was no evidence of deep follicular or vascular damage. Electron microscopy showed enlarged, focally disrupted, and centrally electron-lucent melanosomes within affected melanocytes and basal keratinocytes (Fig. 2), whereas organelles of adjacent nonpigmented cells (for example, Langerhans cells) were unaltered. Biopsies taken immediately after exposure disclosed similar changes occurring selectively in melanosomes; these results suggest that these melanin-containing organelles are the primary sites of injury. Grossly acute inflammation for several days was followed by hypopigmentation developing 7 to 10 days after exposure, without gross epidermal sloughing. Exposed sites then gradually repigmented without apparent scarring.

The feasibility of vascular, cellular, and ultrastructurally specific SP is apparent from this work. Whatever usefulness SP of vascular or pigment cell targets may have, the general technique may find many biomedical applications. As a microsurgical technique, cell-specific SP affects large cell numbers without widespread tissue damage. In tissues such as the central nervous system where surgery is hazardous and single cells are the functional operating units, SP may be especially valuable. If tunable lasers and cell-specific dye delivery systems can be used, choice among many targets is possible. The biologic repair of such highly specific damage needs to be understood.

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Brief Deprivation of Vision After Unilateral Lesions of the Frontal Eye Field Prevents Contralateral Inattention

Abstract. *Brief deprivation of vision after unilateral lesions of the frontal eye field prevents the appearance of contralateral inattention to visual, auditory, and somatosensory stimuli. The forced circling that accompanies inattention, however, is not affected. An equivalent preoperative period in the dark only partly reduces inattention symptoms. Visual deprivation does not reduce or prevent inattention resulting from lesions of the superior colliculus.*

In primates a small region of dorsolateral frontal cortex, the frontal eye field, plays a specialized role in eye movements, attention to visual and other sensory stimuli, and spatial alternation and learning (*1–4*). This frontal area is distinguished by a pattern of connections with other brain regions that displays three significant features: (i) polysensory corticofrontal input and a diffuse sensory, visceral, and emotional relay from the dorsomedial nucleus; (ii) motor involvement through projections to the motor and premotor cortex and the neostriatum; and (iii) tectal projections by which retinal input to the superior colliculus may be modulated (*5*). We may thus expect that damage to the frontal eye field will be reflected in each sensory modality and in intermodal association, that a performance disorder will contribute to the attentional and spatial deficits, and that there will be affinities to the symptoms of superior colliculus lesions. Each expectation is borne out experimentally (*2, 6–8*).

There is a similar frontal specialization in the rat. Anatomically, inputs to an anteromedial cortical area from the dorsomedial nucleus and outflow to the striatum and tectum significantly resemble the picture seen in the primate (*9*). Electrical stimulation of this region yields eye movements (*10*), and lesions result in attentional and spatial deficits (*11, 12*).

Unilateral lesions of the frontal eye field produce marked contralateral inattention to polysensory stimuli and forced ipsiversive circling. Monkeys largely recover from these effects in 4 to 6 weeks, rats in about 3 weeks (*2, 3, 11*). Sectioning the corpus callosum after recovery from the cortical lesion reinstates inattention, but recovery again follows (*3*). This recovery from deficits that are initially severe demonstrates the remarkable modifiability of neural systems in response to injury.

Another body of research has established that the conditions attending the lesion may alter its consequences. Preoperative dieting, for example, attenuates the aphagia and sensorimotor deficits produced by lateral hypothalamic destruction, while preoperative fattening exacerbates them. Maintaining animals in the dark pre- or postoperatively minimizes the motor symptoms of lateral hypothalamic lesions (*13*). This research suggests that altering relevant experience in the perisurgical period might modify the symptoms of inattention that follow lesions of the frontal eye field. What experience would be relevant? Anatomical, physiological, and behavioral data on the frontal eye field point to the visual modality. In an earlier experiment on the question (*11*), rats were trained to discriminate patterns before being given unilateral lesions of the anteromedial cortex or, in the case of the controls, of the dorsolateral cortex. One group of animals with anteromedial lesions was kept in darkness except during daily testing; the other group was maintained in the light. The latter group took significantly longer than the controls to make a correct choice, reflecting impaired attention (the impairment was contralateral to the lesion). The response latencies of the visually deprived animals, however, resembled those of controls; thus there was no attentional impairment.

We report here the effects of visual deprivation on symptoms resulting from lesions of the anteromedial cortex or superior colliculus, as determined by sensory tests in visual, auditory, and somatosensory modalities. Male Long-

Evans hooded rats weighing 250 to 300 g were individually housed and given unlimited food and water. They were exposed to a diurnal 12-hour light-dark cycle and handled daily in the week preceding surgery.

Unilateral lesions were placed in anteromedial cortex, dorsolateral frontal cortex, or superior colliculus (Fig. 1) (*14*). Testing began 2 days after surgery and was conducted 3 days a week for 3 weeks. Visual, auditory, and somatosensory inattention and circling were assessed by a series of tests originally adapted from clinical techniques to investigate the sensory and motor effects of lesions of the superior colliculus (*15, 16*).

In the first experiment animals received anteromedial or dorsolateral lesions. Ten rats with the anteromedial lesion experienced the normal light-dark cycle postoperatively; five were kept in a totally dark room for 3 weeks and were exposed to light only during testing. As we found previously (*11*), the rats maintained in light showed marked inattention in each sensory modality and circled more to the lesion side. Inattention was less severe in the second week, and recovery was largely complete by the third week. The animals with dorsolateral lesions had no sensory deficits, but, in contrast to our earlier results, they circled ipsiversively. In the visually deprived group with anteromedial lesions there was no evidence, in 3 weeks of testing, of visual, auditory, or tactile inattention [median weekly orienting score of 6 on each test (*16*)]; there was, however, circling toward the lesion side. We next limited the period of visual deprivation to 2 days. In a group of ten rats with anteromedial lesions, the median orienting score was 6 on every test in each of the 3 weeks. Circling was again predominantly ipsiversive.

Isolation in a darkroom diminishes the sound and activity to which rats are exposed in a normal colony environment. Therefore the effects of increases in the ambient sound level and of maintaining visually deprived animals in their home room were studied in two further experiments. Ten rats with anteromedial lesions were sequestered in the dark for 2 days. For 12 hours daily, loud music and news from a local radio station were broadcast at frequent intervals. Another ten rats had their eyelids sutured shut after receiving anteromedial lesions and were returned to the colony room. Like the controls with dorsolateral lesions and the visually deprived groups, both these groups had median orienting scores of 6 on the sensory tests and both circled toward the side of their lesions.

To determine whether the effect of visual deprivation is specific to the anteromedial cortex or can be obtained after structures with comparable functions are damaged, ten rats with unilateral lesions of the superior colliculus were visually deprived. Visual inattention was profound and did not change over the period of testing. The vibrissae test (*16*) also revealed consistent inattention over the 3 weeks, but there were no deficits on the other two sensory tests. The animals circled equally to either side in the first week but thereafter showed pronounced ipsiversive turning.

The data were subjected to a two-stage analysis. First the four visually deprived groups were compared. Individual analyses showed no main effects for any sensory test or for weeks 1 to 3. A second analysis revealed a strong main effect for ipsiversive circling in all groups [$F(1, 31) = 21.52$, $P < .001$]. A significant group effect for circling was found, with less circling overall in the rats exposed to the blaring radio and the rats whose eyelids were sutured [$F(1, 31) = 4.88$, $P < .01$]. This similarity between the deprived groups made it appropriate to pool them for the second stage of the analysis. Here, we found a significant groups × weeks interaction for each sensory test: vision, $F(8, 140) = 29.94$, $P < .005$; audition, $F(8, 140) = 17.31$, $P < .005$; vibrissae, $F(8, 140) = 16.62$, $P < .005$; and toe pinch, $F(8, 140) = 14.40$, $P < .005$. Analysis of simple main effects showed that on each sensory test the visually deprived group with anteromedial lesions and the controls with dorsolateral lesions did not differ, and that they were markedly different from the light-maintained group with anteromedial lesions. The group with lesions of the superior colliculus reliably differed from the controls and the visually deprived animals on the vision and vibrissae tests. Of the groups with anteromedial lesions, the light-maintained animals but not the visually deprived group showed a significant increase in orienting scores from weeks 1 to 3 on all the sensory tests [$F(1, 140)$

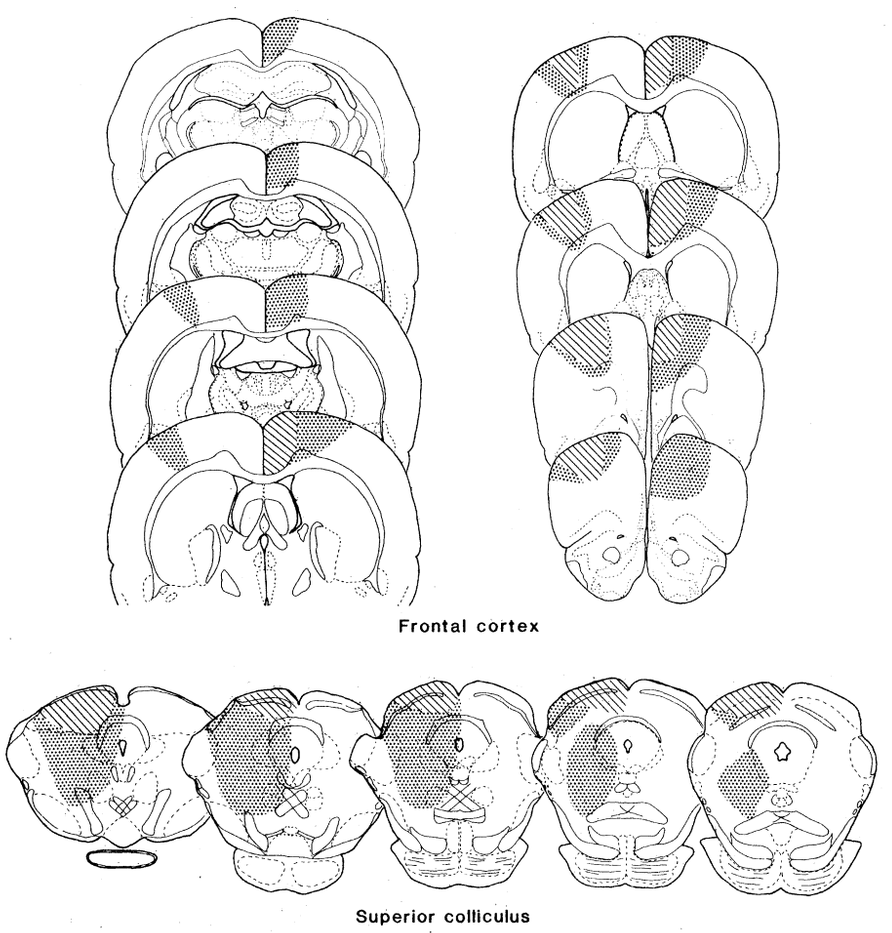

Fig. 1. Histological reconstructions, in the coronal plane, of the anteromedial, dorsolateral, and superior colliculus lesions. The lesions were equally distributed between the hemispheres, but for simplicity are shown in a single hemisphere. Cross-hatching marks the area of the smallest lesion and stippling the additional tissue destruction of the largest. The cortical sections are 1.0 mm apart and the superior colliculus sections are 400 μm apart.

each at $P < .005$]. The group with lesions of the superior colliculus circled more than the others [$F(2, 61) = 5.94$, $P < .005$]; all groups circled more to the lesion side [$F(1, 61) = 55.01$, $P < .005$]; and, irrespective of its direction, circling was depressed in the first week [$F(2, 122) = 6.61$, $P < .005$] (Fig. 2).

These findings show that the usually pronounced inattention to stimuli resulting from unilateral lesions of the frontal eye field is virtually eliminated in visual, auditory, and somatosensory modalities by no more than two postoperative days in the dark. Strong replication in four groups and in two different experimental situations are assurances of a robust experimental treatment. The results for the group exposed to the blaring radio and the group with sutured eyelids make clear that deprivation of visual experience is the critical variable, not a general sensory restriction or minimization of stress resulting from isolation in the dark. Manipulations of nonvisual experience during time in the dark had no effect. Furthermore, there was nothing in the behavior of the visually deprived animals to suggest that increases or decreases in emotionality or general reactivity influenced their responses on the sensory and motor tests. They did not show more circling activity than the two control groups, and their sensory responsiveness, both ipsilateral and contralateral to the lesion, was indistinguishable from that of the controls.

Can inattention also be prevented by preoperative visual deprivation? In ten rats kept in darkness for 2 days immediately before surgery there was only a small meliorating effect. On each sensory test they differed from the postoperatively deprived animals and also from the light-maintained group with anteromedial lesions [$F(4, 70)$ each at $P < .005$]. Their orienting scores increased from weeks 1 to 3 [$F(3, 140)$ each at $P < .005$] on every sensory test. Visual deprivation had its major influence when it succeeded the lesion.

Sensory and motor effects can be dissociated, as others have reported (*17*), with recovery occurring at different rates. Here, visual deprivation preserved orienting behavior but had no effect on motor behavior. The frontal eye field is involved in attention, but it also has distinct motor functions—probably mediated, in the case of circling, by projections to the neostriatum—and indeed it gained its name from its oculomotor role.

Lesions of the anteromedial cortex produce sensory and motor symptoms resembling those resulting from superior colliculus damage, but there are major distinctions. In the group with lesions of the superior colliculus, no auditory or toe pinch deficits were found, visual inattention was enduring, circling was more pronounced, and there was no response to visual deprivation. The anteromedial cortex appears to have a more extensive polysensory role than the superior colliculus, and damage is compensated more readily.

After cortical injury, function is suddenly inhibited in other brain areas anatomically connected to the injured site through fiber tracts. This is the diaschisis phenomenon of von Monakow. Depriving damaged brain systems of normal sensory stimulation may prevent diaschisis or markedly reduce its duration. When parallel mechanisms exist, they can thus immediately provide compensatory function. The involvement of the frontal eye field in attentional processes suggests another interpretation. A substantial proportion of neurons in the frontal eye field are visually responsive and have large, nonspecific receptive fields that are well adapted to stimulus detection and orienting (*18*). The hypothesis is that these neurons provide the input for model-comparator processes by which significant stimuli are recognized. Disruption of frontal eye field output would severely perturb such processes in target structures, resulting in failure to recognize incoming stimuli and direct appropriate orienting movements.

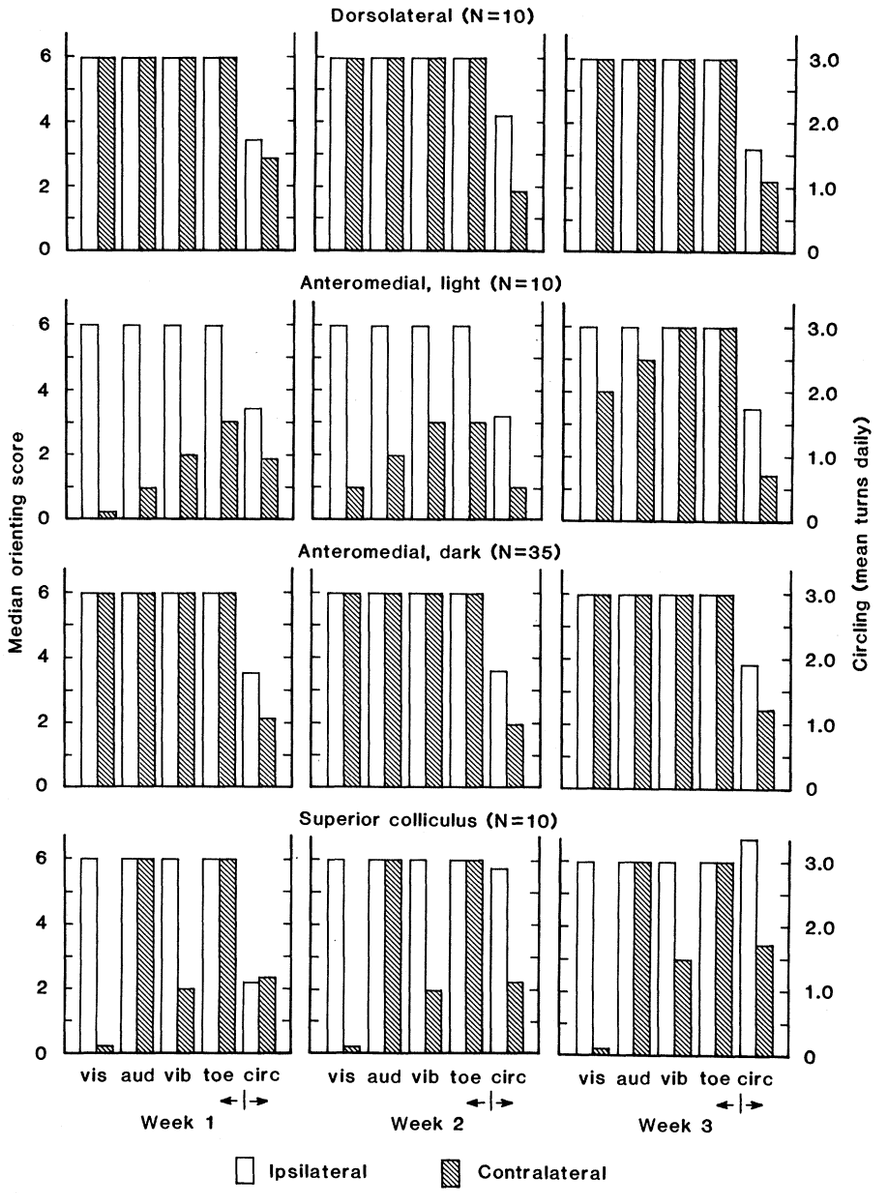

Fig. 2. Orienting and circling in the various groups. A median orienting score of 6 indicates complete responsiveness on each of the three test days in a given week. The four sensory tests are identified as vision (*vis*), audition (*aud*), vibrissae (*vib*), and toe pinch (*toe*) [circling (*circ*)].

Postoperative visual deprivation would leave the animal with old but still serviceable representations that could provide for function until compensatory mechanisms take effect.

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Spontaneous Orofacial Dyskinesia and Dopaminergic Function in Rats After 6 Months of Neuroleptic Treatment

Abstract. *A syndrome of spontaneous orofacial dyskinesia was identified in groups of rats treated for 6 months with a wide range of neuroleptic drugs. Phenothiazines, thioxanthenes, and substituted benzamides were particularly likely to induce the syndrome. It was observed in the presence of a functional blockade of dopamine receptors and endured for at least 2.5 months after drug withdrawal. There was no relation between the syndrome and changes in striatal dopamine receptors, as indexed by the binding of tritiated spiperone and tritiated* cis*(Z)-flupenthixol. The syndrome parallels several of the features of clinical tardive dyskinesia, whose pathophysiology thus may not involve changes in the characteristics of striatal dopamine receptors.*

The abnormal, involuntary movements of the orobuccolingual area seen in some schizophrenic patients have been termed tardive dyskinesia. This disorder, which is generally believed to emerge as a late-onset side effect of several years of treatment with neuroleptic drugs (*1*, *2*), may be traceable to striatal dopaminergic hyperfunction, possibly through the supersensitivity of dopamine (DA) receptors in the basal ganglia (*1*). When neuroleptics are given to rodents for weeks, subsequent withdrawal rapidly and reliably results in enhanced perioral stereotypies on challenge with DA agonists and increased striatal binding of tritiated neuroleptic ligands; however, rodents so treated do not show enduring spontaneous orofacial dyskinesia (*1*, *3*). The clinical syndrome can emerge during ongoing treatment with neuroleptics. Withdrawal of these drugs, while sometimes exacerbating existing dyskinesia or unmasking latent dyskinesia, is not always required for its manifestation.

Not all schizophrenics develop dyskinesia. Those who do have usually received neuroleptics for several years. It can appear despite continuing antipsychotic activity and functional blockade of at least some forebrain DA receptors (*1*). Thus, the rodent perioral stereotypies induced in previous studies are at variance with several characteristics of the clinical syndrome. We describe here the characteristics of spontaneous orofacial dyskinesia that emerged during treatment of rats with a range of neuroleptic drugs for periods constituting a substantial proportion of their adult lifespan.

Male Sprague-Dawley rats (250 to 450 g) were treated continuously through their drinking water (*4*) with the butyrophenone haloperidol, the phenothiazines fluphenazine and trifluoperazine, the thioxanthene piflutixol, or the substituted benzamide metoclopramide. Other rats were given 0.2-ml intramuscular injections of fluphenazine as the decanoate (25 mg/ml in oil) or of oil vehicle alone at 2- to 3-week intervals (*5*). The doses selected were proportionate to those used clinically (Fig. 1) (*6*). Spontaneous behavior was observed both in animals that continued to receive neuroleptics and in animals from which the drugs were withdrawn (*4*). Striatal tissue was removed to assay the specific binding of [^{3}H]spiperone (0.8 n*M*) and [^{3}H]*cis*(Z)-flupenthixol (2 n*M*) (*7*).

A syndrome of spontaneous perioral movements was noted in the animals. These movements, while similar to chewing, were not directed onto physical material. A prominent characteristic was a grating sound produced as the teeth were drawn across one another by lateral jaw movements. This sound was the most reliable index of the syndrome when assessed by an experimenter with no knowledge of the treatment history, and the syndrome was judged to be present or absent on the basis of this auditory criterion.

During the sixth month of treatment the prevalence of spontaneous orofacial dyskinesia was 2.5 times higher in the groups treated with fluphenazine, trifluoperazine, piflutixol, or metoclopramide (mean prevalence, 53 percent; $N = 62$) than in the matched controls (mean prevalence, 21 percent; $N = 55$) [χ^2 (1) = 12.20, $P < .01$] (Fig. 2). The syndrome occurred slightly less frequently in haloperidol-treated rats (18 percent; $N = 45$) than in their matched controls (23 percent; $N = 70$). After completing these behavioral studies, we withdrew the neuroleptics. Seven to eleven days later, striatal binding of [^{3}H]spiperone was equally elevated in animals that had received haloperidol, fluphenazine, piflu-