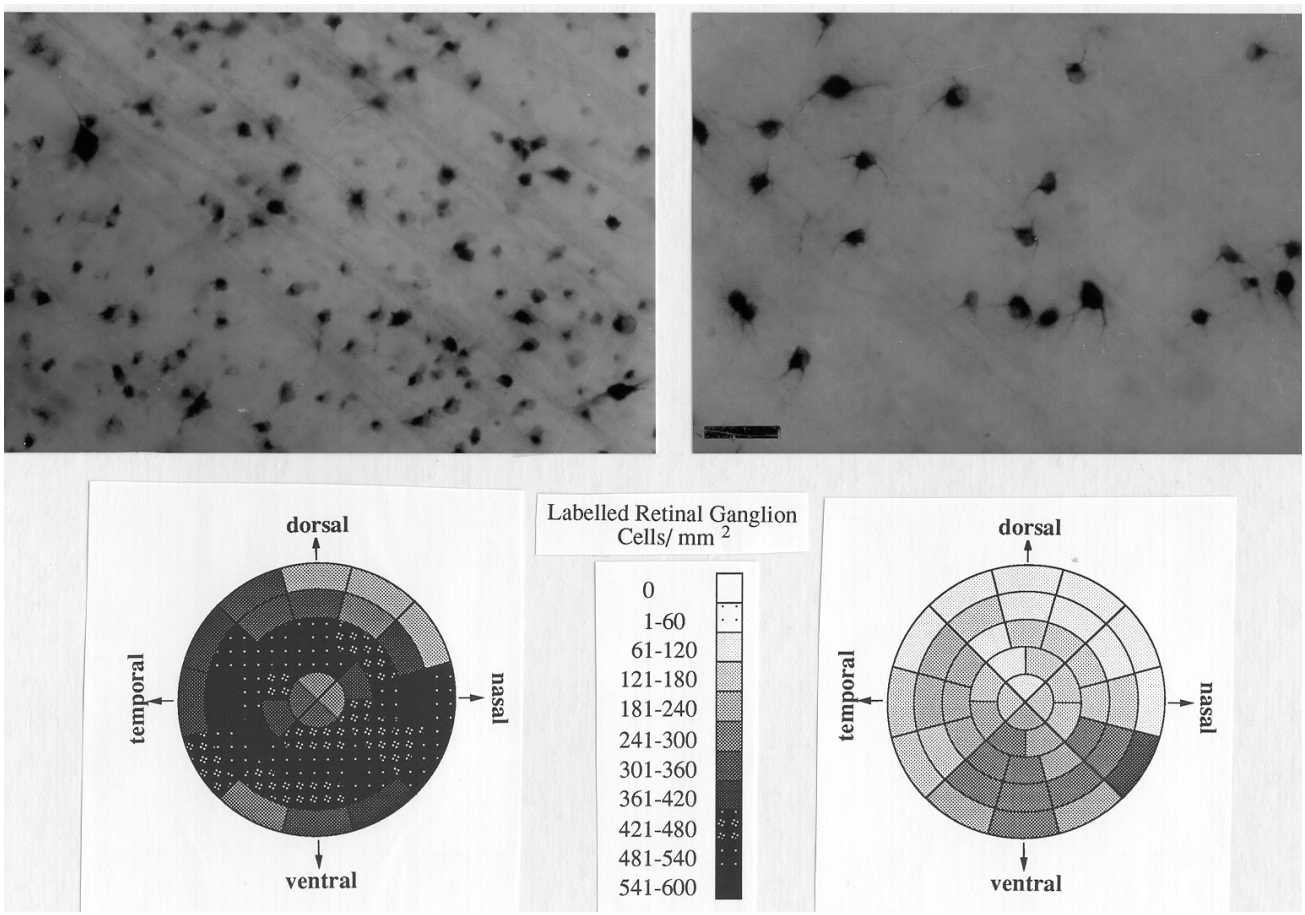


Fig. 5. Upper panels: micrograph of retrogradely labeled retinal ganglion cells (RGC) surviving optic nerve crush in retina flat mounts 2 (left) and 14 days (right) after the injury. The cells are retrogradely labeled by HRP which was injected into the superior colliculus 2 days before sacrifice. Note the declining number of cells with increased survival as well as the relatively high proportion of large-diameter cells. Scale bar = 50 µm.
Lower panels: RGC density charts at corresponding survival times. Note that the entire retina is affected by RGC loss, with no area of sparing.

and Sabel, unpublished observations) we correlated the reversal of cell size increases *in vivo* as visualized by ICON with recovery of contrast discrimination ability. In this protocol, ICON was applied every five days while, in parallel, the same animals were tested for their contrast discrimination ability. We found that the time course of moderate soma swelling mirrored the recovery of contrast discrimination ability (Fig. 6). In addition, the number of cells with moderate swelling correlated highly ($r = 0.97$) with behavioral outcome. Though a correlation does not provide information about causality, we suspect that retrograde soma swelling may be a mechanism whereby rats recover visual functions. Only additional studies will reveal, however, if there is indeed a causal relationship between the morphological change and the behavioral recovery.

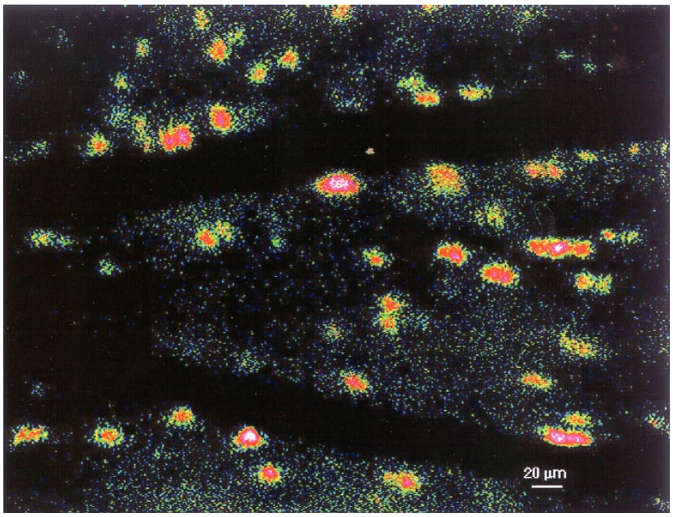
When interpreting these retrograde labeling experiments some caution, however, is appropriate. The number of HRP positive cells does not necessarily equal the number of cells still connected with their target. It cannot be determined at the present time if and how many HRP-negative RGCs remain in axonal continuity with their target, being unable to maintain a normal retrograde transport. In fact, we have obtained evidence of recovery of anterograde axonal transport, implying that the transport itself may be altered after injury [145,146]. This renders any anatomical analyses that depend on tract tracing somewhat dubious in their interpretation (for anterograde transport findings see below).

In summary, the retrograde transport studies revealed an on-going degeneration within the first two weeks, where about 70 % of the RGCs experience an immediate loss of axon transport and subsequent cell death, about 20 % experience a delayed axon transport loss with subsequent cell death, and about 10 % of the RGCs permanently survive the injury and maintain connection with their target. About 20 % of the cells are disconnected from their target, but the cell body survives without the axon. Of all the surviving cells in the retina, about half undergo compensatory soma size increases which correlates well with the animals ability to recover visual functions (unpublished observations).

3.5.2. Cell death characteristics

There are at least two ways whereby cells can die: necrosis due to membrane damage or apoptosis due to DNA-fragmentation. Necrotic cells were visualized with the nucleoso-

A



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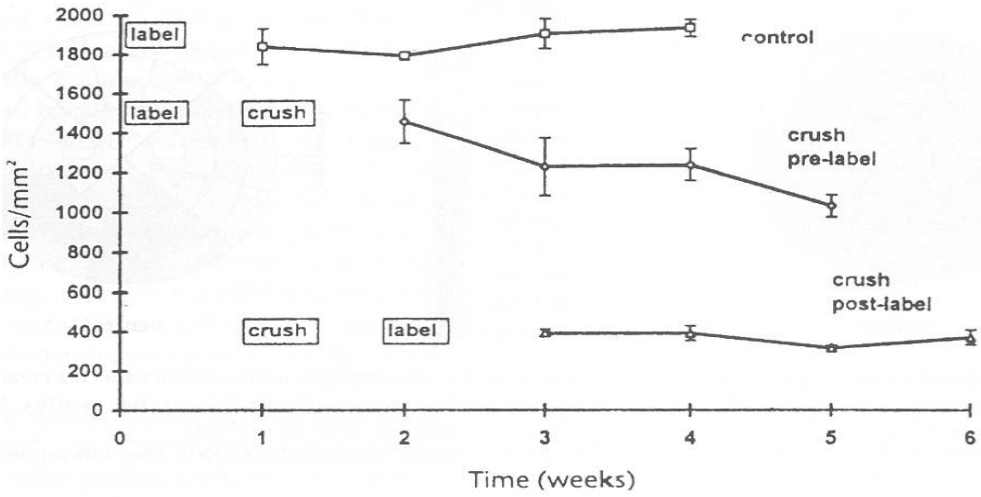

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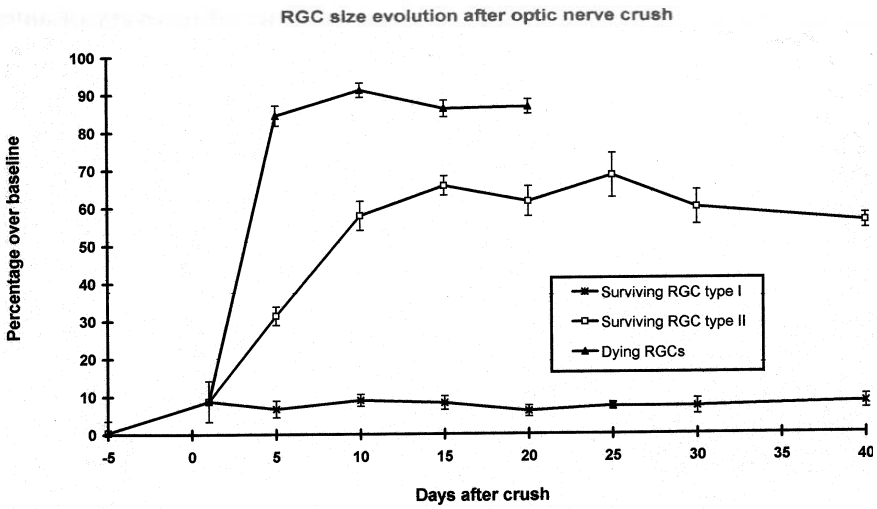

Fig. 6. Part A: Retinal ganglion cells in the living retina as imaged with the ICON technique as described in [108].
Part B: *In vivo* observation of RGC loss with ICON. If RGCs are labeled retrogradely before the crush, the ongoing loss of all RGCs in the retina after crush can be seen repeatedly in the same animal with ICON. If retrograde tracer is injected into the superior colliculus after the crush, only those cells can be counted which remain connected with their principle brain target. This cell number does not decline significantly over time after injury.
Part C: If the cell size of the surviving RGCs is followed over time with ICON, many cells are found which rapidly and massively increase their cell body diameter and ultimately die. Of those RGCs which survive, about half also undergo a cell diameter increase, but this is slower and less pronounced; the other half remains unchanged. This cell size increase may be a compensatory, adaptive reaction of the surviving cells to trauma.

mal Sytox-stain and apoptosis with the in situ end-labeling of DNA fragments using the TUNEL method. We have characterized the time course of these two types of cell death [10] with the following results: at early stages of RGC degeneration, necrosis dominates, with a maximum number of necrotic profiles at post-lesion days 2–5. Both types of cell death follow a distinctly different time course: apoptosis can first be found at post-operative day 5, it peaks at 2 weeks and gradually declines thereafter. Thus, RGCs die due to either necrosis or apoptosis, both of which follow a distinctly different time course after ONC (ONC).

3.5.3. Anterograde degeneration of axons and their terminals in the midbrain

RGC death invariably leads to loss of axons and terminals in the various brain target areas. Because the distribution of retinofugal fibers may be critical for understanding any residual visual functions, we have also evaluated anterograde degeneration in the midbrain tectum. By using the Fink-Heimer silver stain technique we visualized degenerating axons and axon terminals which were found in high density in all visual targets [112]. Just as no retinal sector was spared from the crush injury, also no area in the tectum was spared from anterograde degeneration. Degenerating terminals were most abundant in the midbrain tectum, forming dense fields of degeneration products. The entire stratum griseum superficiale of the superior colliculus was filled with degeneration products as were all other structures innervated by the optic tract, including the dorsal (LGd) and ventral (LGv) nuclei of the lateral geniculate body of the thalamus. The total density of degeneration products or their pattern was indistinguishable among the various lesion groups (mild, moderate or severe injury); in fact, they appeared very similar to those seen in rats with complete optic nerve transections.

Thus, the anterograde degeneration stain, when viewed in light of survival of about 10 % of RGCs, confirms the uniform and diffuse nature of the injury, leaving no area of the retina or tectum uninjured. Only few, sparsely distributed fibers survive within a field of massive degeneration.

3.5.4. Recovery of anterograde transport

Axons of the rat optic nerve are organized retinotopically, projecting primarily to the superior colliculus (SC) and, via collaterals, to the lateral geniculate nucleus of the thalamus (LGd and LGv). The retino-tectal topography is highly regular, with the entire visual field of the contralateral eye being represented in the SC. Obviously, to obtain a complete picture of the post-injury response, we need some idea of the state of anterograde axonal transport of retinofugal fibers surviving the injury.

When injecting a tracer directly into the eye of normal rats, the tracer is transported along the axons and fills the superficial layers of the superior colliculus. As one would expect, ONC leads to an impressive loss of label throughout retinofugal projection fields which is not surprising at all, given the loss of about 80–90 % of RGCs. However, following the fate of anterograde transport over time a marked recovery of anterograde transport occurs, leading to the re-appearance of labeling predominantly in the rostromedial sector of the SC at 6 weeks post-injury, with a clear gradient in the rostrocaudal axis [145,146]; see also Fig. 7. Interestingly, “recovered” anterograde label is restricted to the rostro-medial area which is the same area where metabolic recovery occurs (see below). In the lateral sector of the SC no recovery of anterograde transport nor recovery of 2-DG activity was seen.

This re-appearance of labeling in the rostro-medial SC may indicate either (i) a massive reorganization of retinofugal fibers in the tectum similar to that described by others [35,37,38] and/or (b) recovery of anterograde axonal transport itself. We have therefore quantified the intensity of anterograde labeling in the optic tract in areas where retinofugal fibers not yet branch off to innervate the various visual targets. This would ensure that increased labeling intensity would not be confounded with possible axon sprouting, though the likelihood of sprouting to occur is small [39]. Much to our surprise, even in these non-terminal regions, which contain axons only, we observed recovery of anterograde label in an extent similar to that of the terminal fields. This clearly shows that there is some recovery of anterograde transport itself. Whatever the mechanism of this process may be, this unexpected form of plasticity points toward a role of anterograde transport in recovery of function, an issue which certainly deserves closer attention in future studies. In fact, similar observations were made by Foerster [48], though she interpreted the recovery of anterograde labeling as a sign of axon regeneration.

3.5.5. Relationship between morphology and behavioral performance

The extent to which neuroanatomical structures contribute to recovery of visual functions can be determined with two methods: firstly, by determining how the time course of anatomical and behavioral recovery compare, and secondly by correlation analysis of anatomical and functional parameters in individual animals.

With regard to the first, we found that despite continued retrograde cell loss to about 11 % of the normal RGC number (Fig. 6), restoration of visual function occurs within the first 2–3 weeks post-crush (Fig. 4). Thus, the extent of retrograde cell survival and of recovered visual functions are clearly not associated.

Also, there was a surprising lack of any correlation between behavioral outcome and the number of RGCs surviving the injury. Specifically, while there is a tight correlation between cell number and behavioral performance immediately after the visual system injury, due to the enormous plasticity of the brain this correlation disappears within two weeks [110]. It is interesting to note that lack of correlation between retrograde cell survival and visual functions can also be observed in other instances: (i) drug induced-improvement of visual performance can occur in

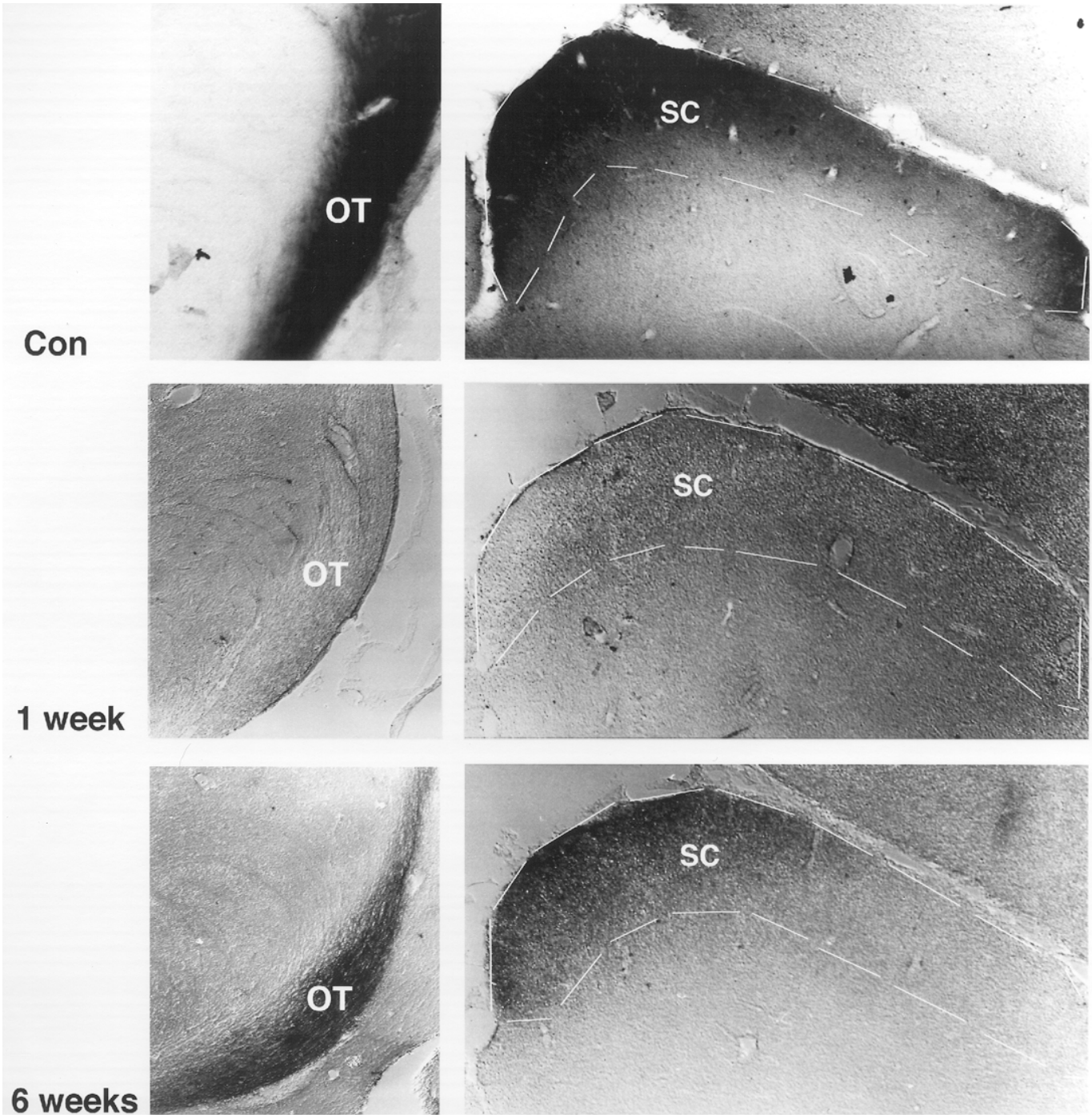

Fig. 7. Anterograde axonal transport after crush as visualized in adult ONC rats following intraocular injections. Upper panels: control; middle panels: 1 weeks after ONC; lower panel: 6 weeks after ONC; Left panels display the optic tract at a level rostral to the lateral geniculate nucleus of the thalamus, the right panels display with superior colliculus; both contralateral to the site of ONC.

the absence of improved cell survival [116] and (ii) visual recovery improvements by drugs are, in fact, sometimes accompanied by additional RGC loss [117]!

Whereas a minimum number of cells is required for information transfer from the retina to the brain, the lack of a correlation of RGC cell number with behavioral performance is a clear sign that recovery of vision does not primarily depend on the number of surviving cells in the area of primary injury but must be mediated by mechanisms in other downstream structures. Thus, the number of surviving cells does not predict the long-term behavioral outcome. While it is still reasonable to assume that improving the morphological condition may be of functional benefit, the reverse conclusion, namely that histological improvement is a necessary condition for functional improvement, is not supported by our observations in the visual system.

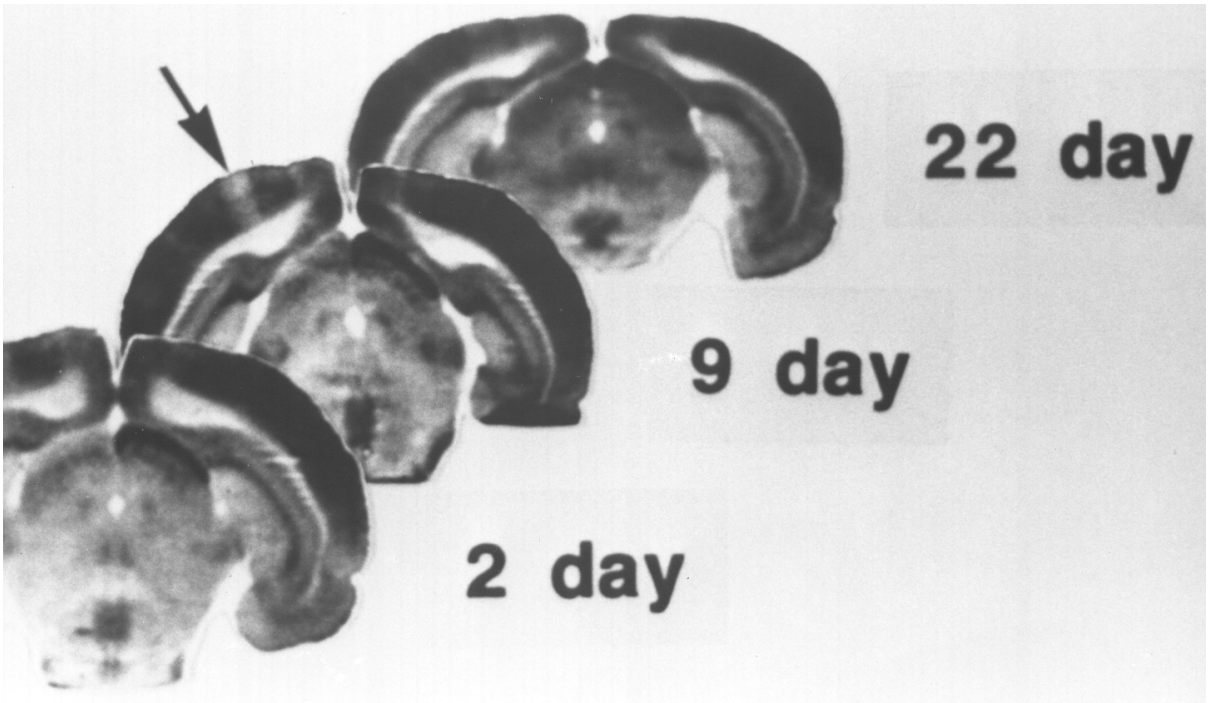

Fig. 8. Metabolic activity in the deafferented tectum of rats at various times after ONC. Note the loss at 2 days post-injury and the subsequent recovery (at 9 days) in the left superior colliculus (sc). The contralateral side was left uninjured (except for the minor loss of ipsilateral projections from the ONC).

3.6. Metabolic correlates of recovery of vision in down-stream areas

To better understand the functional state of the deafferented, down-stream target structures, we have quantified the basic metabolic activity of the principle optic tract targets in the brain using the 2-deoxy-glucose technique (2-DG) [124] which measures local cerebral glucose use (LCGU). At intervals of 2, 9, and 22 days after mild ONC 2 DG activity was measured in different brain areas, including the superficial layers of the SC, the lateral geniculate nucleus of the thalamus (LGN), and the monocular representation in the visual cortex (VC) [115]. Two days after ONC, we observed a metabolic depression in the deafferented, contralateral hemisphere to only 50 % of control values in the SC, 60 % in the LGN, and 87 % in visual cortex.

However, just as with behavioral performance, LCGU partially recovered on post-operative days 9 and 22, with significant improvement of LCGU in the contralateral SC and LGN to 68 % and 79 %, respectively. The largest increase occurred in medial sectors of the SC, which is the very area where anterograde transport recovery was noted as well (see above). Surprisingly, in VC, which was not directly deafferented by the optic nerve lesion, the LCGU did not recover at all. This might be explained by the fact that recovery of LCGU requires the presence of some degeneration products which is in agreement with previous reports that intraocular tetrodotoxin (TTX) administrations, used to produce a functional, but not a structural, blockade, leads to loss of LCGU with no subsequent recovery [134,135]. Evidently, structural denervation is necessary for LCGU recovery to occur.

Interestingly, recovery of metabolic activity in the target does not require, nor depend on, the presence of a retinotectal input: Firstly, after complete destruction of retinofugal fibers, with no residual fibers surviving the injury, LCGU nevertheless recovers in the tectum. Cooper and Thurlow [21] showed restoration of metabolic activity in SC within 7 days after complete deafferentation due to eye removal or complete destruction of the photoreceptor layer. Secondly, an acetylcholinesterase inhibitor, physiostigmine, which stimulates the synaptic transmission of retinofugal fibers, does not elevate the recovery rate of LCGU whatsoever [118].

Thus, hypometabolism recovers in a time course of 2–3 weeks which mirrors the time course of recovery of vision (see Fig. 8). That LCGU recovers even after total deafferentation implies the existence of local, deafferentation-induced neuroplasticity which is independent of retinofugal inputs, probably involving yet undefined intrinsic processes such as local neuronal circuitry reorganization (similar to those reported in [14,35]). It also suggests the presence of a local, deafferentation-dependent signal or signals which must trigger neuroplasticity in the target and suggests that the deafferented target structure itself is a major contributor to recovery of vision. The role of the minute residual fibers may just be to provide a minimum amount of input to the deafferented target, which is then amplified by the target to a functionally meaningful signal.

3.7. Electrophysiological correlates of recovery of vision

3.7.1. Recovery of evoked potential after ONC

Together with my collaborators I have studied recovery of the visual evoked potential in adult rats with optic nerve injury [143] and found that the amplitude of the evoked visual potential dropped down but recovered in a period of about 2 weeks, mirroring the time course of metabolic and functional recovery (Figs. 4 and 6). Because this potential is a compound potential recorded from visual cortex, little specific information of cellular mechanisms can be derived from this study.

3.7.2. Receptive field reorganization after retinal and cortical lesions

One of the major events after lesions in the visual system is the considerable receptive field reorganization. After retinal lesions, for example, the receptive field size increases by as much as 5 degrees of visual angle [67] and direct injury to visual cortex produces a local reorganization of receptive fields [35] and a proximal penumbra of hypoexcitability and a distal penumbra of hyperexcitability around the lesion site [35]. Some of this reorganization has been attributed to long-range intracortical horizontal connections which are either activated after deafferentation [25] or which undergo axonal sprouting [24].

While receptive field reorganization is discussed in greater detail by Eysel et al. [35], in the context of the present discussion synaptic reorganization should be discussed in passing, as it is directly relevant to the question of mechanisms of visual restitution. How exactly visual field reorganization comes about is not entirely clear, but it may involve structures which may contribute to normal visual system functions, exerting powerful lateral influences along the entire visual system axis [57]. It has been noted that receptive fields may change their sizes, perhaps due to activation of lateral influences through mechanisms similar to long term potentiation [36]. Though one generally thinks of the visual system as a point-to-point network with retinotopic order, neuronal networks do not terminate precisely. Rather, information spreads laterally such that excitation may reach areas which are larger than one would presume if a simple point-to-point connection was made [26]. This spread of visual information has a considerable uncertainty or "diffusion" which may normally be suppressed by lateral, inhibitory influences [72].

There are several biological substrates of such an information spread. One of the contributing factors is the considerable divergence of fibers in the visual pathway [23]. Another substrate for such lateral influences are the extensive horizontal connections known to exist in visual cortex which transmits information to widespread cortical areas up to about 5° of visual angle, a process which is apparently important for normal vision as well [26].

If we assume that lateral spread of synaptic information occurs at all levels of the visual system, then it would be predicted that the size of the receptive fields should increase the higher up we go along the neural axis. Indeed, this seems to be the case both in monkeys [156] and in humans [72] where receptive fields not only show considerable overlap, but they increase their size in higher areas of the visual system.

Lateral influences have also been proposed to underlie the "filling-in phenomenon", i.e. the curious observation that a retinal scotoma is subjectively much smaller than expected, and cortical interneurons have been proposed to contribute to this [92]. In fact, the compensation potential of the normal brain is so great that by "filling-in" missing gaps even large areas of blindness in the visual field (e.g. the blind spot) can escape conscious detection. In addition, the size of the receptive field varies considerably in the normal brain, depending on the brain's synchronization state [151], underscoring the tremendous flexibility of visual system organization.

Thus, receptive fields are altered considerably by lateral influences from neighboring regions, which could be either inhibitory or excitatory. It is likely that the visual system may very well make use of these mechanisms also to compensate for functions which were lost after traumatic injury. Whether lateral influences actually contribute to recovery of vision and to what extent they do, however, is not known at the present time (see also [14]).

4. Experimental manipulation of recovery

Whatever the neurobiological mechanisms of recovery of vision may be, the final and ultimate question is to what extent recovery of vision can be manipulated experimentally towards useful, clinical goals with training or drugs. Whereas drugs are primarily aimed at enhancing cell survival after injury ("neuroprotection"), the idea of training visual functions rests on the assumption that – similar to learning processes – repetitive use of either alternative pathways or residual fibers improves performance. Both areas of research have received only little attention in the animal literature and, aside from a few older reports, experimental manipulations of restoration of vision were not systematically explored.

4.1. Training visual functions

Considering that the normal brain is already equipped with different ways to spread information laterally and that these mechanisms are involved in normal visual functions, then it would be reasonable to assume that plasticity of the visual system should be responsive to training. Indeed, recent clinical trials conducted in my laboratory [70] demonstrated the efficacy of training to restore some visual functions lost after stroke or trauma by regular visual restitution training (VRT) on a home-based computer monitor. As these studies are discussed in greater detail in the accompanying article [68], they will not be discussed in detail here.

That training may restore lost vision had been suggested before, but the evidence has been weak. Indeed, several decades ago animal studies already indicated a possible benefit of visual training to restore vision. Though these studies suf-

fered numerous methodological problems (such as small number of subjects, insufficient control procedures etc.), in hindsight the value of these studies has not been fully appreciated. Some of the evidence comes from the serial lesion literature in which animals have been trained on visual tasks between the two serial lesions (see discussion above). Though these studies did not control the training effects systematically (they usually lack a non-trained control group), training appeared effective to restore lost visual functions.

4.1.1. Rats

In the Stein and Weinberg study [131] some of the rats received repeated testing between the two-stage tectal lesions (which was essentially a training-type situation). This led to a somewhat better performance in the brightness discrimination task than non-trained controls, though the difference just missed significance. As the training was not very intensive one might expect more clear-cut results had the training time per day been greater.

Also, Spear and Barbas [125] used a horizontal/vertical stripe pattern discrimination paradigm which eliminates contour-length and luminous flux cues to test rat vision and subsequently completely removed visual cortex in two stages bilaterally with visual training between the two operations. Under those conditions, 9 out of 10 rats relearned the visual task, and even some rats with total one-stage lesions, though more impaired than the two-stage rats, were able to relearn pattern discrimination with extensive training. While much of the improvement may be due to the training, some rats recovered visual performance even if as little as 300 trials were given (which can hardly be considered an intensive visual training).

4.1.2. Cats

Another line of evidence demonstrating the efficacy of visual training derives from studies where functional deafferentation was achieved by eye-closure early in life. Dews and Wiesel [27] and Ganz and Fitch [51] had already shown that visually deprived cats can regain light-dark discrimination. Chow and Stewart [18] showed that in newborn kittens which had one eye sutured for a period of 16–24 months, subsequent reopening of the sutured eye, together with the forced use of it (visual "training"), was beneficial. Initially, upon reopening the eye, the kittens appeared not to use their deprived eye but rather relied on their intact eye to perform visual tasks, as if the deprived eye had been "switched off". The animals kept walking into objects, failed to follow a moving light and did not blink in response to a suddenly approaching hand. Over the course of several months, however, vision gradually returned until there was little sign of blindness. This confirmed earlier studies by Riesen [104] and Ganz and Fitch [51] who also found a rather slow recovery after deprivation. Chow and Stewart attributed much of the recovery to the several hundred trials (training?) the animals received in a pattern discrimination task. Again, it is unfortunate that the study did not separate training effects from spontaneous recovery. Yet, it highlights the fact that the deprivation effects were not permanent, even when the eye re-opening occurred well after the "critical period".

In adult cats, sequential bilateral removal of the visual cortex and the superior colliculus results in severe loss of flux discrimination performance which does not recover. When receiving a massive training of about 1200 trials, however, the cats are able to relearn brightness discrimination [137].

4.1.3. Monkeys

In 1967 Cowey [22] observed in two rhesus monkeys with macular blindness that training was ineffective, but cortical damage, in contrast, led to a visual field defect which responded to training with a reduced sensitivity threshold. Also Pasik and Pasik [99] studied monkeys with bilateral occipital cortex lesions. The animals were initially blind, but three months after the injury the monkeys showed evidence of brightness discrimination as they were again able to reach for visual stimuli. Whereas unoperated controls had an error rate of only 1.5 % in this type of visual task, in animals with occipital cortical injury and subsequent training this error rate remained only at 10 %. As in other studies at that time, the effects of massive testing (between 300 and 6000 trials with visual tasks) – which essentially was a training situation – was not controlled for by comparing the performance with untrained monkeys. Therefore, whether the recovery of brightness discrimination was due to training effects or due to spontaneous recovery is inconclusive.

Moore et al. [91] describe a single case of an adult monkey (subject A3) with a large unilateral striate cortex ablation in which visual deficits were assessed in different sectors of their visual field about 1.5 years after the injury. The testing consisted of about 128 saccadic eye movements daily which were induced by the presentation of visual stimuli in different sectors of the defective hemifield. This testing consisted of a total of 12 daily sessions (128 stimuli each), lasting a total of about two weeks (about 1500 stimulus presentations), where monkey A3 improved gradually due to repeated testing (i.e. training) from about 75 % error rate to only 25 %. Another monkey, A1, which had not profited from repeated testing at that time, however, profited at later time points (2 years after injury), when it received a more massive training of over 5500 trials. A1 now also improved from a 75 % error rate to about 25 %, similar to A3s performance earlier (Moore, personal communication). Interestingly, the retrieval of residual vision was easier when the fixation point was not present during target stimulus presentation and recovered (retrained) functions were lost again when the luminance of the target stimuli were reduced.

In the Mohler and Wurtz study [90] macaque monkeys were also trained to perform saccadic eye movements with subsequent unilateral striate cortex removal. Initially, the animals were unable to detect stimuli unless the luminance was increased to 1700 cd/m^2. Within one month of training, however, the monkeys were again able to respond to lower luminance stimuli. As in patients (see [68]), only those areas of visual field which were trained but not those which were

not trained recovered. Monkeys made fewer detection and saccade errors in the trained area.

Thus, single case reports in monkeys clearly show that visual training is beneficial after striate cortex injury, but regaining vision required extended visual testing in the order of several thousand stimulus presentations. There are numerous reports of training-induced recovery of vision across species. However, the evidence is still somewhat circumstantial as it is often not obtained with properly controlled experiments and frequently relies on the description of single cases, particular in the cat and monkey work. Yet, these findings are in line with the human studies [68,70], and future experiments will show to what extent such training effects are mediated by synaptic reorganization.

4.2. Drug treatment of visual system damage

There are just a few isolated reports of drug-induced visual system restoration. With the exception of the amphetamine studies, these experiments follow the "neuroprotection approach". Neuroprotection assumes that if a greater number of cells are maintained after injury, fewer deficits would result. Strictly speaking, the term "neuroprotection" does not qualify as a recovery mechanism because restoration implies return of functions which have previously been lost and not the maintenance of performance or sparing of such functions. However, for the practical purpose of clinical usefulness I prefer to define visual restoration rather broadly to include neuroprotection approaches.

4.2.1. Amphetamine

Probably the first and – to this date most effective – pharmacological treatment of CNS-based visual deficits is the application of the catecholaminergic agonist, amphetamine. Braun et al. [9] were the first who noted restoration of some visual functions with amphetamine. They found a restoration of brightness discrimination learning after visual cortex lesions in rats by repeated low-dose amphetamine injections which were given just 15 min prior to the behavioral trials. Because amphetamine did not improve the acquisition of the learning itself but rather restored the lost visual function (enhanced retrievel), they concluded that "something that is modified survives the operation, and the drug provides access to the engram, just as it is capable to giving access to residual visual placing mechanisms" [8, p. 82].

Subsequently, Feeney and Hovda [42] administered four repeated doses of amphetamine to cats which – due to bilateral visual cortex ablations – had a complete deficit in binocular depth perception. If no treatment was given, there was no spontaneous recovery of depth perception. In contrast, rats treated repeatedly with amphetamine experienced an almost complete restoration of the depth perception deficit which was maintained well beyond the last amphetamine injection. However, when the animals were dark reared during the treatment, no recovery occurred. This suggests an interaction between drug treatment and visual experience and – to this day – this is the most dramatic example of drug-induced restoration of visual functions. These findings were later confirmed by Hovda et al. [63] who noted that the therapeutic effects were greater in cats with symmetric than in those with asymmetric lesions. As haloperidol blocked amphetamine-induced recovery it was concluded that catecholaminergic mechanisms are involved in the amphetamine-induced restoration of vision.

4.2.2. Trophic factors

It is frequently assumed that death of RGCs results, at least in part, from the disruption of the supply of trophic factors from target tissues due to loss of retrograde transport [4]. Despite a massive retrograde cell death after axotomy or ONC, some RGCs survive axotomy for periods up to several months [106,111]. Trophic factors, such as nerve growth factor (NGF) or fibroblast growth factor (FGF), may play an important role in permitting or supporting cell survival and axonal growth [8] because trophic factors increase survival and axonal outgrowth of adult central neurons both *in vitro* and *in vivo*. For example, when injected intraocularly in rats after optic nerve section, NGF promotes the survival of retinal ganglion cells [13] and FGF treatment improves the survival rate of RGCs *in vitro* [3,83] and following axotomy *in vivo* [121] as well. Therefore, a therapeutic opportunity exists to improve visual functions by trophic factor application, particular in view of the special role trophic factors play in developmental neuroplasticity (for review see [8]).

Unfortunately, the effects of trophic factors on behavioral outcome in our own experience are not impressive. Stoehr [132] has treated rats with optic nerve injury by intraocular injection of NGF and found no enhanced retinal ganglion cell survival and also no effect on recovery of vision. Similarly, Schmitt et al. [116] studied recovery of visual functions after intraocular injection of FGF and they found that treatment with FGF caused a significant, although small, reduction of the initial behavioral deficit. Despite this functional benefit, cell counts in the retina did not reveal any survival enhancing effects of FGF at 25 days post-injury. This is at variance with previous studies by Sievers et al. [121] who found an increased RGC survival after transection of the adult rat optic nerve when acidic or basic FGF was given.

Thus, trophic factors, at least in our hands, exerted no neuroprotection and only minor behavioral improvements and rats with improved behavioral performance do not have more neurons. This points towards a structural/functional dissociation and emphasizes the need for further research in this area. Yet, also these observations emphasize the need for further exploration of the role of down-stream structures in the recovery process, especially if one considers that FGF is internalized into the cell body and transported anterogradely by adult RGCs [43], perhaps affecting downstream structures such as the LGN, SC or visual cortex.

4.2.3. NMDA-antagonists: MK 801

The findings with the NMDA-antagonists is even more puzzling. NMDA-antagonists are widely used in neuro-

science research to protect the brain from injury due to the special role glutamate plays in secondary damage. We have therefore treated ONC rats with MK-801 and found that the initial deficit in visual performance was significantly smaller, i.e. MK-801 had a neuroprotective effect behaviorally [117]. However, much to our surprise, MK-801 treated rats had significantly fewer RGCs surviving ONC as assessed by retrograde HRP transport 25 days post-lesion. This finding is at variance with those of Yoles et al. [153] who observed MK-801 to protect RGC loss after optic nerve crush as evident both by retrograde tracing studies and by measurements of the visual evoked potentials. These differences may be explained by the different ways MK-801 was administered in both studies or by the different dosage used. Nevertheless, we have noted behavioral improvements despite exaggerated cell loss in the retina. This unexpected and seemingly paradoxical structural-functional dissociation may yet be another piece of indirect evidence that down-stream structures play a more important role in the recovery process than the structure of primary damage itself.

4.2.4. Gangliosides

Gangliosides are sialic acid containing glycolipids and their therapeutic benefit has been demonstrated both in animals [106] and human spinal cord injury victims [52]. They can be administered intraperitoneally and they have some therapeutic effects after ONC as demonstrated by electrophysiological recordings of the compound action potential (CAP) from excised rat optic nerve [113]. After an early loss of CAP within the first 2 weeks after ONC, rats receiving GM1-ganglioside treatment had significantly larger CAPs compared to operated controls. Loss of vision was evaluated in a visual orienting paradigm where rats also recovered spontaneously within about 2 weeks. Here, GM1-gangliosides significantly reduced the immediate post-lesion deficit, though final outcome remained unaffected. Thus, ganglioside treatment does not affect recovery of vision, but rather it reduces secondary degeneration subsequent to optic nerve injury. Also Zalish et al. [155] administered a 7-day treatment to ON-injured rats and found an increased number of viable axons 2 and 4 weeks after optic nerve injury.

Considering all drug studies sofar, it is clear that drug treatment of visual deficits is a real possibility, but so far – with the exception of the amphetamine studies – the results have not been overwhelming.

5. Multifactorial mechanisms of recovery of vision

What can be concluded from all of the work presented here about neurobiological mechanisms of restoration of vision? Based on our studies of rats with optic nerve crush – when viewed in conjunction with the work by many other laboratories – it is clear that not a single mechanism but many mechanisms contribute to restoration of vision following brain injury. Recovery of vision thus comprises a complex concert of events, all of which act together to produce functional improvement (see Fig. 9).

– Recovery of vision: recovery of vision occurs with a predictable time course of 2–3 weeks, independent of the task used to assess vision or the way in which the lesion is made. What does appear critical is the presence of a minimal amount of residual neurons surviving the injury.

– Retrograde cell reaction: After optic nerve injury, 70 % of RGCs seize axonal transport within 48 hours and subsequently die several weeks thereafter. Additional, secondary cell death, some due to necrosis but most due to apoptosis, of a further 20 % occurs up to 2 weeks, with as little as about 10 % (5–20 %) of the RGC maintaining axon transport and long-term survival. At least half of the surviving RGCs undergo a remarkable cell soma swelling which is probably adaptive.

– Recovery of anterograde axon transport: Some cells remaining connected to their principal target in the brain, the LGN and the SC, have an impaired axon transport one weeks after the ONC. Within 6 weeks, however, some of the anterograde axon transport resumes, but for reasons currently unknown fibers with such an intact transport preferentially innervate the medio-rostral sector of the tectum.

– Molecular plasticity: Surviving cells in the retina and in the deafferented target undergo considerable changes on the molecular level, including alterations of the immediate early gene, NMDA receptors and the trophic factor signaling cascade.

– Metabolic activity: In the medio-rostral area of the tectum, a significant loss of glucose metabolism is followed by recovery at about 2–3 weeks, mirroring the time-course of behavioral recovery. This metabolic recovery is in part due to the reorganization of retinal fibers (“extrinsic” recovery) but mostly due to other, yet unknown, “intrinsic” recovery processes in the deafferented structure itself.

– Electrophysiological plasticity: down-stream structures deafferented by the lesion undergo synaptic reorganization which may or may not have morphological correlates.

The post-lesion plasticity response thus entails multiple events (Fig. 9). In fact, there is a remarkable correlation in time between restoration of vision of 2–3 weeks and most of the physiological plasticity markers (cell soma swelling, anterograde transport, metabolic activity and electrophysiological activity) which all follow roughly the same time course. I therefore suggest that the sum of all these simultaneous changes provides the neurobiological substrate of recovery of vision. As long as a critical number of cells survive the injury (see the “minimal structure hypothesis”, [107]), and it does not matter how the lesion is made (crush versus NMDA injection) or which behavioral task is used to test the function (orienting performance, brightness, and pattern discrimination), recovery of vision takes place. One note of caution, however: *complete* restoration of vision does normally not take place, as some residual dysfunctions always remain.

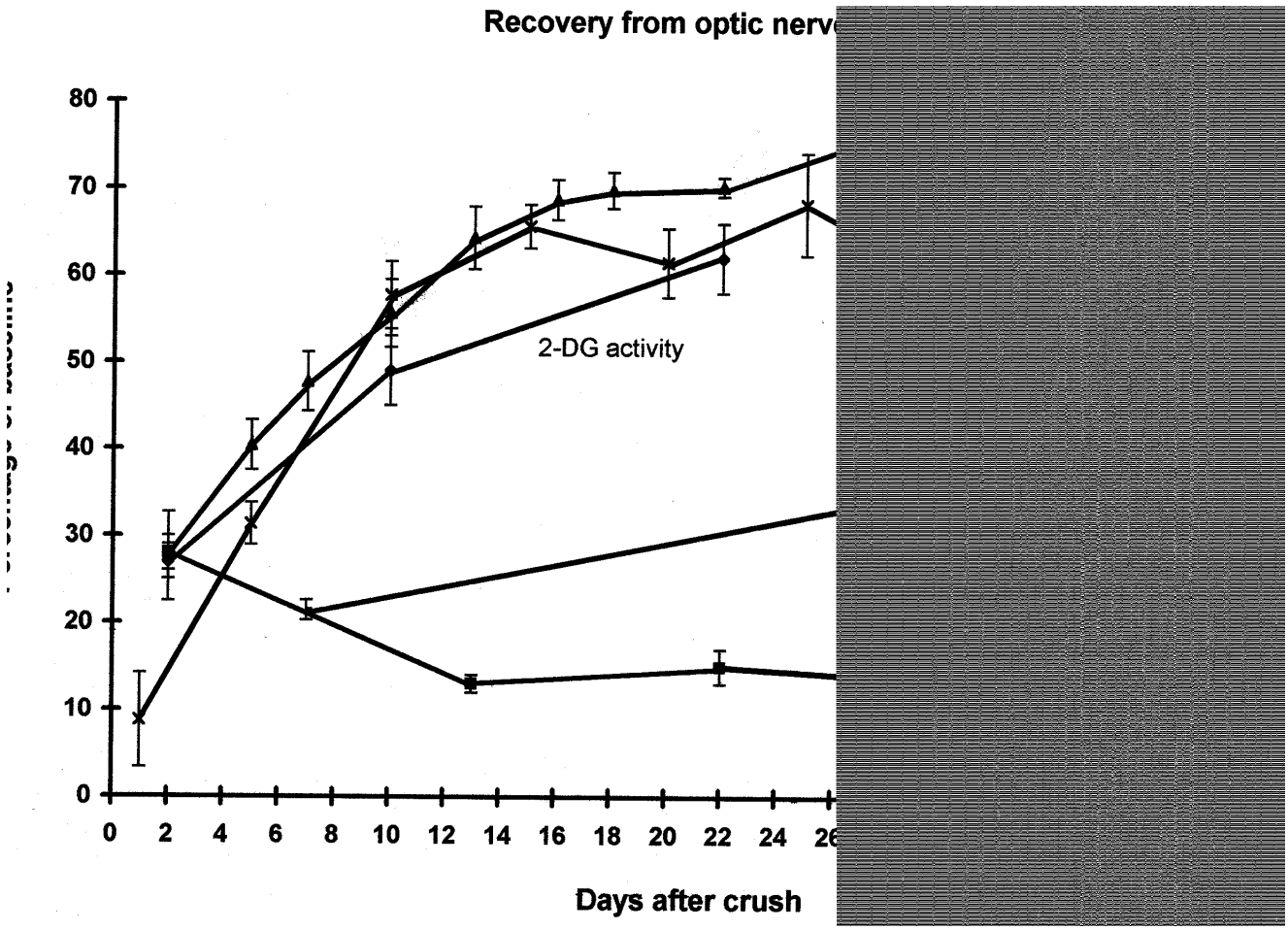

Fig. 9. Physiological correlates of restoration of vision. Behavioral and physiological parameters are plotted over time after optic nerve crush in adult rats, expressed as percent of control (except for the soma size change which is displayed as percent over baseline). Some data are taken from previously published experiments (connected RGCs from [108,112], 2-DG activity from [115]); vision performance is the average of all lines of Fig. 4 (± SEM). The anterograde tract-tracing data and the soma size plot are non-published observations. The starting point of the 2DG-data is selected arbitrarily, as the areas of hypometabolism still have some residual activity. The line "connected RGCs" is actually a composite graph from the data published in [108,112].

Recovery is therefore achieved by multiple, simultaneous events in the damaged system itself as well as in downstream structures. These downstream structures (tectum, lateral geniculate and visual cortex) probably play the most essential role in vision restoration, but the nature of receptive field reorganization via altered neuronal connectivity in the target and their precise relationship to visual performance still requires further exploration.

Even if our knowledge of the recovery mechanisms is still incomplete at this time, attempts to manipulate recovery either by drugs or training were at least partially successful, though more systematic studies are urgently needed. Unexpectedly, some drugs appear to exert a behavioral protection despite a lack of any effect on cell survival. One drug (MK-801), in fact, accelerated recovery while – at the same time – more RGCs were killed.

Progress in restoration of vision will require more knowledge of plasticity at all levels of the injured visual system, including the retina, the optic nerve, the primary, secondary and tertiary cortical structures. One fact emerges time and again: whether vision returns does not primarily depend on the precise number of cells surviving the injury. As long as a minimal cell number survives, higher cortical areas manage quite well with the little information they receive. Exactly how this is achieved, still remains a mystery.

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