correct, and between a vertical cue and green being correct. This induced our subjects to a greater flatness of slope than those without prior training, a distinct trend towards the base-rate error (see Fig. 4). The average difference between matching 'green' and matching 'blue' was 20% for subjects for no prior training, but only 6% for those with prior training.

Base-rate neglect has previously been obtained[5–7] in experimental settings. However, this has generally involved cues and choices with some prior relationship, such as symptom and disease, but not in as dependable a relationship as identity. By using elements with either no prior relation or a lock step relation of identity, we have isolated the effects of what is previously known (Experiments 2 and 3) from that which is learned during an experimental session (Experiments 1 and 3). These experiments demonstrate a base-rate error that depends on learned probabilistic relationships: pre-existing associations between cue and outcome can prevent learning from experience. □

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Orientation selectivity of thalamic input to simple cells of cat visual cortex

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More than 30 years after Hubel and Wiesel[1] first described orientation selectivity in the mammalian visual cortex, the mechanism that gives rise to this property is still controversial. Hubel and Wiesel[1] proposed a simple model for the origin of orientation tuning, in which the circularly symmetrical receptive fields of neurons in the lateral geniculate nucleus that excite a cortical simple cell are arranged in rows. Since this model was proposed, several experiments[2–6] and neuronal simulations[7,8] have suggested that the connectivity between the lateral geniculate nucleus and the cortex is not well organized in an orientation-specific fashion, and that orientation tuning arises instead from extensive interactions within the cortex. To test these models we have recorded visually evoked synaptic potentials in simple cells while cooling the cortex[9], which largely inactivates the cortical network, but leaves geniculate synaptic input functional. We report that the orientation tuning of these potentials is almost unaffected by cooling the cortex, in agreement with Hubel and Wiesel's original proposal[1].

Whole-cell patch recordings were obtained from 10 simple cells in layer 4 of the cat primary visual cortex. Orientation selectivity was measured from the responses to drifting sinusoidal luminance gratings, which evoked approximately sinusoidal modulations of the membrane potential with peak-to-peak amplitudes of up to 25 mV. Once the normal tuning properties of each cell were characterized, the cortex was cooled.

During cooling, seven different aspects of the responses of layer 4 cells to electrical and visual stimulation changed. The temperature at which these changes occurred (4–14 °C) varied from cell to cell, presumably depending on the depth of recording. 1) Visually and electrically evoked action potentials were gradually reduced in number until they disappeared entirely. Other neurons within layer 4 and in layers closer to the cooling plate were also likely to have been silenced. 2) Disynaptic inhibitory postsynaptic potentials (i.p.s.ps) evoked by electrical stimulation of the lateral geniculate nucleus (LGN) disappeared (Fig. 1*a*). Before cooling, the i.p.s.p. peak amplitude averaged 6 mV; during cooling the average amplitude was reduced by 95% to 0.28 mV. In six cases, cooling completely suppressed the i.p.s.p. and the membrane potential never dipped below rest. It appears, then, that during cooling, most inhibitory interneurons no longer responded to electrical stimulation. 3) Most excitatory interneurons were also silenced. During cooling, all visually and electrically evoked synaptic potentials, including excitatory postsynaptic potentials (e.p.s.ps), disappeared in four of the five complex cells recorded, all of which lacked monosynaptic excitation from the LGN. 4) The electrically evoked monosynaptic e.p.s.p. gradually increased in latency by a factor of 2–3 (Fig. 1*b*), presumably as a result of slowed synaptic release in geniculate afferent terminals. The latency of the augmenting response, a monosynaptic potential mediated by antidromic activation of layer-6 corticogeniculate neurons, increased along with the latency of the geniculocortical input (Fig. 2). 5) The electrically evoked monosynaptic e.p.s.ps were reduced in amplitude (Fig. 1*a*); the average reduction in 10 cells was to 40% of normal. 6) Visually evoked responses were also reduced in amplitude (Fig. 1*c*, *d*), but this reduction was proportionately greater than the reduction in the electrically evoked e.p.s.p. In addition, the noise of the traces was sharply reduced so that the signal-to-noise ratio was hardly changed (compare Fig. 1*c*, *d*, and note change in vertical scale), suggesting that a large component of the noise was synaptic in origin. 7) The resting input resistance of the recorded cell approximately doubled, presumably because of the reduction in spontaneous synaptic activity. Taken together, these changes indicate that cortical activity was significantly depressed by cooling, but that the geniculate input remained functional.

Although cortical activity in layer 4 and above was strongly suppressed by cooling, cells in layer 6, being farther from the cooling plate, may have been warm enough to remain active. These cells provide strong excitatory input to layer 4 (refs 10, 11), and their synapses, although weakened, still functioned, as indicated by the response to electrical stimulation of the LGN (Fig. 2*b*). To determine whether the layer-6 cells remained visually responsive during cooling, we recorded extracellularly from three sites in layer 6. At the cooled temperatures used in the intracellular experiments, visually evoked multi-unit activity fell by an average of 85%. Considering the strong temporal facilitation observed in the synapses between layer-6 and layer-4 cells[11], a six-fold decrease in activity in layer 6 will result in a much larger reduction in synaptic input to layer-4 cells. This reduction, when compounded with the direct effect of cooling on the layer-6 cell's synapses in layer 4 (Fig. 2*a*, *b*, downward arrows), should result in a 25-fold or greater reduction in the amplitude of the input from layer 6. We conclude from these observations that cooling severely disrupted activity in the entire local cortical circuit underneath the cooling plate.

With activity in the cortical circuit strongly suppressed, the orientation tuning of the remaining monosynaptic geniculate input to simple cells could be studied. If the model proposed by Hubel and Wiesel[1] is correct, synaptic input should be as well tuned in the cold as at normal temperatures. On the contrary, the cortically based models predict that the response of the geniculate

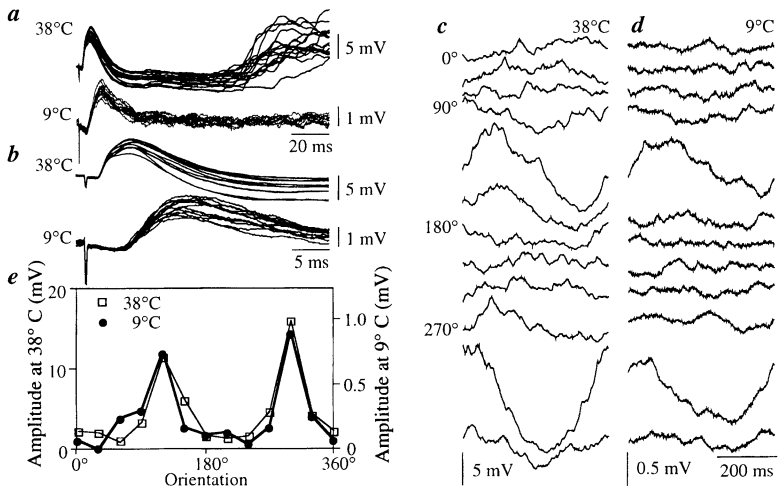

FIG. 1 The effects of cooling on the visually and electrically evoked responses of a layer-4 simple cell. *a*, response of a simple cell to electrical stimulation of the LGN (1 mA, 200 μs) recorded at normal temperature and during cooling. *b*, Similar traces shown at a different time scale. The short (1.8 ms) and stable latency of the e.p.s.p. indicates that this cell received monosynaptic excitation from the LGN. The monosynaptic e.p.s.p. was followed by a long-lasting (150 ms) i.p.s.p. of disynaptic origin. When the cooling plate temperature was lowered to 9 °C, the latency of the e.p.s.p. increased to 5 ms, its rise time was dramatically slowed, and its amplitude was reduced; the i.p.s.p. disappeared. *c*, The cell's response to drifting gratings of 12 different orientations. Each trace is the averaged response to 20 grating cycles. *d*, Responses to the same visual stimuli as in *c*, but with the cortex cooled. The responses are similar in shape to those in *c*, but more than 17-fold smaller in amplitude (note different vertical scales in the figure). *e*, Orientation tuning curves constructed from the records of *c* and *d*. Each point indicates the peak-to-peak amplitude of the first harmonic (2 Hz) component of the corresponding trace. Once again, note the different vertical scales for the two plots.

METHODS. Whole-cell patch recordings in current-clamp mode were obtained from barbiturate-anaesthetized, paralysed adult cats[18]. The cortex was cooled by an L-shaped copper plate[9,30]. The horizontal portion measured 4 × 4 mm and rested on the cortical surface near the area 17/18 border between 2 and 6 mm posterior of Horsley-Clarke 0. A hole (0.9 mm in diameter) in the cooling plate allowed the insertion of electrodes into the cortex. A thermocouple embedded in the top surface of the plate indicated the plate temperature. The vertical portion of the plate was pressed against a Peltier device. In some experiments a second L-shaped copper plate rested on the visual cortex of the opposite hemisphere. Warm agar (3% in physiological saline) sealed the cooling plate to the surrounding bone and sealed the electrode in place. Drifting sinusoidal gratings of optimal spatial frequency, 2 Hz temporal frequency, and 64% contrast were presented monocularly on an oscilloscope screen (mean luminance of 15 cd m^{-2}) using an image generator (Innisfree, Cambridge, MA). Electrical stimuli were delivered through a sharpened tungsten electrode to the optical radiations just overlying the LGN. Layer-4 simple cells were identified by the presence of two or three subregions in their receptive fields[1], and by their characteristic response to electrical stimulation of the LGN[11]. Layer-6 corticogeniculate cells were identified in extracellular recordings by antidromic activation from the LGN and by subsequent histology.

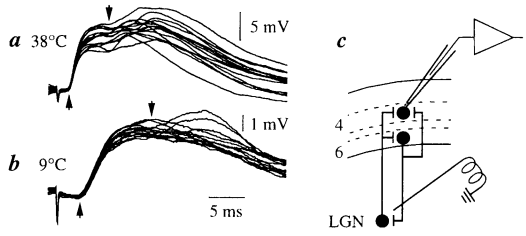

FIG. 2 The effect of cooling on the latency of electrically evoked monosynaptic potentials. *a*, Response to electrical stimulation of the LGN at 10 Hz. At this high frequency, a long-latency e.p.s.p. component (downward arrow) rises out of the monosynaptic response to geniculate relay cell activation (upward arrow). It reflects a monosynaptic potential mediated by the antidromic activation of layer-6 corticogeniculate neurons and their collaterals in layer 4. Its long latency is a result of the slowly conducting corticogeniculate axons[11]. *b*, When the cortex was cooled, the latencies of the two components increased by a similar factor. *c*, A diagram of the connections between the cortex and the LGN that mediate the two potentials seen in *a* and *b*.

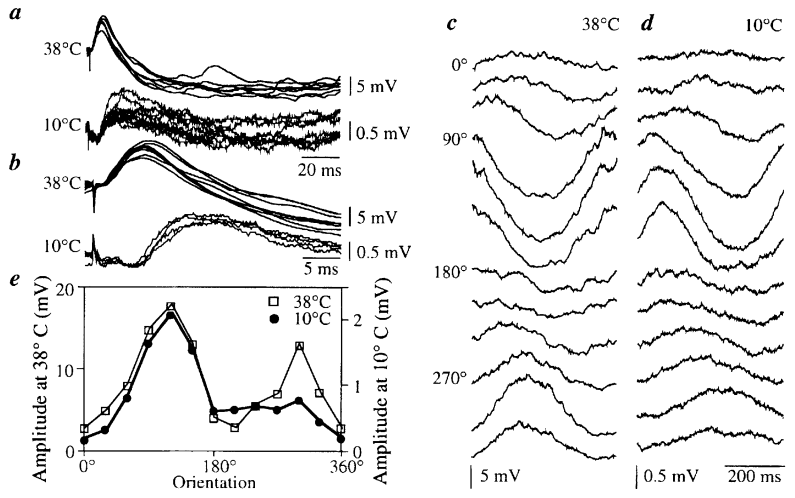

FIG. 3 The effects on the visually and electrically evoked responses of a second simple cell. The layout is identical to that of Fig. 1. Slight shifts in the temporal phase of some of the visually evoked responses were apparent during cooling (compare *c* and *d*). These shifts were not present in the cell shown in Fig. 1. They were probably caused by small (<0.5 °) shifts in the position of the eyes; in other cells, similar shifts over time were observed independently of cooling. In this cell, cooling increased direction selectivity.

input alone should be poorly tuned for orientation compared with the total synaptic input. Our data from layer 4 conform more to the prediction of Hubel and Wiesel's model[1]: the amplitude of visually evoked responses declined during cooling (Fig. 1*e*, note different vertical scales), but the orientation tuning remained virtually identical. In addition, the overall time course of individual responses changed little (Fig. 1*c*, *d*). When tested, rewarming restored the responses nearly to their original amplitudes. The effects of cooling on a second neuron are shown in Fig. 3, and a summary of the effects of cooling on the ten neurons in our sample is shown in Fig. 4. The consistent broadening of orientation tuning predicted by the cortically based models was not apparent.

The data in Fig. 4 may be used to estimate the contribution of thalamic inputs to the visually evoked responses recorded at normal temperatures. We first assume, from the disappearance of polysynaptic postsynaptic potentials, that all but the thalamic component of the visually evoked response are virtually eliminated by cooling. We then assume that cooling reduces the amplitude of the thalamic component of the visually evoked responses and the amplitude of the electrically evoked monosynaptic e.p.s.p. by the same factor. If our assumptions are correct then the amplitude of the thalamic component of the visually evoked response at normal temperatures will equal the amplitude of the cooled visually evoked response divided by this factor. If R is the amplitude of a given response, then

$$R_{\text{visual, warm}}(\text{geniculate component}) = R_{\text{visual, cold}} \times \frac{R_{\text{electrical, warm}}}{R_{\text{electrical, cold}}}$$

This calculation applied to Fig. 4 indicates that the LGN contributes between 21% and 63% of the visually evoked responses. The mean contribution (37%) matches well with direct autoradiographic measurements of the proportion of excitatory terminals in layer 4 that originate in the LGN (28%) (ref. 12).

Although cooling the cortex surrounding the recording site strongly inactivated the local circuit, three remote sources of orientation-selective input in addition to the LGN might have remained active: area 18 (ref. 10); uncooled parts of area 17 projecting by means of long-range horizontal connections[13]; and areas 17 and 18 of the opposite hemisphere[14,15]. These projections largely target neurons outside layer 4. Furthermore, the suppression of nearly all measurable visually evoked activity in neurons without direct input from the LGN indicates that these sources do not provide significant input during cooling. Nevertheless, three procedures were conducted to control for the possible effects of these inputs: to limit input from area 18, all neurons were recorded near the border between areas 17 and 18, so that the cooling plate spanned both areas; to limit input from uncooled parts of area 17, for four cells (Fig. 4*a*–*d*) the visual stimulus, normally 8° in diameter, was limited in area to no more than twice the diameter of the receptive field; and to limit input from the opposite hemisphere, for three cells (Fig. 4*b*–*d*) the cooling plate was enlarged to cover corresponding regions of areas 17 and 18 in both hemispheres. None of these manipulations significantly affected the results.

Early cortically based models of orientation selectivity relied on lateral inhibition among neurons with different preferred

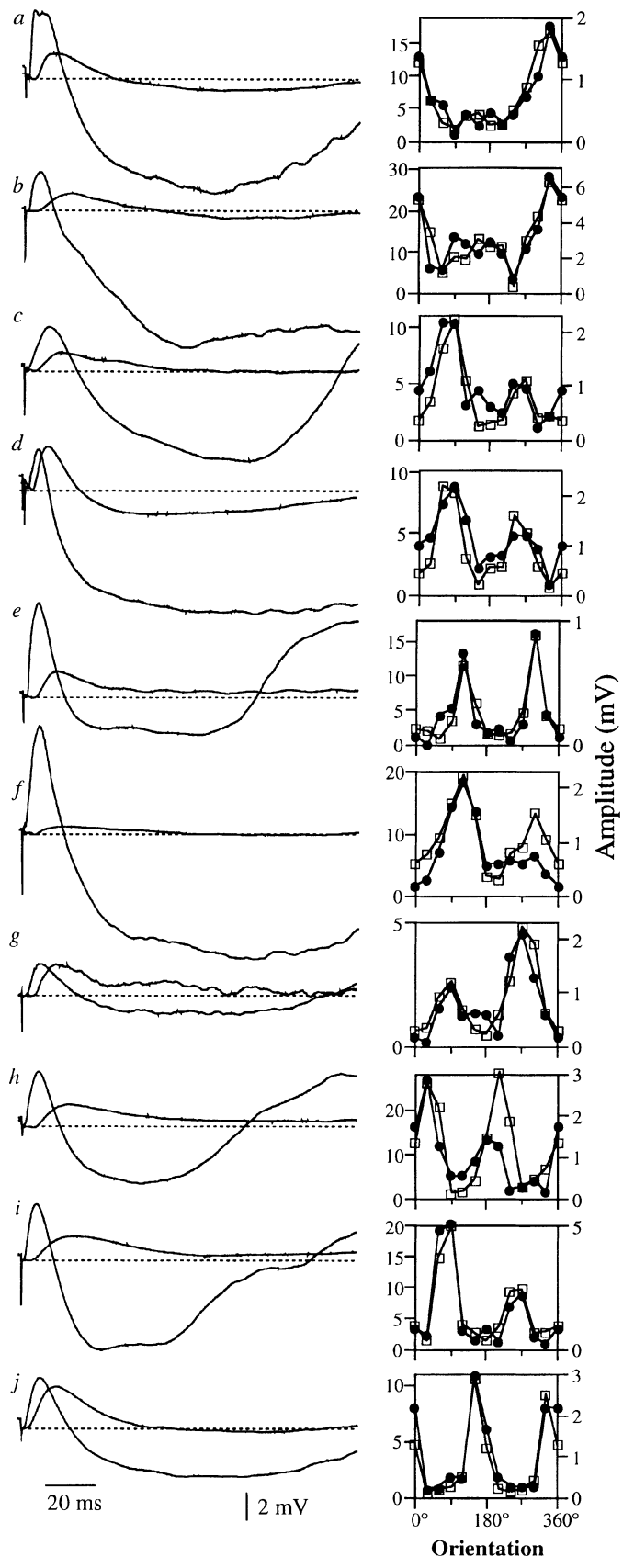

FIG. 4 Left, averaged responses to electrical stimulation of the LGN for each of the ten cells in our sample. In each case, the larger of the two responses was recorded at normal temperature and the smaller during cooling. V_{rest} is indicated by the dotted lines. Right, orientation tuning curves for each cell at normal and cool temperatures. Responses recorded at 38 °C (open squares) are plotted at the scale to the left of each tuning curve. Responses recorded at cool temperatures (filled circles) are plotted at the scale to the right of each tuning curve. In *a*–*d*, the visual stimulus was restricted to twice the size of the receptive field. In *b*–*d*, the cortex was cooled bilaterally. Cool temperatures for the 10 cells were: *a*, 5 °C; *b*, 14 °C; *c*, 9 °C; *d*, 4 °C; e, 9 °C; *f*, 10 °C; *g*, 6 °C; *h*, 14 °C; *i*, 8 °C; *j*, 10 °C.

orientations[2]. These models were supported by the observation that removal of inhibition by extracellularly applied $GABA_A$ antagonists broadened or even abolished orientation selectivity[4]. Intracellular records, however, failed to reveal the significant inhibition that was predicted by lateral-inhibition models to be evoked by stimuli at the non-preferred orientation[16–18]. In addition, intracellular blockade of inhibition within a single neuron did not change orientation selectivity[19]. As a result, it has been suggested that orientation selectivity might arise not only from cortical inhibitory interactions, but from selective amplification of geniculate inputs by excitatory feedback within the cortical column[7,8,20]. The cooling experiment shows, however, that severely disrupting interactions within the cortical column, including excitatory feedback, leaves orientation tuning intact. In layer 4, therefore, the synaptic input from the LGN that remains during cooling is sufficient to determine orientation selectivity.

Similar questions arise concerning the origin of direction selectivity. Saul and Humphrey[21] suggested that direction selectivity is generated from temporally and spatially offset input from lagged and non-lagged geniculate neurons. On the other hand, the cortical amplification mechanisms that were applied to the problem of orientation selectivity can also be adapted to direction selectivity[7,20,22,23]. Our results are consistent with Saul and Humphrey's model[21]. In no case did cooling significantly decrease direction selectivity (Fig. 4). In two cases, cooling increased direction selectivity (Fig. 4*f*, *h*), as if the cortical inputs were supplying excitation in the non-preferred direction. The basis for direction selectivity, like orientation selectivity, may therefore be established by geniculate input.

As predicted by Hubel and Wiesel[1], on and off subregions do seem to originate from monosynaptic input from on- and off-centre geniculate cells[24,25]. It has been argued[26] from precise extracellular measurements of the shapes of simple cell on and off subregions that the elongation of these subregions is often sufficient to account for orientation selectivity. An anatomical substrate for the formation of elongated subfields by geniculate has been suggested[27], as the receptive fields of geniculate afferents innervating a small region of cortex are arranged along lines parallel to the preferred orientation of neurons within the column[27]. It now remains to be determined how this complex organization of geniculate inputs develops during the prenatal period in the absence of visual input[28,29]. □

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Functional recovery in parkinsonian monkeys treated with GDNF

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PARKINSON 's disease results from the progressive degeneration of dopamine neurons that innervate the striatum[1,2]. In rodents, glial-cell-line-derived neurotrophic factor (GDNF) stimulates an increase in midbrain dopamine levels, protects dopamine neurons from some neurotoxins, and maintains injured dopamine neurons[3–9]. Here we extend the rodent studies to an animal closer to the human in brain organization and function, by evaluating the effects of GDNF injected intracerebrally into rhesus monkeys that have had the symptomatology and pathophysiological features of Parkinson's disease induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[10–14]. The recipients of GDNF displayed significant improvements in three of the cardinal symptoms of parkinsonism: bradykinesia, rigidity and postural instability. GDNF administered every four weeks maintained functional recovery. On the lesioned side of GDNF-treated animals, dopamine levels in the midbrain and globus pallidus were twice as high, and nigral dopamine neurons were, on average, 20% larger, with an increased fibre density. The results indicate that GDNF may be of benefit in the treatment of Parkinson's disease.

GDNF has been proposed as a potential treatment for parkinsonism on the basis of its effects on rodent dopamine neurons[3,4,7,8], but little is known about its actions in non-human primates. Therefore, we have evaluated the effects of GDNF in rhesus monkeys with stable parkinsonian features induced by the infusion of MPTP through the right carotid artery three months earlier[10–14]. In the first experimental series, sterile MRI-guided stereotaxic procedures[11] were used to deliver a single injection of human recombinant GDNF into the right side of the brain of the rhesus monkeys by one of three routes: intranigral ($n = 2$, 150 μg), intracaudate ($n = 2$, 450 μg) or intracerebroventricular (ICV; $n = 2$, 450 μg). Controls (intranigral, $n = 2$; intracaudate, $n = 2$; or ICV, $n = 3$) received vehicle (10 mM PBS) injections. Using a non-human primate parkinsonian-rating scale[10], parkinsonian features were scored blindly by at least two raters from standardized video tapes made biweekly for the 4-week period before GDNF or vehicle administration and for the 4-week period following treatment. GDNF recipients showed significant functional improvements (Fig. 1*a*) after all three routes of administration by two weeks post-treatment, which continued for the remainder of the 4-week test period.

Testing was continued on the ICV-treated animals to assess the ability of the animals to respond to repeated dosing and to measure dopamine levels in the brain following GDNF treatment. The sample size was increased by adding one additional animal to the group treated with 450 μg and three treated with 100 μg GDNF ICV. Each of the animals treated with vehicle and trophic factor received three injections into the right lateral ventricle spaced at least 4 weeks apart. In recipients of 100 μg and of 450 μg GDNF, the behavioural effects were very pronounced by the third