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RESEARCH NOTE

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Differences in the temporal dynamics of the visual ON and OFF pathways

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Abstract The temporal structure of spike trains recorded from optic fibers and single units of the lateral geniculate nucleus (LGN) and primary visual cortex of the cat was studied with a novel method of inter-spike interval analysis. ON type relay cells of the LGN exhibited a multimodal interval distribution preferring a distinct interval (fundamental interval) and its multiples during the sustained light response, whereas most OFF cells showed a broad, unimodal distribution. The general pattern of the interval distribution was relatively independent of stimulus size and contrast and the degree of light adaptation. Simultaneously recorded S-potentials originating from the retinal input generally produced only a single peak at the fundamental interval length. Therefore, the multimodal interval distribution of LGN cells seems to be a result of intra-geniculate inhibition. Cortical cells also showed a weak tendency to fire with spike intervals similar to LGN cells. Therefore, the regular firing pattern observed at peripheral stages of the visual pathway can persist at higher levels and might promote the occurrence of oscillatory activity.

Key words Visual channels · Lateral geniculate nucleus · Visual cortex · Cat

Introduction

Analysis of images in the visual system is initiated by the separate treatment of light and dark features in the ON and OFF pathways (Schiller 1992). From a functional viewpoint, these pathways represent antagonistic tools to implement linearity in a pulse-coded information processing system which lacks negative impulse rates. An antagonism between the visual subsystems in the sense of a sign inversion is mainly supported by the *spatial* response profile of cells in the retina and the first visual relay station, the lateral geniculate nucleus (LGN) (Kuffler 1953; Hubel and Wiesel 1961; Rodieck and Stone 1965). The question arises, however, of whether the *temporal* pattern of the cells' spike activity during a response may be more than a mere antagonism. Most averaging methods commonly used for the analysis of neuronal spike activity offer only a limited resolution for the temporal structure of the spike trains. The applicability of single spike analysis, on the other hand, is restricted because of response variability and the existing noise. Especially when the firing rate changes in relation to the stimulus a method is needed which limits averaging to short time periods. Therefore, we have developed a combined peristimulus time inter-spike interval histogram (PST-INTH) which displays the varying interval distributions for small time windows during the cell's response. Applying this method, we found that during the tonic light response most geniculate ON cells exhibit, on average, an interval pattern different from that of OFF cells.

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Materials and methods

Results were obtained from 15 anesthetized and paralyzed (N_2O/O_2 70:30, halothane 0.2–0.4 %vol, alcuronium chloride 0.15 mg/kg/h) cats. During surgery, anesthesia was deepened with ketamine hydrochloride (20–25 mg/kg i.m.) and xylazine (1 mg/kg, i.m.). A sufficient depth of anesthesia was ensured by continuously monitoring the EEG and the intra-arterial blood pressure. A more detailed description of the experimental procedures is given in Funke et al. (1993). A total of 42 cells in area 17 and 161 cells in the LGN were recorded extracellularly during visual stimulation. The geniculate cell classes X and Y were predominantly determined by the spatial characteristics of their receptive fields (Derrington and Fuchs 1979). The spatial resolution of receptive fields was tested with flashing spots of different size and moving gratings of varying spatial frequency. The spatiotemporal integration characteristic of the receptive field was further estimated by the cell's response to a large, fast-moving stimulus of a polarity adequate to excite the receptive field surround. In five experiments we additionally used the axonal delay of responses to bipolar electrical stimulation of the optic chiasm to classify cells (Stone and Hoffmann 1971). The result of electrical stimulation was found to closely match that of receptive field tests (see also Eysel et al. 1979). Since the test of spatial summation (Enroth-Cugell and

Robson 1966; Hochstein and Shapley 1975) was used only occasionally, cells are referred to as X- or Y-like. However, a clear distinction between X and Y cells is of little importance since X and Y cells of the ON type as well as X and Y cells of the OFF type exhibited very similar interval distributions.

Flashing spots of different size (0.2–5.0 deg) or slowly (0.1–5.0°/s) moving light bars were used as visual stimuli. Visual stimulation of ON- and OFF-center cells was performed in two different ways: Light spots of varying illumination (max. 10 cd/m^2) were either switched on for stimulation of the ON cells, or switched off to background (0.1 cd/m^2) for the OFF cells, or spots were switched brighter (max. 20.0 cd/m^2) or darker (min. 0.1 cd/m^2) on an intermediate background of 2.0 cd/m^2 to stimulate ON or OFF cells, respectively. The adaptational status for both cell types was different in the first case, but equal in the second. Contrast between spot and background was varied between 0.05 and 0.9 ([Lmax–Lmin]/[Lmax+Lmin]). For most cells, at least contrasts of 0.2–0.9 were compared. Retinal illumination was in a range of 0.89–3.19 log 'cat trolands', within the range also used by Troy and Enroth-Cugell (1993) for the determination of response versus contrast curves. In all but one control experiment, background room illumination was 0.1 cd/m^2. In that one control experiment, background room and screen illumination was varied widely (between 0.01 and 10.0 cd/m^2, in increments of 1 log unit) and cells were allowed to adapt for up to 30 min after each step to test the response variability also as a function of the level of adaptation. Visual stimuli were generated by a computer-controlled, image generator (Picasso; Innisfree, Cambridge, Mass.) and presented on an oscilloscope screen (Tektronics 608) 0.28 m in front of the cat's eyes. The frame rate of the system was 200 Hz. Stimulus cycles were composed of 400 ms stimulus off, 800 ms on and finally 800 ms off. Each record contained between 100 and 500 sweeps of stimulus presentations. Recordings were preferentially made during periods when the EEG had a weak power in the delta range, because increased delta activity strongly reduces the tonic light response (Funke and Eysel 1992).

To visualize the temporal structure of spike trains, a sliding window inter-spike interval analysis was performed in small, 90% overlapping time frames (see Fig. 1A, diagram, not to scale). All data were analyzed with 1 ms resolution. For comparison, a regular peristimulus time histogram (PSTH) is plotted downward on the time axis and a summed inter-spike interval diagram (Summed INTH) on top. A time window of 100 ms duration is shifted downward along the time axis in 10-ms steps. For each step the inter-spike interval distribution is computed and plotted to the right as a color pixel line (Time Window INTH) centered with respect to the corresponding time window (see also Fig. 1B). A temperature-like color scale is used to encode the number of intervals per bin. The length of the time-window and degree of overlap between time-windows was found to have no effect on the pattern of the interval distribution. The window length was appropriate to count intervals that frequently occurred between 2 and 50 ms, the overlap results in a smoothing effect (sliding local averaging).

Results

The joint-peri-stimulus time interval plot shows that the apparently constant firing of a cell during its sustained visually driven response actually can consist of a temporally structured activity pattern (Fig. 1B). Mainly the ON cells and only few OFF cells respond with a multimodal interval pattern. A comparison of two typical cells is given in Fig. 1B, F which shows the dynamic changes in the interval distribution during a light response for an X-like ON cell (B) and an X-like OFF cell (F) recorded from the cat LGN and stimulated with a flashing dot. At the moment of stimulus onset, both cells respond transiently with short intervals in the 2- to 4-ms range. After having settled to sustained firing, the cells display a clearly different behavior. The ON cell produces a pattern of rather sharp interval bands centered around multiples of 7 ms, which is the shortest average interval size during the sustained response and will be denoted the *fundamental interval*. This clear, band-shaped pattern can even be seen in the regular interval histogram (Fig. 1B, top; but cf.

Fig. 1 Data analysis schematic (**A**), differences in the temporal structure of an ON cell (**B–E**) and an OFF cell (**F, G**) and model of the connectivity (**H**). **A** Schematic drawing of the organization of the time window PST-INTH. The time axis runs from top to bottom. A conventional PSTH is plotted downwards, the time axis to the left. The number of intervals in a 100-ms time window is plotted as a horizontal color pixel line at the position of the time window on the time axis. Then, a new interval distribution is obtained for the same time window, but shifted 10 ms along the time axis. The total number of intervals is summed in the INTH on top. Temporal resolution 1 ms for both axes. **B, F** Time window INTH for an X-like ON cell (**B**) and an X-like OFF cell (**F**) stimulated with a 0.5° spot switched dark on the intermediate background level (see Materials and methods) for the OFF cell and with bright for the ON cell (switched contrast change about 0.8 for the ON and 0.9 for the OFF cell). Very short intervals (2–4 ms) occur only during the transient response. The ON cell (**B**) produces sharp interval bands centered around 7 and 14 ms, whereas the interval distribution is broad and diffuse for the OFF cell (**F**). **D** Time window INTH for the same ON cell as in (**B**), but spot size increased to 2.0°. The first two interval bands remain centered around 7 and 14 ms, but a third interval band appears at ≈21 ms. **C, E, G** Autocorrelograms for responses in (**B, D, F**). Note that (**C**) and (**E**) do not show a clear difference. **H** Simple qualitative model for the generation of interval bands also tested quantitatively in computer simulations (not shown). Retinal receptive fields are drawn as disks with white-gray center-surround structure. Stimuli are *black disks*. Spikes are indicated as *black bars*. The retinal response does not change strongly with increasing stimulus size (*bottom row, left vs middle*). The inhibitory interneuron (*center row*) fires with a low frequency during stimulation with a small spot (*left*) but faster in response to a larger stimulus (*middle*). Without inhibition a 'one-to-one' transmission between retina and LGN is assumed (*top row*), with inhibition individual spikes are blanked out (*dashed lines*). Interval bands of unit size ´1, 2 and 3´ are obtained this way

Fig. 2A–I Interval band structure and cross-correlograms in simultaneous recordings of retina and LGN (**A–F**) as well as LGN and area 17, layer IV (**G–I**). A total of ten retina-LGN and four LGN-cortex cell pairs showed correlated firing. Cross-correlations (**C, F, I**) are shown after subtraction of the shift predictor. **A, B** Time window INTH for a retinal prepotential recorded together with an LGN X-like ON cell (stimulus: spot, 1.0°, 10 cd/m^2, on background 0.1 cd/m^2). Multiple interval bands occur only at the level of the LGN. **C** The cross-correlation between the activities in (**A**) and (**B**) shows the direct link between prepotential and LGN cell spike (Mastronarde 1992) and an additional long-lasting oscillatory pattern. **D, E** Time window INTH for a retinal prepotential recorded together with the LGN X-like OFF cell activity (stimulus: spot 0.5°, 10 cd/m^2, switched off to background 0.1 cd/m^2). No interval bands for occur. **F** The cross-correlation is flat except the direct link at ≈1 ms. **G, H** Time window INTH for an LGN Y-like ON cell and a cortical complex cell stimulated with a slowly moving light bar (size 0.5°×10.0°, speed 3.0°/s, orientation 85°, 10 cd/m^2, background 0.1 cd/m^2). Multiple interval bands occur in LGN and cortex. **I** A weak cross-correlation is found between **G** and **H** at 4–9 ms delay (Tsumoto et al. 1978)

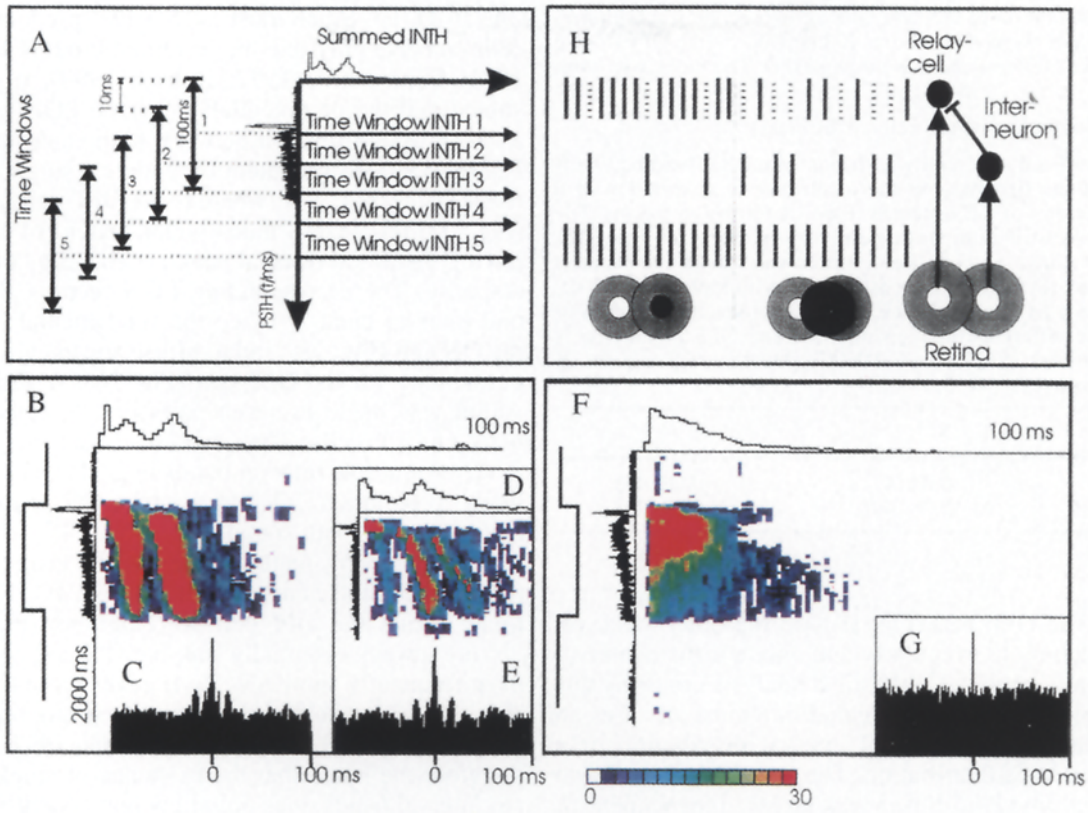
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Fig. 1

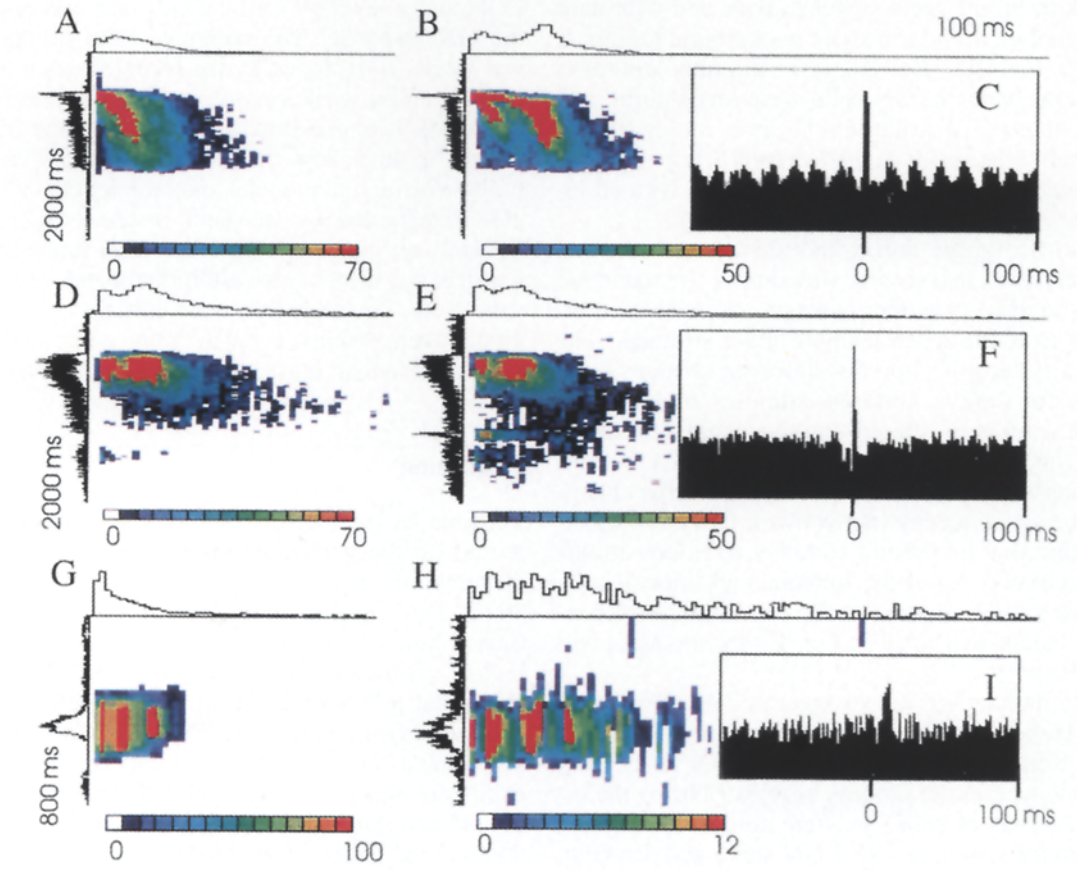
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Fig. 2

Table 1 Distribution of ON and OFF cells producing sharp interval bands. Cells were classified as X-like ON, X-like OFF, Y-like ON, or Y-like OFF (*numbers in parentheses*). The index was computed as:

index=(cells with bands)/(all cells in the class)

A cell was defined as a 'cell with bands' if the half-width at half-height ∅ of the first peak in the local interval distribution of a characteristic part of the sustained response fell below 3.5 ms. The local interval distribution was determined by averaging five adjacent time windows, placing the first time window at 400 ms after stimulus onset (800 ms on time scale). Since multiple stimulus situations were used, the smallest ∅ determined the classification of the cell. The difference between the ON and OFF population is highly significant (χ^2=29.2, P<0.00001) but that between the X and Y cells is not (χ^2=0.55, P<0.54)

	X	Y
ON	0.82 (47)	0.59 (46)
OFF	0.28 (40)	0.29 (28)

Fig. 1D). The OFF cell (Fig. 1F), on the other hand, responds much more irregularly and only a diffuse interval distribution is obtained. Statistical analysis confirms this result (Table 1). OFF cells yielded in almost all cases an either wide and unstructured interval distribution or a single broad band distribution. The general spike interval pattern (multimodal/diffuse) was largely independent of the level of adaptation and the contrast and size of the stimulus. OFF cells exhibited a diffuse interval distribution, both with bright spots switched dark and with dark spots presented on an intermediate background (compare Fig. 1F and Fig. 2D, E). At low stimulus contrasts (<0.2), interval bands of ON cells were less sharper and the overall interval distribution became more diffuse. This is probably the result of the lowered firing rate (longer fundamental interval) which is associated with an increased jitter in interval length.

The mean firing rate during the tonic response of an LGN cell decreases in a similar way during the reduction of stimulus contrast or while increasing the surround inhibition, for example when using a larger stimulus. The band-shaped pattern of intervals, however, changes quite distinctively for the two different stimulus situations. A reduction in contrast or the progressive adaptation to the stimulus during the 800 ms of presentation shifts the fundamental interval to the right, probably due to the changing retinal firing frequency (not shown). Quite unexpectedly, we found that increasing stimulus size does not affect (or affects very little) the fundamental interval size, but results in a *redistribution* of the activity into the longer interval bands, as shown in Fig. 1D for the same cell as in Fig. 1B.

Inhibitory interactions are stronger in the LGN than in the retina (Hubel and Wiesel 1961; Levick et al. 1972; Sillito and Kemp 1983), so that intra-LGN processing should be involved in the process of redistributing the intervals. In a subset of cells, we were able to record retinal prepotentials together with LGN spike activity (Fig. 2A, B, D, E). Since most LGN cells (predominantly X-cells) receive only one major retinal input (Cleland et al. 1971; Mastronarde 1992; Robson 1993), it can be assumed that the prepotentials drive the LGN cell as soon as the cross-correlation between both is strong (Fig. 2C, F). The ON-cell prepotential renders a single narrow interval band (Fig. 2A), whereas the OFF-cell prepotential (Fig. 2D) produces a much wider 'patch' of activity following the initial interval peak generated by the transient response. The corresponding LGN records show a second interval band at twice the fundamental interval for the ON cell (Fig. 2B) and a diffuse and even more spread out activity for the OFF cell (Fig. 2E). A similar observation was made in seven pairs of ON cells and three pairs of OFF cells. Thus, we concluded that the occurrence of multiple interval bands in LGN ON cells is very likely to be due to inhibitory intra-LGN processing of a regular retinal input signal.

An interesting feature arises in the cross-correlation (Fig. 2C, F) and auto-correlation (Fig. 1C, E, G) functions: While the OFF-cell correlograms (Fig. 1G, Fig. 2F) are always essentially flat, the ON-cell correlograms most frequently show few (1–4) peaks close to the origin (Fig. 1C, E) but sometimes exhibit a strong repetitive oscillation (Fig. 2C) (Ghose and Freeman 1992). It should, therefore, be noted that the existence of single or multiple interval bands does not allow any conclusion about a long-lasting oscillation and vice versa.

Fig. 2G, H shows simultaneous recordings from an LGN and a layer IV cortical cell that was dominated by the ON response. The receptive field of the LGN cell was totally overlapped by the receptive field of the cortical cell and a weak cross-correlation between them was found (I). Using a slowly moving bar, the band-shaped pattern is much less pronounced, but still visible in the LGN with a fundamental interval length of 6 ms (Fig. 2G), intermixed by transient responses (2–3 ms). The cortical cell also responded with this fundamental interval size, but shows some additional bands at longer intervals. Note, however, that most cortical cells, even in the input layer, display a much more complicated interval band pattern than those shown in Fig. 2G, H.

Discussion

Multimodal interval distributions have been already reported for the geniculate maintained activity at a steady illumination level (Bishop et al. 1964; Eysel and Gaedt 1971). During stimulation, however, an analysis of small time windows is needed to make the local interval distribution visible. Clearly, the joint PST-INTH diagrams show that a "constant" firing rate actually consists of a structured firing pattern in ON cells. Most OFF cells did not show a multimodal spike interval distribution. They exhibited either a Poisson-like distribution or a single broad band during almost all stimulus situations. Indeed, this interval pattern seems to be independent of the stim-

ulus used. For a single cell, the general pattern of the interval distribution did not change with changes in contrast or in the level of light adaptation or with reversal of the stimulus situation (a light spot switched off instead of a dark spot 'switched on').

A simple model for the generation of multimodal interval distributions assumes, in the optimal case, a one-to-one transmission from the retina to the LGN (Mastronarde 1992) (Fig. 1H) together with an additional inhibitory input located in the surround of the target cell's receptive field (Bishop et al. 1964). With increasing stimulus size two effects should occur: The inhibitory interaction in the LGN efficiently deletes individual retinal EPSPs. At the same time, the retinal firing frequency decreases, but this effect is less pronounced because of the weaker surround inhibition in the retina (Hubel and Wiesel 1961; Sillito and Kemp 1983). For the OFF cells, the same connectivity pattern can still be used, but the retinal activity would have to be more diffuse, as has been shown previously (Troy and Robson 1992; Levine 1991).

The differences in the temporal structure of ON and OFF cells are more pronounced at the geniculate level than in the retina because of the higher capacity of ON cells to exhibit a multimodal interval distribution. Since cortical cells in part reflect the LGN interval pattern, it is possible that these differences persist in higher brain regions and are perhaps finally expressed at a behavioral level. Differences have, indeed, been observed between the ON and OFF subsystems in psychophysical experiments (Weale 1975; Gelb and Wilson 1983; Wehrhahn and Rapf 1992).

As a first approximation, the throughput of any neuronal processing stage is reflected in the mean firing rate. Its regulation is usually assumed to be a rather continuous and gradual process. In the LGN, the mean firing rate passed on to the visual cortex can still be changed gradually by redistributing a few intervals between the bands. However, the interval pattern further supports the view that the LGN truly functions like a gate. Since the first band of the multimodal interval distribution predominantly observed in ON cells mirrors the firing frequency of the retinal input, it can be concluded that there exists little spatiotemporal summation of retinal EPSPs at the level of a geniculate relay cell during the tonic light response. A shift in the membrane potential due to modulatory influences can, in a gate-like manner, switch the tonic light response on or off when the single retinal EPSPs reach the firing threshold or not, respectively. Evidence for such a mechanism comes from the rather strong, EEG-dependent changes in the LGN light response (Livingstone and Hubel 1981; Funke and Eysel 1992).

At the same time, a structured interval pattern allows for a much easier synchronization between cortical cells because the fundamental interval is very similar for their afferents, which could facilitate a phase-locking process. This mechanism should be more efficiently induced by bright stimuli from the ON subsystem as opposed to a dark OFF type stimulation.

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