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Regeneration of the retinotectal projection following compression onto a half tectum in goldfish

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SUMMARY

This study tested whether regeneration of the optic nerve following half-tectal compression in goldfish leads to the immediate reestablishment of the compressed projection or to an initial half map followed by the gradual compression. Half of the tectum was removed and the optic nerve crushed in large 12–18 cm goldfish which were kept at 20 °C and later mapped either in air or in water. At 35 to 41 days, the maps showed the presence of the nasal field projection and only the first 27 degrees of the temporal field. Most of the temporal field was represented after 200 days or more. After 253 to 343 days when the compression was largely complete, the optic nerve was recrushed. The projections mapped 35 to 41 days later were always compressed with up to 99 % of the temporal field represented, as were projections regenerated at 28 °C and mapped at 23–25 days. Regeneration after compression restores the compressed projection, consistent with the concept of altered tectal markers.

INTRODUCTION

In amphibians and teleosts, the retinal ganglion cells regenerate their axons, following crush of the optic nerve, and reestablish retinotopic connections within the brain, the major target being the optic tectum (Sperry, 1944; Gaze, 1959). In goldfish, Attardi & Sperry (1963) demonstrated the selectivity of regeneration by removing portions of the retina, crushing the optic nerve, and showing histologically that the regenerating fibres bypassed empty areas to arborize only in appropriate tectal areas. Sperry (1963) explained this selectivity by postulating that during development, the cells of both the retina and the tectum acquired individual 'cytochemical tags' and that ingrowing axons linked only with those neurons carrying similar tags via the 'specific chemical affinities' between them.

Within a few years, however, experiments employing partial ablations of either the retina or the tectum demonstrated that the projection, as assessed by electrophysiological mapping, is capable of reorganization so that the remaining portion of retina projects topographically to fill the available tectal area ('systems matching', Gaze & Keating, 1972). A remaining half tectum can receive fibres from both halves of the retina (Gaze & Sharma, 1970; Yoon, 1971; Schmidt, Cicerone & Easter, 1974) and likewise a remaining half retina can

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project over both halves of the tectum (Schmidt, Cicerone & Easter, 1978; Horder, 1971; Yoon, 1972). The regenerating fibres first occupy the appropriate sites, but after several months move to new locations (Gaze & Sharma, 1970; Sharma, 1972; Schmidt *et al.* 1978).

The altered projections are inconsistent with Sperry's (1963) formulation of neuronal specificity and several explanations have been advanced to account for the new results. First, there is the possibility that the adult goldfish retains the embryonic property of regulation by which a halved retina or tectum would automatically take on the full set of cytochemical markers (Yoon, 1976). At least in the half retinal case, this has been shown not to occur (Schmidt, 1978). A second possibility is that tectal markers are merely a relative set of preferences. However, in the case of half-retinal expansion, fibres which are not deprived of their site of first preference still move to gain more territory in spite of the difference of the markers. In addition, tectal markers appear to change during the expansion of the half-retinal projection as indicated by the formation on those tecta of expanded half projections even from normal intact eyes (Schmidt, 1978). Finally, the changeable nature of tectal markers is supported by studies dealing with regeneration of projections to tecta that had been denervated some months before. In the half tectal case, Romeskie & Sharma (1977) found immediate compression upon regeneration to a long-term denervated tectum. Correspondingly, regenerating fibres from a half retina immediately expand their map across the previously denervated tectum (Schmidt, 1978). In these cases the fibres were not constrained by a normal set of tectal markers, consistent with the idea that tectal markers are dependent upon the previous projection. Thus after a normal map there would be normal markers; after an altered map altered markers; and after prolonged denervation, no markers. Willshaw & von der Malsburg (1979) have constructed a computer model based on retinal induction of tectal markers which accounts for the above mentioned phenomena as well as many others. Since such positional markers would not be present during development, there must be separate cues for the orientation of the map. Chung & Cooke (1978) concluded that the tectodiencephalic boundary provides the necessary polarity information.

Recently Cook (1979) has disputed the finding of Yoon that regeneration taking place after compression restores the compressed projection onto a half tectum. Instead he has claimed that in the second regeneration there is initially a normal half projection followed by a gradual compression, suggesting an unchanged set of markers. The purpose of the present study was to reexamine this question and to see if it was possible to demonstrate evidence for possible changed markers following compression onto a half tectum.

METHODS

Goldfish 12–18 cm in length were obtained from either Ozark Fisheries (Stoutland, MO USA) or Grassyforks (Martinsville, IN USA) and maintained either at room temperature (20 °C) or at 28 °C.

Surgery

Fish were anaesthetized by immersion in a 0·1 % solution of tricaine methanesulfonate. The left tectum was exposed by cutting a patch out of the overlying cranium. The caudal half of the tectal lobe (including the ventrolateral portion) was completely removed by aspiration. The boundary was first delineated via an incision placed approximately at the projection of the vertical meridian as determined previously (Schmidt & Easter, 1978). The lesion removed approximately 60 % of the exposed surface viewed dorsally. It appeared to be more than half because, even though the projection is of roughly uniform magnification on the tectal surface (Schmidt *et al.* 1978), a significant portion curves under at the rostral pole. Following tectal ablation, the cranial patch was sealed in place with dental acrylic or cyanoacrylate. The crush of the right optic nerve took place in the orbit as described previously (Schmidt *et al.* 1978).

Recording

Under anaesthesia the tectum was re-exposed. It was viewed dorsally during the recordings which were made with Wood's metal-filled pipettes introduced at a slight angle (20–30 degrees from the vertical) rostrally. Penetrations were made at regular grid intervals. Further details are given elsewhere (Schmidt *et al.* 1978; Schmidt & Edwards, 1983). The eye was centred on the hemisphere as determined by the position of the optic disc, normally 6 degrees nasal and 12 degrees dorsal of the optic axis (Easter *et al.* 1977). The disc position was continually monitored to correct for any drift of the eye. For all maps, rostrocaudal and mediolateral magnification factors (RCMF and MLMF), defined as the distance in micrometers on the tectal surface per degree in the visual field, were calculated by regression analysis. Distances on the tectum were measured from the rostralmost penetration in each row to all other penetrations in that row. Corresponding distances across the visual field were measured as the number of degrees between the respective receptive field centres. A single regression line, constrained to pass through the origin, was fitted to the pooled data from each map, and the slope of that line was the RCMF. The MLMF was similarly computed.

An early group of fish were mapped with the eye in air, and a later group with the eye in water. In order to permit the comparison of results from the two groups, the position of each receptive field mapped in air was later corrected for the enlargement of the visual field in the air, using standard spherical trigonometry (Schmidt *et al.* 1978, appendix). Theoretically the visual field in air is larger than it is in water, and the amount of the enlargement was checked experimentally in two ways. First, the magnification factors were calculated for two groups of normal fish of the same size: one group mapped in air (N = 8) and the other in water (N = 13). On the average, the rostrocaudal magnification factor was 13 % larger in water than in air, and the mediolateral factor was 20 %

larger (Table 2). A second check was done by recording the same fish both in water and in air. The average increase in rostrocaudal MF was 17 % (N = 6, S.E. = 3·0). Since these experimental values were in reasonable agreement with those previously calculated, the theoretical values of 19 % (horizontal) and 14 % (vertical) enlargement of the visual field in air were used in the corrections (Table 2).

Calculation of the percent of temporal field represented

The percentage of the temporal half of the visual field was computed from the positions of the centres of the most temporal visual fields in each row. First the optic disc was referred to its standard position using spherical trigonometry and each receptive field position was corrected for this shift. The normal temporal field was defined as the temporal 90 degrees of the hemispheric visual field in water. The actual temporal field represented was then taken as the weighted average of the longitudinal coordinates of the centres of the most temporal receptive fields (vertical meridian = 0), and was expressed as a percentage of the normal field. In the calculations, each longitudinal coordinate was weighted by the cosine of the latitudinal coordinate to reflect the area at each latitude (Fig. 1).

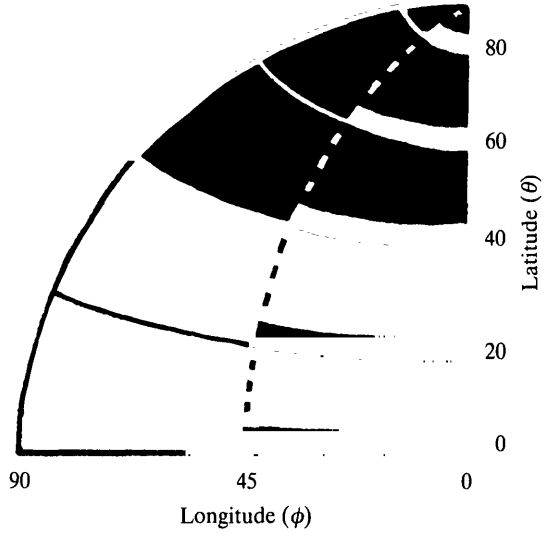


Fig. 1. Diagram of the temporal portion of the hemispheric surface showing the method used to calculate the percent of the temporal field using the weighted average of the longitudinal coordinates. Each longitudinal coordinate contributes an area proportional to that of a bar whose length is $\phi \times r \times \cos\theta$ and whose width $r \times \Delta\theta$ is held constant. The factor of cosine θ comes into play because the circles get smaller and smaller at higher latitudes. Thus the weighted average longitudinal coordinate is given by

$$\phi_{Avg} = \frac{\sum_i \phi_i \cos\theta_i}{\sum_i \cos\theta_i}$$

Normal fish, which see about 91 degrees off axis in each direction (Easter *et al.* 1977), are assumed to have 100 % of their temporal field represented, although the map extends into the inaccessible curved portion caudally. Since the caudal half of the tectum was removed, this was not a problem in experimental fish.

RESULTS

A total of 49 maps were recorded from 18 half-tectal (HT) fish and 21 normal fish. Two HT fish were mapped four times, and six were mapped twice to follow the progress of compression in the same fish. Maps obtained from HT fish were compared with those of normal fish in two ways. The first was through the calculation of magnification factors, particularly in the rostrocaudal direction which reflected the compression. Secondly the percent of the temporal field represented upon the half tectum was computed and compared to normals.

Time course of compression

Within 35 days after nerve crush combined with half-tectal removal, the nasal half of the visual field projection was reinstated upon the rostral half tectum (Figs 2A, 4). In addition, a thin strip of the temporal field near the vertical meridian was also represented. This strip averaged 27 degrees (30 % of the temporal field). This additional area represents plasticity during regeneration, since the edge of the ablation was placed at the average location of the visual field meridian (Schmidt & Easter, 1978). This same pattern was seen in all five fish mapped from 35 to 41 days postcrush.

This early partial compression upon regeneration was also investigated in two smaller (8–10 cm) fish mapped 42 and 44 days postcrush. These had a still larger area of temporal field represented, 45 and 47 % respectively. This was significantly greater (t-test, $P < 0{\cdot}16$) than the 29·88 % average for the 12 to 18 cm fish, indicating that the rate of compression may be faster in smaller fish.

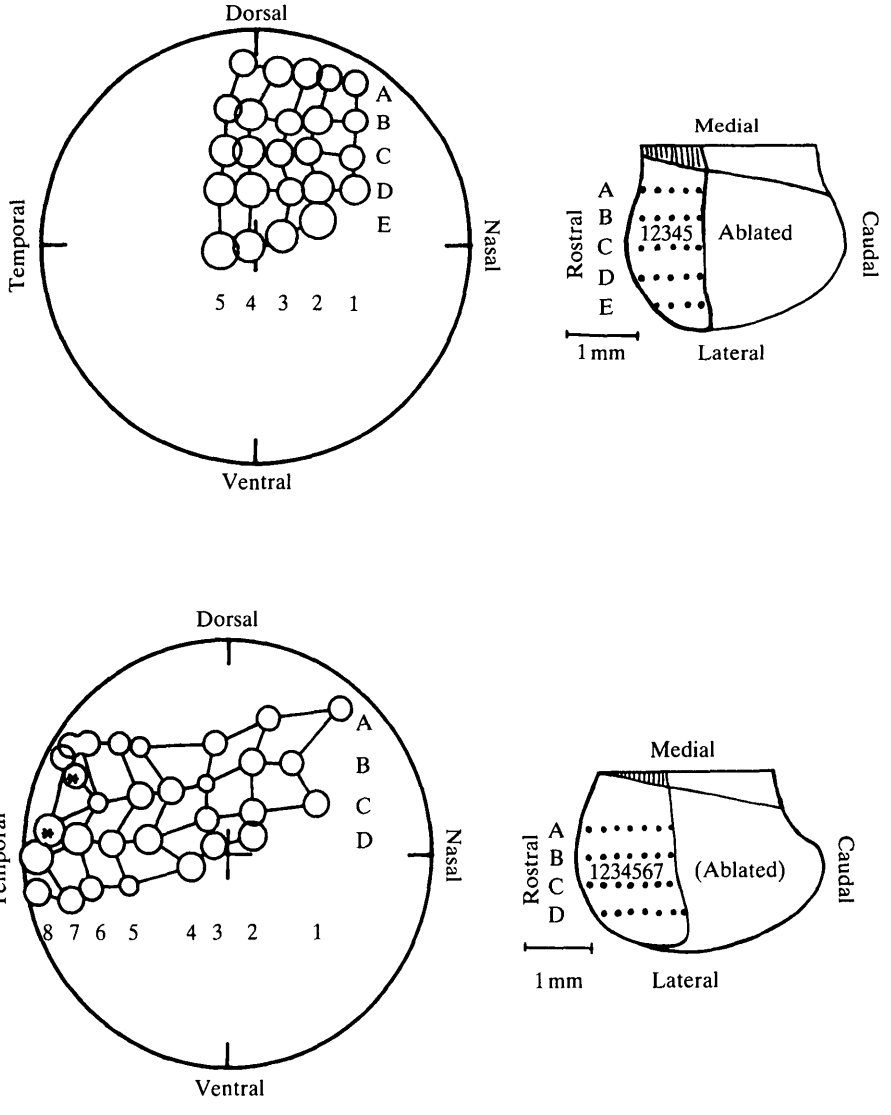
Two of the five large fish were remapped at 93 days. The maps showed only a very small change in that an average of 36 *vs* 27 degrees of the temporal field was represented at that time. Further increases in temporal field representation in these and other fish occurred gradually and with a certain amount of variability, until around 250 to 300 days when most of the temporal field was represented (Figs 2B and 4). This gradual process could be seen in four fish mapped at least twice – first when compression was at intermediate stages and also later at more advanced stages (Fig. 4).

Some of the fish used to establish the time course of compression did not have their nerves crushed (Triangles in Fig. 4). These projections compressed with much the same time course as those receiving the crush at the time of the ablation of the caudal tectum, with the exception of one fish which took somewhat longer. This is consistent with Gaze & Sharma's (1970) findings that compression

proceeds in goldfish with or without nerve crush but may take slightly longer without the crush.

Recrush after compression

Because compression was well advanced by 250 to 300 days, this time was chosen for recrush of the optic nerve. An initial group of four fish were mapped in air. Their nerves were crushed from 267 to 318 days after half tectal ablation, and the projections were mapped in air from 39 to 41 days postcrush. The nerves of three of the four fish were then recrushed and their projections mapped again at 34 to 35 days postcrush. All seven maps had very large areas of the temporal



Figs 2A & B

field represented, an average of 83·4 % in air and 71·8 % after correction. One of these maps, recorded at 34 days, is shown in Fig. 3.

A second group of three fish were mapped in water. Their nerves were crushed 253, 253 and 343 days after half tectal ablation, and the projections were mapped 36 to 38 days postcrush. One of these maps is shown in Fig. 2C. An average of 95·8 % of the temporal field was represented in these fish. In two of the fish the nerve was recrushed a third time, and they were allowed to regenerate at 28 °C to test the effect of temperature. The two maps recorded at 23 and 25 days were fully compressed with 97 and 99 % of the temporal field represented.

In summary, twelve maps were recorded following regeneration after compression, five mapped in water and seven mapped in air. The average portion of the temporal field represented was 82 %, very nearly the same as the average for fish mapped 200 or more days after half tectal ablation, and more than 2·5 times that of fish mapped at 35 to 41 days after crush combined with half tectal ablation (Table 1). There was no overlap at all in the data from the two groups (Fig. 4). Projections mapped in water had a larger portion of temporal field represented

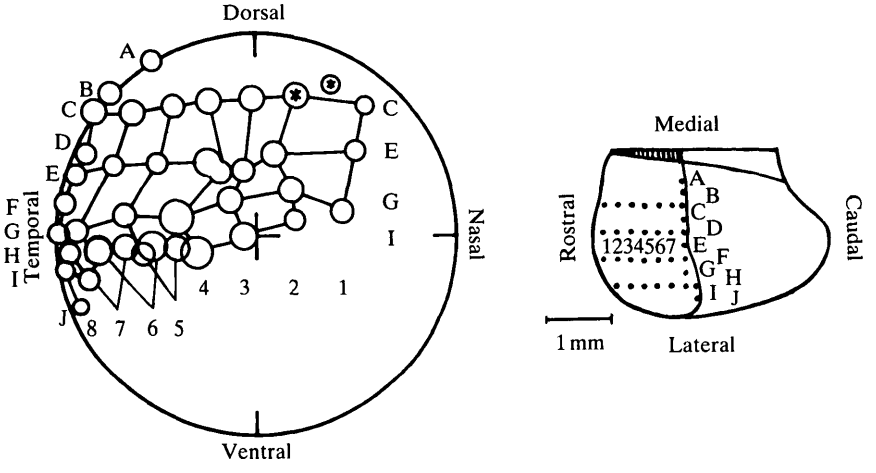


Fig. 2C

Fig. 2. Retinotectal maps recorded in water from half-tectal fish: A, 36 days after nerve crush and half-tectal ablation; 18 % of temporal field represented. B, 343 days after nerve crush and half tectal ablation; 90 % of temporal field represented. C, same fish as in B, mapped 37 days after recrush of the optic nerve at the time of the recording in B; 96 % of temporal field represented. In each case the visual field (hemisphere) is represented in the large circle on the left. Approximate sizes of the receptive fields are given by the small circles. The dorsal surface of the tectum is seen on the right, and the dots arranged in the grid pattern mark the positions of the electrode penetrations. The two dimensions of the grid are denoted by letters and numbers, and these coordinates correspond with those of the receptive fields in the visual field. To show the degree of order of the receptive fields, lines have been used to connect those in each row and column. Two separate receptive fields were occasionally found at one electrode position. These are shown either with asterisks (as in B) or with thin lines connecting them to their coordinate numbers (as in C).

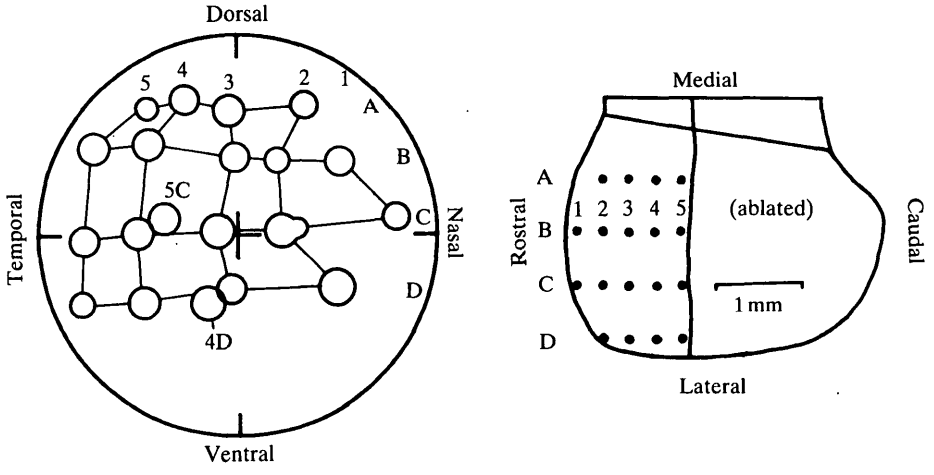


Fig. 3. Retinotectal map recorded in air from a half-tectal fish. The nerve was crushed 362 days after half-tectal ablation, and the projection was mapped 34 days postcrush. The map is not corrected for the enlargement of the visual field in air. Some 78 % of the temporal field is represented (after correction 67 %). Duplicate receptive fields are marked. Other conventions as in Fig. 2.

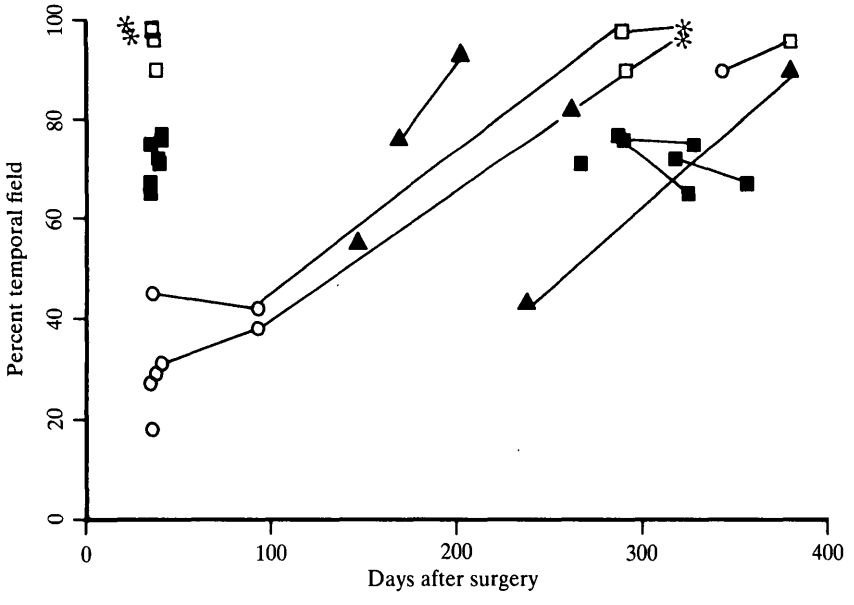


Fig. 4. A plot of the percentage of the temporal field represented in the retinotectal maps as a function of the time after surgery. Filled symbols represent fish mapped in air and corrected; open symbols and asterisks represent fish mapped in water. Triangles represent fish with half tectal ablations but no nerve crush; circles, those fish mapped after nerve crush and half tectal ablation; squares, fish mapped after recrush following compression. These are represented twice – at the total number of days following the initial surgery, and at the number of days after the second nerve crush. Asterisks are the same as squares, except they regenerated at 28 °C instead of 20 °C. Lines connect symbols representing maps from the same fish.

Table 1. *Percent of temporal field represented*

Group	% Area (S.E.M..)	Comments
I. Mapped 35–41 days after crush at time of half tectal ablation (N = 5).	29·88(3·87)	Slight compression
IIA. Mapped 35–41 days after crush following compression (N = 10).	78·8(3·5)	Advanced compression
IIB. Mapped 23–25 days after crush following compression (T = 28 C,N = 2).	97·9(0·7)	Advanced compression
Total for Group II (N = 12).	82·0(3·6)	Advanced compression
III. Mapped 202–380 days after half tectal ablation (N = 5).	79·47(8·4)	Advanced compression

Table 2. *Magnification factors*

Group	RCMF (S.E.M.)	MLMF (S.E.M)
I. Mapped 35–41 days after crush at time of half tectal ablation (N = 5).	14·9(1·0)	21·8(0·9)
IIA. Mapped 35–41 days after crush following compression (N = 10).	11·4(0·4)	22·1(0·8)
IIB. Mapped 23–25 days after crush following compression (T = C,N = 2).	11·7(1·3)	22·3(0·2)
Total for Group II (N = 12).	11·4(0·4)	22·4(0·8)
III. Mapped 202–380 days after half tectal ablation (N = 5).	11·19(1·2)	21·82(1·1)
IV. NORMALS (N = 13) Mapped in water	20·16(1·4)	24·68(0·9)
NORMALS (N = 8) Mapped in air	17·9(0·9)	20·4(1·1)
(Corrected: 19,14%)	21·3(1·1)	23·3(1·3)

(97 %) than those mapped in air (83·4 % or 72 % after correction). In six fish maps were made both before and after nerve crush. The average change in the percent of temporal field represented following regeneration was −0·80 % (±2·62 S.E.M.), an insignificant amount. Thus regeneration restores the compressed projection.

This restoration of the compressed projection is also reflected in the rostrocaudal magnification factors for these same groups (Table 2), although it is a somewhat less-sensitive indicator. Regeneration following tectal surgery gave an average rostrocaudal magnification factor of 14·85, less than the normal 20·16 and reflecting the fact that 30 % of the temporal field was already represented (Fig. 2A, Table 2, group I). Fish mapped more than 200 days after surgery had much lower MFs averaging 11·19 in the rostrocaudal direction, or roughly

half the normal value. In cases of regeneration following compression, the RCMF was close to that expected for a compressed map, averaging 11·45. As expected, there were no significant changes in the mediolateral magnification factor.

DISCUSSION

The primary conclusion of this study is that regeneration following an interruption of a compressed projection results in the immediate reestablishment of the compressed projection as soon as the projection can be mapped electrophysiologically. The large fish used here are an ideal specimen for study of this phenomenon. The initial compression takes much longer than in smaller fish (about 150 to 200 days in 12–18 cm fish *versus* 40 to 60 days in Cook's 6 cm fish). It is therefore easy to distinguish between the alternatives – immediate restoration of the compressed projection *versus* recapitulation of the slow compression process. Both this study and Cook's (1979) study agree that regeneration immediately after half-tectal ablation results in a half map on the half tectum, followed by a gradual compression.

One unexpected finding here was that immediately upon regeneration, some 30 % of the temporal field was immediately represented on the rostral half tectum. Thus fibres at the edge of the ablation were displaced by ones that would normally project some 500 μm more caudally, in the ablated half. Schmidt *et al.* (1978) reported a similar finding after regeneration following half retinal ablation. The RCMF was increased by 18 %, indicating that the fibres moved caudally some 300 μm beyond their usual sites. Both of these findings point to a limit of resolution of the tectal markers in their guidance of regenerating fibres. This point was also demonstrated in a study of projections regenerated during a block of activity (Schmidt & Edwards, 1983). Multiunit receptive fields were enlarged to 40 degrees in diameter. Thus markers may guide fibres to within 400 μm of their appropriate sites on the tectum.

The main conclusion of the present study concerns the extent to which tectal markers may change during compressions as indicated by the regeneration of a compressed projection. The present findings demonstrate a consistent restoration of the compressed projection immediately upon regeneration following compression, in agreement with those of Yoon (1972, 1976), but not with those of Cook (1979). It is also consistent with the idea that altered projections change the tectal markers as assayed in subsequent regenerations (Schmidt, 1978). There are several differences between Yoon's studies, Cook's study and the present study which could possibly account for the discrepancy in results. These include 1) the size of the fish, 2) the temperature, 3) the time allowed for compression before recrush of the nerve, 4) mapping in air *versus* water, and 5) the incomplete removal of the half tectum. These are examined below.

The size of the fish is unlikely to account for the different results. Yoon used

6- to 9-month-old fish, which are likely to be very small (Johns & Easter, 1978), and later (1976) he used fish 55 to 65 mm in length. The present results on 120 to 180 mm fish are consistent with his results but not with the results of Cook. Therefore the size of the fish cannot be the critical factor.

Likewise the temperature at which the fish were housed does not appear to be a factor. Although most of the data of this study were gathered from fish at 20 °C, two fish regenerated at 28 °C (the same as Cook's fish) and gave the same results. Yoon's fish were kept at an intermediate temperature of 22 °C. The question of temperature also relates to the time of mapping since the results of Springer & Agranoff (1977) suggest a Q10 of approximately 2·0 for time of regeneration. This would imply a factor of 1·74 between the times postcrush at 28 °C and 20 °C, and this is consistent with the ability to record regenerated projections by 23 and 35 days for the 28 °C and 20 °C fish respectively. The recording times in this study are comparable to the earliest (22 days) in the Cook study, particularly when one considers the fact that in these larger fish the regeneration pathway is longer.

A third factor might be the amount of time allowed for compression before the second nerve crush. The 85 days allowed by Cook (*versus* 227–343 in this study) may have been too short for remyelination (Wolberg, 1981) or some other process that might have stabilized the compressed markers. This, however, cannot account for the difference since Yoon waited only 83 days at a lower temperature of 22 °C.

A fourth factor is mapping in air *versus* water. In air, several limitations were noted in the present study. First there is a limitation of the amount of the temporal field that can be mapped because the fish's body blocks the line of sight temporally at approximately 90 degrees. After correction for the enlargement in air, this corresponds to approximately 76 degrees temporal. This limit is somewhat variable depending upon the angle of the eye in the head. A second effect is that units in far temporal field are extremely difficult to drive effectively because 1) the effective aperture of the pupil is much smaller at large angles, and 2) the light strikes the air–cornea interface at a very shallow angle and is largely reflected. The first applies also to mapping in water, but when both are combined there is a vast decrement in the amount of light entering the eye. This decrement could be especially significant in the mapping of immature newly regenerated fibres which are less responsive. In the present study, some differences were noted between maps made from regenerated fish in air and water. Newly regenerated compressed maps in water showed many duplicate receptive fields at far temporal positions (an average of seven per map; see Fig. 2C). Those mapped in air had many fewer such duplications (average of 1·1 per map), and they tended to occur away from the temporal margin. Thus in far temporal field many duplicate receptive fields may have been missed during mapping in air because of the difficulty in stimulating units there.

Yoon and Cook both mapped in air with opposite results, but neither gave any indication of special measures taken to stimulate units in far temporal field.

Therefore it remains uncertain whether this factor contributed to the discrepancy in the results.

A final difference is the failure of Cook to remove the entire caudal half tectum. Both here and in Yoon's study 'the entire caudal half of the tectum' (Yoon, 1976) was removed, while Cook's surgical technique generally left intact a prominent 'ventrolateral remnant'. Since a large portion of the tectum curves under ventrolaterally, Cook must have removed approximately one quarter rather than one half of the tectum. Compression in such cases has been analysed previously (Schmidt & Easter, 1978) and the maps were similar to his cases with ventrolateral remnants (e.g., Cook's fig. 8), in that compression was well underway in the dorsotemporal field but not nearer the horizontal meridian. Such an inhomogeneity in compression could result because there is a great distortion where the map curves around the corner of the ablation and into the ventrolateral remnant. It is possible that upon regeneration the fibres entering via the ventrolateral tract would deploy across the full rostrocaudal extent (as they had before) and thus begin to form a normal uncompressed map there in conflict with the compressed map forming medially. Cook mapped none of his fish before the second crush and did not probe around the corner afterward, so it is not possible to ascertain whether this occurs in his fish. In fact, his failure to probe along the edge at the corner may give an erroneous estimate of the amount of temporal field represented since Schmidt & Easter (1978) earlier showed that much of it is represented at or just around the corner in such cases.

In short it is difficult to ascribe the differences, between Cook's results on the one hand and the present results and Yoon's on the other, to any one factor alone. Yet because these results replicate those of Yoon; because in both this study and Yoon's studies the fish were mapped both before and after the second crush; and because unlike Cook's results, the results here were not complicated by incomplete half tectal ablation; I am led to conclude that regeneration following compression generally restores the compressed projection. This is consistent both with the half retinal case where a crush interrupting an expanded projection results in an immediate restoration of the expanded projection and with cases of regeneration following long-term denervation where immediate compressions (Romeskie & Sharma, 1977) and expansions (Schmidt, 1978) also occur. Thus tectal positional markers appear to be a transient trace left behind by a previous projection which can serve to bias the formation of subsequently regenerated projections.

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