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# Temporal Aspects of Contrast Visual Evoked Potentials in the Pigmented Rat: Effect of Dark Rearing

TOMMASO PIZZORUSSO,*†‡ MICHELA FAGIOLINI,*† VITTORIO PORCIATTI,† LAMBERTO MAFFEI*†

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**Cortical visual evoked potentials (VEPs) in response to gratings temporally modulated in counterphase were recorded in normal and dark-reared pigmented rats. Temporal modulation was either sinusoidal (0.25–15 Hz, steady state condition) or abrupt (0.5 Hz, transient condition). In normals, the amplitude spectrum of contrast VEPs has two peaks (at about 0.5 and 4 Hz) and a high temporal frequency cut-off of the order of 11 Hz. The VEP phase lags with temporal frequency, showing two different linear slopes for separate frequency ranges (0.25–1 Hz and 1–7 Hz) centred on the peaks of the curve. The different slopes correspond to apparent latencies of 500 and 136 msec, respectively. Dark rearing reduced the cut-off frequency by about 3 Hz and increased apparent latencies by about 42 msec in the low temporal frequency range and 30 msec in the high temporal frequency range. The latency of the first peak of transient VEPs was increased by about 47 msec. Results indicate that the frequency response of rat contrast VEPs is qualitatively similar to that of other mammals (including human), albeit shifted to a lower range of temporal frequencies. Dark rearing significantly alters the VEP temporal characteristics, suggesting that visual experience is necessary for their correct development. Copyright © 1997 Elsevier Science Ltd**

Plasticity Visual cortex Critical period Visual deprivation

## INTRODUCTION

In the modern approach to the study of the central nervous system (CNS), correlating biochemical and molecular data with functional properties has became a useful, and sometimes necessary, strategy. The availability of genetically manipulated mice, the use of the slice of rat visual cortex as a favourable preparation for cellular electrophysiological studies, and the feasibility of molecular and biochemical analysis, have provided powerful tools for the study of development and plasticity of the visual system in the rodent model. On the other hand, a systematic investigation of the physiological properties of the visual system of rodents is still lacking. Available studies have mainly dealt with spatial aspects of the response of cortical neurons in developing and adult rats (Shaw *et al.*, 1975; Wiesenfeld & Kornel, 1975; Parnavelas *et al.*, 1981; Harnois *et al.*, 1984; Domenici *et al.*, 1991; Fagiolini *et al.*, 1994a). The overall temporal characteristics of rat visual cortex have not been investigated in detail. Yet, temporal aspects of visual evoked potentials (VEPs) have been proven in humans to represent one of the most powerful indexes of function of the visual pathway [see Regan (1989) for review].

Studying VEP dynamics can give hints on frequency resolution, signal transmission through different (sustained and transient) channels and on neuronal integration underlying the cortical response. In addition, VEP latency analysis may provide an index for the evaluation of the state of maturation of the visual pathway. Indeed, VEP latency is probably dependent on a number of factors, including the conduction velocity of afferent fibers, the properties of synaptic transmission throughout the visual pathway, the temporal spread of afferent volleys, and the pattern of connectivity. Most of these factors are known to mature gradually during development (Tennekoon *et al.*, 1977; Shatz, 1990; Carmignoto & Vicini, 1992).

In the present paper we characterize the frequency response of VEPs recorded from the rat visual cortex. To verify whether the temporal aspects of VEP are modified by treatments known to affect the normal maturation of the visual cortex, we have repeated the same temporal analysis in dark-reared rats. Dark rearing is known to interfere with the development of the visual system in many mammals (Movshon & Van Sluyters, 1981; Sherman & Spear, 1982; Fregnac & Imbert, 1984 for reviews) in such a way as many properties of cortical neurons resemble those of young immature animals (Benevento *et al.*, 1992; Fagiolini *et al.*, 1994a). Our results show that dark rearing increases VEP latency and decreases temporal resolution.

*Scuola Normale Superiore, Pisa, Italy.
†Istituto Neurofisiologia CNR, via S.Zeno, 51, 56127 Pisa, Italy.
‡To whom all correspondence should be addressed.

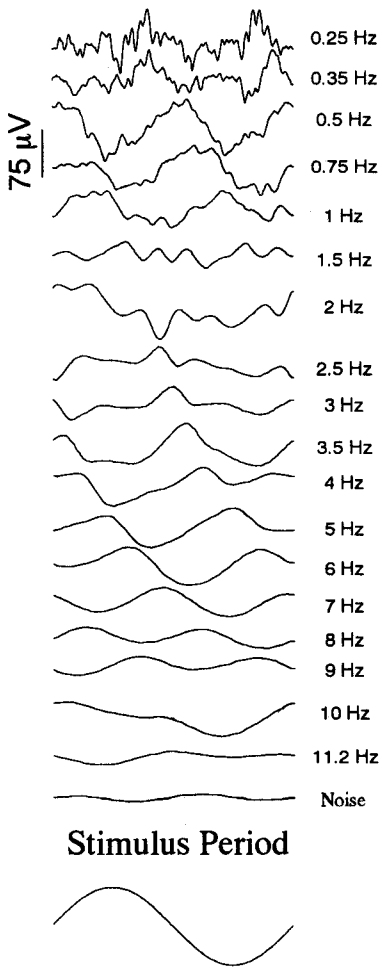


FIGURE 1. Examples of VEP responses to gratings modulated sinusoidally in counterphase at various temporal frequencies. VEPs were recorded by means of a micropipette located 500 μm below the cortical surface of the binocular subfield of rat area 17 (area Oc1b). Responses show a modulation at twice the stimulus period. Note that the response is maximal at 0.5 Hz and at around 5 Hz and tends to vanish at 11.2 Hz.

## METHODS

### *Animal treatment*

VEPs were recorded from two groups of rats on postnatal day 45 (P45):

1. 13 rats reared with a normal 12 hr light–12 hr dark cycle; and
2. 12 rats reared in a light proof room from birth.

All the manipulations of dark-reared animals were performed adopting an infrared visor in the presence of an infrared source.

### *Electrophysiological technique*

The technique for electrophysiological recording has been described in detail elsewhere (Domenici *et al.*, 1991; Fagiolini *et al.*, 1994a). Briefly, animals were anesthetized with an intraperitoneal injection of urethane (Sigma, 20% solution, 6 ml/kg). Body temperature was maintained at 38°C by means of a electric blanket and the electro-cardiogram was continuously monitored. The brain surface overlying the primary visual cortex (area Oc1b, stereotaxic coordinates 4 mm from the central fissure) was exposed through a small hole, and the dura removed. In the rat, Oc1b corresponds to the binocular portion of the primary visual cortex (area 17), mapping the upper nasal visual field (Sefton & Dreher, 1985). A glass electrode (3 μm tip, 3 M NaCl filling) was inserted into the cortex perpendicularly to the stereotaxic plane. At the end of the experiment, electrolytic lesions (20 μA for 10 sec) were made at several cortical depths to mark the electrode track. Animals were then perfused with 4% paraformaldehyde. The whole brain was removed and cryoprotected with 30% sucrose overnight. Sections of the visual cortex (40 μm) were obtained using a freezing microtome, stained with Cresyl Violet (0.1%), dehydrated, covered and examined. Cortical layers were defined according to Kolb and Tees (1990). Due to the curvature of the brain surface, the electrode track resulted somehow angled (about 20 deg) as compared to the cortical layers. This small angle in electrode penetration was adopted in previous studies in order to reduce bias in single unit sampling, and was maintained in the present study to exploit previous data addressing, in detail, the relationship between electrode track and cortical layers by means of electrolytic lesions (Maffei *et al.*, 1992; Berardi *et al.*, 1993; Fagiolini *et al.*, 1994a). Recordings were typically performed with the tip of the recording electrode positioned 500 μm below the cortical surface at which VEPs had their maximal amplitude. This was established in three rats in which VEP recordings were performed every 100 μm until 1000 μm along the cortical depth (see results).

Steady-state VEPs were evoked by an optimal sinusoidal grating (0.1 c/deg, contrast 90%, mean luminance 15 cd/m$^2$, 24 × 26 cm area) reversed in contrast sinusoidally at variable temporal frequencies (0.25–15 Hz). To record transient VEPs, the stimulus was reversed abruptly at 0.5 Hz. The screen was positioned at 27 cm distance from the eye, in such a way as to include the binocular field. The eye contralateral to the recorded visual cortex was kept open and fixed by means of a metal ring positioned at the equatorial portion of the eye bulb (Parnavelas *et al.*, 1981). The cornea was protected from drying with frequent instillation of artificial tears (Lacrinorm, Farmigea, Pisa). The pupil was not dilated.

Electrical signals were amplified (5000-fold), band pass filtered (0.2–200 Hz, −3 dB/oct) and digitized (12 bit resolution). A PC computer averaged at least 300 sweeps for each condition in synchrony with the stimulus contrast reversal rate, and performed a discrete Fourier analysis to estimate the amplitude and phases of the first four harmonics. Presented data refer to the second harmonic component, which yields most of the response energy (see Fig. 1). Signals were also averaged asynchronously at 1.1 times the temporal frequency of the stimulus to give an estimate of background noise.

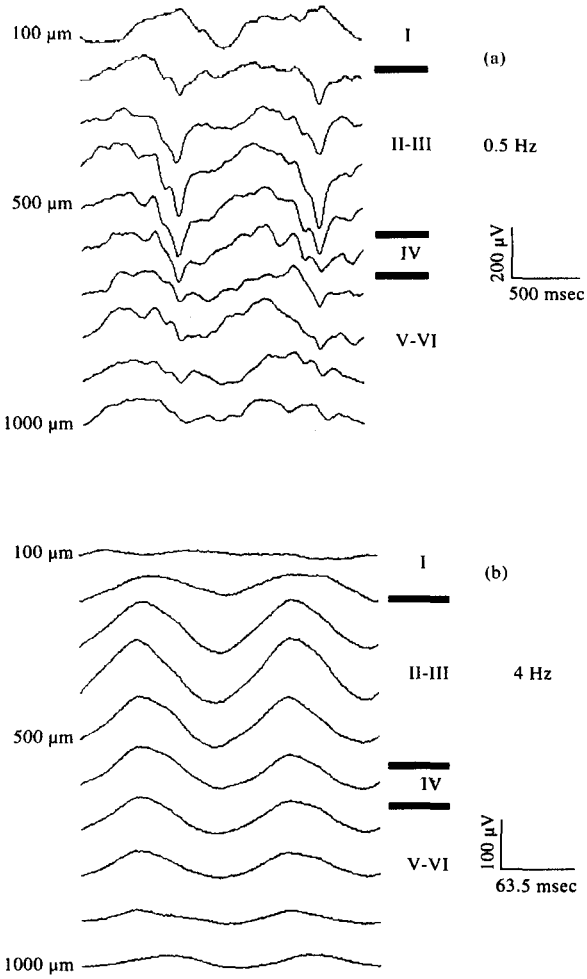


FIGURE 2. VEPs recorded as a function of the depth of the recording electrode below the cortical surface (100 μm steps) in response to gratings alternating at either 0.5 Hz (A) or 4 Hz (B). The delimitation of cortical layers is also indicated.

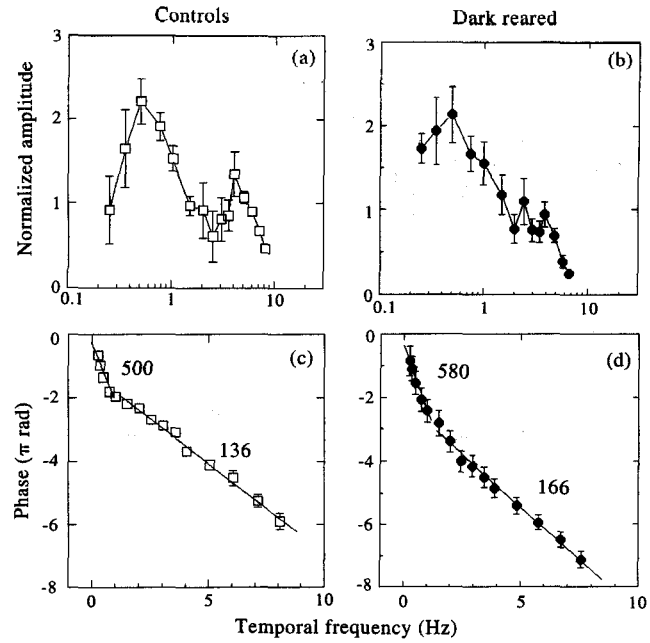


FIGURE 3. Amplitude (a, b) and phase (c, d) of the VEP second harmonic as a function of temporal frequency in normal and dark reared rats. The amplitude characteristic of dark reared rats (B) has a lower temporal resolution as compared to normals (A). The phase characteristics were fit with two different regression lines for the frequency range 0.25–1 Hz and 1–7 Hz. Note that the apparent latencies (indicated by numbers above the regression lines) are longer in dark reared (d) as compared to normals (c).

## RESULTS

### *Steady state VEPs in the rat*

Figure 1 shows examples of steady-state VEPs recorded intracortically (500 μm below the cortical surface) in response to gratings reversing sinusoidally in contrast at different temporal frequencies. Responses above the noise level can be obtained in the frequency range 0.25–10 Hz, and all show a strong modulation at twice the stimulus frequency, in keeping with the typical behaviour of the pattern reversal VEPs (e.g. Strasburger, 1987). Thus, the second harmonic component well represents the main response modulation. It can be seen in Fig. 1 that the largest response amplitudes are obtained in two different frequency ranges, namely around 0.5 and 4–5 Hz. A question posed was whether this complex pattern of response amplitude vs frequency depended on VEP sampling at a particular cortical depth. Indeed, the activity of distinct VEP generators having different temporal characteristics and depth location might sum up at the electrode, thereby creating peaks and troughs in the amplitude vs frequency function. If this were the case, then the presence and the relative amplitude of different peaks should depend on microelectrode position. In three animals, VEPs at 0.5 and 4 Hz have been recorded as a function of cortical depth (100 μm steps). Figure 2 summarizes the VEP depth profile for one of them. Comparable profiles have been obtained in the other animals. The VEP depth profile is virtually identical for both frequencies, indicating little role of cortical depth in shaping the form of the frequency function. The VEP amplitude peaks at about 500 μm, at the level of target cortical layers for thalamic fibers (Kageyama & Robertson, 1993). It is worth noting that contrast VEPs are postsynaptic in nature, since they are entirely abolished after blockade of the postsynaptic activity with muscimol (not shown in figures). The cortical depth (500 μm) at which VEPs display their maximal amplitude has been adopted for all recordings presented in this paper.

### *Effects of dark rearing*

Steady-state VEPs have been systematically recorded in normal rats and in rats reared in complete darkness from birth. Recordings were done at P45, when the anatomical and functional development of the visual pathway is virtually completed in normal animals (Fagiolini *et al.*, 1994a). Figure 3 summarizes the average VEP amplitude and phase as a function of temporal frequency. In normal rats, the amplitude characteristic of the VEP second harmonic [Fig. 3(a)] displays a major peak at 0.5 Hz and a secondary peak at around 4 Hz. Beyond 4 Hz, the VEP amplitude progressively decreases, eventually vanishing for frequencies around

10 Hz. An index of temporal resolution was obtained by extrapolating (linearly) to 0 V the set of data points recorded at the highest resolvable (above the noise level) frequencies. On average, the temporal resolution of normal rats is in the order of 11 Hz (see also Fig. 4). Figure 3(c) shows the phase spectrum associated with the amplitude spectrum of Fig. 3(a). The VEP phase decreases progressively with increasing temporal frequency, showing a discontinuity at around 1 Hz. The phase characteristic could be best fit by two linear regression lines having different slopes for the frequency ranges (0.25–1 Hz and 1–7 Hz), corresponding to the peaks of the amplitude characteristic. The slope of the regression of phase with temporal frequency gives an estimate of response latency (apparent latency) (Regan, 1966; Porciatti *et al.*, 1992) according to the formula:

$$\text{Apparent latency (msec)} = \frac{\text{Phase} \times \text{slope } (\pi \text{ rad/Hz}) \times 1000}{4 \text{ (period of the second harmonic : } 2 \times 2\pi \text{ rad)}}.$$

The apparent latencies for the frequency ranges 0.25–1 Hz and 1–7 Hz corresponded to 500 and 136 msec, respectively.

In DR rats the VEP frequency response is qualitatively similar to that of controls. That is, the form of the amplitude characteristics [Fig. 3(b)] shows a major peak at 0.5 Hz and a shoulder at 3–4 Hz. The phase lags with temporal frequency [Fig. 3(d)] with two different slopes for the frequency ranges 0.25–1 Hz and 1–7 Hz. As compared to controls, however, the amplitude curve appears to have a lower temporal resolution. In addition, the slopes of the phase plot are steeper, corresponding to apparent latencies of 580 msec (0.25–1 Hz) and 166 msec (1–7 Hz). Values of temporal resolution and apparent latencies for the two different slopes of the phase plots have been measured in individual control and dark-reared animals, and the average results plotted in Fig. 4 as histograms. As compared to normal rats, the temporal resolution [Fig. 4(a)] is lower in dark-reared animals (11.7 Hz vs 8.3 Hz; *t*-test $P < 0.01$). The VEP apparent latency is significantly (*t*-test, $P < 0.05$) longer for both the low [Fig. 4(b)] and high [Fig. 4(c)] frequency range (542 vs 441 msec, and 160 vs 136 msec, respectively). These values of apparent latency are in the range of those presented in Fig. 3, which were obtained by fitting data averaged over all animals.

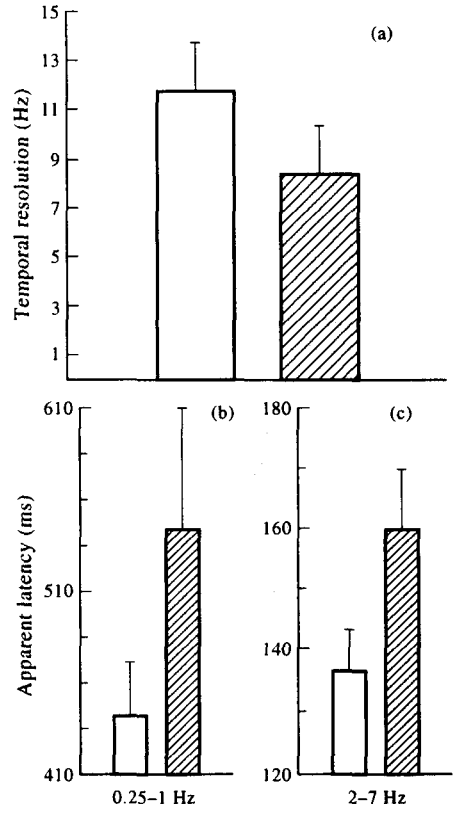


FIGURE 4. Effects of dark rearing on temporal aspects of VEPs. (a) Mean temporal resolution ±SD of normal (white bars) and dark reared (hatched bars) rats. Dark rearing significantly reduces VEP temporal resolution (*t*-test; $P < 0.01$). (b and c) Mean apparent latencies ±SD of individual normal (white bars) and dark reared (hatched bars) rats. Apparent latencies were derived by double linear fitting of the phase spectra in two ranges of temporal frequency (0.25–1 Hz and 1–7 Hz).

*Transient VEPs*

As an independent measure of latency, transient VEPs were also recorded in response to abrupt reversal (0.5 Hz) of the same stimulus grating. Figure 5 displays the grand mean responses (normalized to an average amplitude of 1) across control and dark-reared rats. The waveform of individual responses did not differ substantially from the grand mean (more detailed description of rat transient VEPs can be found elsewhere; Fagiolini *et al.*, in preparation). In both normal and DR rats, the waveform of the intracortical transient VEPs consists mainly of an early negative wave, peaking between 100 and 200 msec and a late positive wave peaking between 600 and 800 msec. It can be noted, however, that transient VEPs of DR appear somewhat delayed as compared to those of normal controls. In particular, in DR the peak latency of the early negative wave is longer by about 47 msec (168 msec vs 121 msec). These values of peak latencies are in the range of apparent latencies evaluated from the slope of the phase characteristic of steady-state VEPs in the range 1–7 Hz. It is worth noting that the onset latency of the negative wave of transient VEPs is comparable in normal and dark-reared rats. This suggests a comparable pre-cortical transmission time of visual information in the two groups of animals.

## DISCUSSION

A number of recent molecular and biochemical studies have adopted rodents as experimental animals for studies on the development and plasticity of the visual system. In this context, the correlation between molecular and functional aspects requires a better knowledge of the performance of the visual system of rodents. In this paper, we characterize the temporal aspects of contrast VEPs in normal rats. We also show that dark rearing reduces temporal resolution and increases VEP latency.

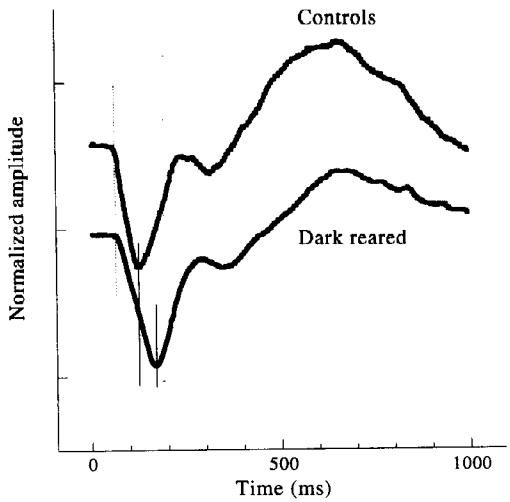


FIGURE 5. Effects of dark rearing on transient VEPs (grand mean responses). Note that the VEP onset latency is simultaneous in dark reared and controls (dotted line). By contrast, the peak latency of the negative peak (solid line) is increased in dark reared by 47 msec.

*The temporal response function of the normal rat*

The amplitude spectrum of contrast VEPs has a complex form, with a main peak at around 0.5 Hz, a local minimum at 1 Hz, a secondary peak at around 4–5 Hz, a local minimum and a high temporal frequency cut-off at *ca* 11 Hz. The phase spectrum lags with temporal frequency, showing two different slopes for separate frequency ranges (0.25–1 Hz and 1–7 Hz) centred on the peaks of the curve. The different slopes correspond to apparent latencies of 500 and 136 msec, respectively. These transfer characteristics suggest that the VEP response may reflect the contribution of two different generators: one generator, slower, responding better to low frequencies and the other, faster, responding better to higher frequencies.

It is interesting that the amplitude and phase spectra of the temporal function of contrast VEPs in the rat are qualitatively similar to those reported for humans (e.g. Simon, 1992; Porciatti *et al.*, 1992). In humans, the frequency response has a main peak at around 8 Hz, and a secondary peak at around 16 Hz. The associated phase spectrum changes in slope between 8 and 16 Hz, indicating different latencies for the lower and higher temporal frequency ranges. The complex form of the temporal curve has been interpreted as reflecting the contribution of distinct temporal channels (Simon, 1992; Porciatti *et al.*, 1992). It is conceivable that the same hypothesis applies to the rat. Indeed, cell populations with different temporal properties have been reported for the rat visual pathway (Reese, 1988 for review). For instance, many cells of the LGN show properties similar to the Y and W cells of the cat (Fukuda *et al.*, 1979; Lennie & Perry, 1981; Sefton & Dreher, 1985). Overall, the main features of the temporal frequency response appear to have many similarities in rats and in the human, the main difference being a shift on the temporal axis. The lower temporal resolution of the rat VEPs, as compared to human, may well be explained on the basis of the different rod–cone contribution to the response (Cicerone, 1976).

A qualitative analogy between the visual system of the rat and that of other mammals has been previously suggested by studies evaluating either spatial contrast properties (VEP contrast sensitivity and visual acuity) or the physiological characteristics of visual cortical neurons (Fagiolini *et al.*, 1994a). For example, neurons of the rat primary visual cortex show well defined receptive fields, selectivity for the stimulus orientation and a high degree of binocularity (80% of binocular cells). These properties develop gradually and their correct development can be affected by interfering with vision (monocular deprivation or dark rearing) during the critical period (Fagiolini *et al.*, 1994a). Similar results have been obtained in studies on the physiological development of single units of the mouse visual cortex (Dräger, 1978; Gordon *et al.*, 1994).

*Effects of dark rearing*

Rearing a mammal in complete darkness from birth induces detrimental effects on the development of the visual system at molecular, anatomical, physiological and behavioural levels (Movshon & Van Sluyters, 1981; Sherman & Spear, 1982; Fregnac & Imbert, 1984; Aoki, 1985; Aoki & Siekevitz, 1985; Kolb & Tees, 1990; Worley *et al.*, 1991; Rosen *et al.*, 1992; Rauschecker, 1995). Many of these effects are reversible unless visual deprivation is prolonged for long periods (Mower *et al.*, 1985; Timney, 1987 for a review). For instance, dark-reared cats have a reduced behavioural visual acuity which can eventually recover to its normal value after reintroduction of the animal in a normal environment (Timney *et al.*, 1978). Behavioural deficits are paralleled by abnormalities of the functional properties of single cortical neurons such as sluggishness of the response, habituation of the cellular response to repeated visual stimulation, poor orientation selectivity (Fregnac & Imbert, 1978; Leventhal & Hirsch, 1980; Sherman & Spear, 1982; Benevento *et al.*, 1992; Fagiolini *et al.*, 1994a; Zhou *et al.*, 1995). In addition, dark-reared rats have been reported to have a reduced VEP acuity (Fagiolini *et al.*, 1994a). Our results show that temporal aspects of VEPs are also affected by dark rearing. The amplitude characteristic of dark-reared rats, as compared to that of normals, displays a lower temporal resolution. In addition, the associated phase spectrum indicates a delay in apparent latency. A delay is also present in the peak latency of transient VEPs.

Several factors could contribute to the effect of dark rearing on temporal aspects of VEPs. These include:

1. precortical neural factors;
2. cortical neural factors;
3. reduced myelination.

*Precortical neural factors.* Visual deprivation is virtually ineffective at retinal level (Sherman & Stone, 1973; Leventhal & Hirsch, 1983; Lau *et al.*, 1990). Therefore retinal factors should not contribute signifi-

cantly to the changes we have found using VEPs. Indeed, in preliminary experiments in rats we have not observed any effect of DR on the spatial–temporal properties of electroretinogram in response to patterned stimuli. Geniculate neurons are known to be relatively insensitive to visual deprivation (Sherman & Spear, 1982; Zhou *et al.*, 1995). It has been shown, however, that cells with phasic responses (Y cells) are less frequent than normal in DR cats (Kalil & Worden, 1978; Kratz *et al.*, 1979). If this finding holds true in DR rats, then a decreased number of phasic cells could account, at least partially, for the reduced temporal resolution we observed.

*Cortical neural factors.* The visual cortex is the classical site of action of interferences with normal vision during development. A number of studies have reported temporal deficits in the response of cortical neurons of DR cats and rats. In particular, a reduction of the cut-off velocity, a longer response latency and habituation to repeated stimulation have been observed (Leventhal & Hirsch, 1980; Benevento *et al.*, 1992; Fagiolini *et al.*, 1994a). These alterations could be reflected in the lower temporal resolution and the increased latency of VEPs we found in DR rats. Several anatomical and/or molecular components could contribute to VEP changes in DR rats, including altered connectivity (Borges & Berry, 1978; Stryker & Harris, 1986; Frost & Moy, 1989), and abnormal synaptic morphology and functioning (Gabbott & Stewart, 1987; Tsumoto & Freeman, 1987; Dudek & Bear, 1989; Bakkum *et al.*, 1991; Carmignoto & Vicini, 1992; Fox & Daw, 1993). All these components may result in a longer integration time, thus supporting a cortical site of action of dark rearing.

*Reduced myelination.* The increased VEP peak latency of DR could originate, at least partially, from a reduced myelination of the visual pathway. While this cannot be excluded, it appears unlikely since our data show that the first sign of postsynaptic cortical activity (first noticeable deflection of transient VEPs) occurs simultaneously in normal and dark reared. The longer time-to-peak of the VEPs in dark-reared rats appears to indicate a longer response duration, rather than a longer transmission delay along the subcortical pathway. A small reduction in the number of oligodendrocytes in layers V and VI of the visual cortex has also been reported in dark-reared rats (Gabbott *et al.*, 1986). A decreased cortical myelination could therefore play some role in the effects of dark rearing.

### *Mechanisms underlying the effects of dark rearing*

Our observations in dark-reared rats consolidate the work of other laboratories showing that visual experience is necessary for a correct development of the visual cortex. The molecular mechanism(s) underlying the effects of a reduced visual experience during development are still substantially unknown. The neural correlate of visual experience is electrical activity. It has been recently shown that the cortical levels of neurotrophic factors depend upon visually driven electrical activity (Castrén *et al.*, 1992; Bozzi *et al.*, 1995). This observation raises the attractive hypothesis that the effects of dark rearing are secondary to the reduction of neurotrophic factors which sustain the development of the visual pathway (Maffei *et al.*, 1992; Cabelli *et al.*, 1995; Riddle *et al.*, 1995). According to this rationale, an exogenous supply of neurotrophic factors in dark-reared animals should limit the adverse effects of visual deprivation. Preliminary experiments in rats have shown that transplantation into the brain of cells producing neurotrophic factors can largely prevent the functional deficits induced by dark rearing (Pizzorusso *et al.*, 1995; Fagiolini *et al.*, 1994b).

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