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## UNITY AND DIVERSITY OF FRONTAL LOBE FUNCTIONS

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*Abstract.* In attempting to summarize recent work on functions of granular prefrontal cortex in primates, including man, and possible homologues of these structures in rodents and carnivores, four questions need to be asked, the questions of 'where', 'when', 'what' and 'how'. Progress since the Pennsylvania Symposium has been considerable for questions of 'where' and 'when': localization of symptoms ('where') yields a double gradient (up-down and back-to-front) in monkeys, and a right-left difference in man; analysis of time factors ('when') distinguishes early and late lesions, single and serial removals, or succeeds in recording and stimulating at critical moments during performance. However, problems of 'what' and 'how' are still largely unsolved: we do not yet know what various prefrontal symptoms signify, in terms of normal function, and are only beginning to see how individual prefrontal neurons act and interact. Advances on these questions are likely if one exploits an extended version of those hypotheses about prefrontal physiology that attribute to these structures neither purely sensory nor purely motor functions but consider them instead as sources of 'corollary discharges' whereby the organism presets its sensory systems for the anticipated consequences of its own action.

At the conclusion of this Symposium on the "Frontal granular cortex and behavior", it remains to attempt a synthesis. We should try to define in what ways our views on this topic have changed since the last major effort at summation, at the Pennsylvania Symposium (Warren and Akert 1964), and we should identify areas of continuing perplexity. Our host, Professor Konorski, has dealt in his chapter primarily with the recent work on carnivores, so that my emphasis will be on primates, including man, with only occasional glances at other mammalian species. Taken in combination, the two concluding chapters should help one to

see to what extent the work done with different species, and with different methods, might fit together.

Progress in any field comes with new methods, with new observations and, perhaps most, with new ways of asking one's questions. Accordingly, I shall structure this review around four simple interrogatives: where? when? what? how? By 'where' I mean the great wealth of new work on localization of symptoms within the frontal lobes, the increasing parcellation of these structures by anatomic, physiologic and behavioral techniques. By 'when' I mean the growing evidence on the role of time in determining the outcome of frontal-lobe lesions, whether incurred by the very young, or by the mature organism, whether inflicted all at once or in successive stages; I also mean the intriguing work on timed electric stimulation and recording, in relation to some possibly critical stages in acquisition or performance of certain behavioral tasks.

It will be apparent that we have learned a great deal since the time of the Pennsylvania Symposium about ways of asking the questions of 'where' and 'when', but considerably less about the questions of 'what' and 'how'. By 'what' I mean the crucial issue of what any particular frontal-lobe symptoms might signify: what is the normal function whose disruption underlies those behavioral alterations that we know must follow focal lesions or stimulation in the frontal cortex, or in related subcortical systems? And this persistent problem of 'what', the meaning of symptoms, blends into the ultimate question of 'how', that is, of how the neurons in diverse frontal regions act individually and together. On this score we are still farthest from our goal, but even here there is some very recent work that promises major advances. It is revealing that during the Pennsylvania Symposium, such studies of single units did not even come up.

In sum, I shall review the state of the frontal-lobe problem under the headings of where, when, what and how, knowing that the available evidence gets sparser and weaker as we go over these four questions in that order; at the same time, the chances for major discoveries seem to line up almost entirely in reverse order, with the most important future disclosures likely to concern the questions of what and how, the physiologic meaning of frontal-lobe symptoms, and the basic mechanisms of normal frontal-lobe function.

Gauged in relation to these goals, our progress may seem small; one is ready to concede, with Sir John Eccles' favorite expression, that we are all still "utter primitives" as we try to deal with the frontal lobes. Yet such an act of contrition does not come at the very beginning of a given scientific development; it marks rather a turning point in the

field, the moment when one has come close enough to the main issues to see the full outline of one's problems. It is a major contribution of this Symposium to have brought this moment upon us; we all grasp much more completely what it might take if we want to understand the complex relationships between the frontal lobes and behavior.

#### A. THE QUESTION OF 'WHERE?'

##### Gradients of localization of symptoms

Over a third of a century ago, Carlyle Jacobsen (1935, 1936) demonstrated the close relationship between frontal lobectomy in primates and deficits on delayed-response tasks. Subsequent work endeavored to define an increasingly sharper focus for that symptom (see, e.g., Blum 1952); as a result, its prominent dependence on the region of the sulcus principalis (still more specifically, its middle third) on the dorsolateral frontal surface is now considered as established (Butters et al., this Symposium). At the same time, however, it seemed inconceivable, for already two decades or more, that this enormous expanse of prefrontal cortex (i.e., all cortex anterior to the primate's arcuate sulcus) should not be subdivisible in such a way that differently localized lesions should have distinctly different behavioral consequences, beyond the focal relationships between certain dorsolateral lesions and delayed response.

Earlier phases in these efforts at fractionation of frontal lobe syndromes, in terms of separately localizable symptoms, already held much of the stage at the Pennsylvania Symposium, at the beginning of the sixties. Now, at the beginning of the seventies, the parcellation has become more subtle and more complete, for carnivores, sub-human primates, and even for man. Yet the question of interpretation of these fractional syndromes has become, if anything, more acute.

##### *1. A two-fold gradient of functional specialization: up-down and back-to-front*

At the Pennsylvania meeting, there was general agreement that a valid distinction could be made, at least for the monkey, and probably for man, between those symptoms that follow dorsolateral frontocortical removals, and those that follow corresponding orbito-frontal destruction. The present Symposium bore this distinction out. Classical deficits on delayed-response and related tasks depend primarily on lesions of dorsolateral cortex, whereas inferior-convexity lesions are mainly followed by trouble with object-reversal tasks (Iversen and Mishkin 1970); quite generally, orbito-frontal lesions tend to create profound disturbances in emotional reactivity and to interfere with appropriate behavior in

social groups (Butter and Snyder, this Symposium, Homskaya, summarizing Luria's views, this Symposium).

Added to this up-down gradient, there is now increasing evidence for a second gradient running at right angles to the first: a back-to-front gradient of specialization along the dorsolateral frontal surface. The existence of such an horizontal gradient was suggested by an early study of Gross and Weiskrantz (1962) and has now been reinforced by Goldman and Rosvold (1970): lesions confined to the transitional, dysgranular cortex of the monkey, between the limbs of the arcuate sulcus, disrupt performance on tasks that seem to contain some crucial spatial element such as "conditional spatial discrimination" where the animal has to turn to the right or left, depending on the frequency of a tone. On such tasks the presence of a delay is irrelevant; the animal with bilateral periarcuate lesions does poorly even if the critical tones are still sounding at the time of his choice.

By contrast, bilateral lesions situated further forward, in the midportion of the sulcus principalis, produce defects on those aspects of delayed-response and delayed-alternation type tasks, for which the delay is crucial. As summarized by Goldman and Rosvold (1970), this back-to-front gradient of localization would thus take one from symptoms related to some *spatial* aspects of the critical tasks, to more definitely *mnemonic* aspects, although it is still far from clear how one should characterize the "spatial" aspects (but see Potegal, this Symposium and see below), or how one should define the "mnemonic" ingredient of the delayed-response type task. Is it memory for a spatial location, in relation to the animal's own body, as we have suggested long ago (Teuber 1955, 1964)? Or is it a special kind of memory that helps one to decide which trial has just gone before, in a series of trials (see Milner 1968, and this Symposium, Pribram 1969)? Or is it both, or neither of these?

Whatever the interpretation, the back-to-front gradient here suggested is curiously reminiscent of another horizontal gradient — the one along the infero-lateral surface of the monkey's temporal lobes, where Iwai and Mishkin (1969) could show predominantly perceptual difficulties on visual-discrimination learning with more posterior removals, and a deficit in learning (rather than perception) with more anterior lesions. This progression may reflect a more general principle that has yet to be formulated.

How does this tentative picture of two intersecting gradients in the frontal lobe, a vertical, or up-down gradient, and a horizontal, or back-to-front gradient, fit into what we have come to know about the anatomy and neurophysiology of the primate prefrontal cortex? And are there analogous subdivisions for carnivores, and for man?

## 2. Anatomic subdivisions

The anatomical affiliations of frontal-lobe cortex received a masterly summary from Professor Nauta at the beginning of this Symposium. Much of the new information since Pennsylvania stems from newly discovered variants of Professor Nauta's method for the staining of degenerating nerve terminals, particularly the Fink-Heimer technique developed in Professor Nauta's laboratory at M.I.T. (Fink and Heimer 1967). From his own work and that of Pandya and Kuypers (1969) and Jones and Powell (1970) it has become abundantly clear that the prefrontal cortex receives partly overlapping, indirect input from all of the major sensory afferent systems and that most of these projections are reciprocal, so that the prefrontal cortex can act back upon these systems as well as upon limbic, diencephalic and even mesencephalic structures.

Yet it is this very abundance of connections that makes it so difficult to assign anatomic counterparts to the limited number of behavioral parcellations thus far achieved. It is not clear whether one should focus one's search primarily on the inflow from subcortical structures, or on cortical outflow into subcortex, or upon the massive cortico-cortical connections that have now been established by these modified Nauta techniques. These procedures are giving us a detailed map of cortical connectivity superseding the one that had been sketchily outlined, decades ago, by strychnine neuronography.

One of the main difficulties is with the up-down gradient, the differentiation of dorsolateral from inferior frontal convexity in primates. Orbito-frontal affinities with limbic and diencephalic structures are well established but unfortunately not unique, since such connections exist also for dorsolateral cortex (Nauta 1964, and this Symposium). Yet the differentiation based on purely behavioral results suggests a fairly definite horizontal boundary. As Rosvold pointed out at this Symposium, this functional dividing line seems to run roughly 5 mm below the principal sulcus and parallel to it; yet there seems to be no obvious anatomic basis for this division. One anatomic feature of orbital cortex is its privileged position with regard to olfactory input; as Nauta suggested at this Symposium, this easy access for olfactory information to orbital cortex may distinguish it from other portions of the prefrontal region, but many questions remain.

Perhaps one can gain additional clues from considerations of cortico-cortical connections, and from further study of differential subcortical inputs into the mediodorsal nucleus of the thalamus. It has long been known (see Pribram et al. 1953) and much discussed in Pennsylvania

(Akert 1964, Nauta 1964) that the mediodorsal nucleus projections are orderly and subdivisible, with the periarcuate region receiving projections from a distinct paralamellar portion, the dorsolateral granular cortex from the parvocellular division of the nucleus, and the orbital-frontal sector from the magnocellular division. Once we know more of the probable differential input into these three different portions of the mediodorsal thalamic complex, we may have some better grasp of the up-down gradient (dorsolateral to orbital) and of the distinction between the periarcuate region and the anterior structures around the sulcus principalis.

The back-to-front gradient (periarcuate to *principalis*) is in any case somewhat less bewildering since we have definite cytoarchitectonic differences (dysgranular cortex in the periarcuate region, and granular around the *principalis*). Yet the most helpful clue for a back-to-front gradient, as Butters and Pandya (1969) have pointed out (*see also* Butters et al., this Symposium), might lie in different cortico-cortical efferents; the cortico-cortical projections from the periarcuate region are primarily directed backward into the interparietal sulcus, whereas the projections of the middle third of the sulcus *principalis* can be shown by appropriate cortico-cortical degeneration studies to course into such juxt-allocortical and allocortical structures as the cingulate, the presubiculum and ultimately the hippocampus. Speaking broadly then, the parietal affinities of the periarcuate, and the hippocampal affinities of the middle *principalis* region, are in surprising harmony with the predominance of spatial symptoms after periarcuate and of mnemonic symptoms after *principalis* removals.

### *3. Parcellation in species other than monkeys*

As regards possibly analogous results for other species there is little doubt that a vertical gradient exists for man where, as Professor Brenda Milner has pointed out, performance on certain sorting tests may be more impaired with dorsolateral involvements; trouble with impulse control is generally considered to follow orbital and medial damage (*see* Homskaya's summary of Professor Luria's views, this Symposium). The situation for carnivores seems fairly similar, at least for dogs; bilateral gyrus-proreus lesions produce severe deficits on delayed-response and delayed-alternation tasks (Ławicka, this Symposium), whereas bimedial lesions interfere with 'asymmetric go-no go differentiation' (Dąbrowska, this Symposium). On the latter task, the dog gets his food by responding to a positive stimulus, and withholding response to a negative stimulus, and it is this kind of differential responding for food that is badly disrupted by more medially located prefrontal lesions. Thus, the

dorsal-to-ventral gradient in primates is at least partly replicated in a dorsolateral-to-medial gradient in dogs.

It is much harder to decide whether there are analogues across species for the other gradient of localization, the back-to-front gradient, which has now been demonstrated for monkeys. To my knowledge, no one has really analysed the available observations on man in quite that way, but some of the laboratory tasks that have been developed (see below, third section of this chapter) might lend themselves to such an analysis in the future. But as regards the carnivores, recent work by Dąbrowska, by Ławicka and by Stępień and Stępień (this Symposium), all from the Nencki laboratories, makes it virtually certain that there are foci in the dog's prefrontal region that are not exhaustively described by the distinction between proreal and medial syndromes.

However, these regional differentiations do not seem to conform in any obvious way to the distinctions made for the monkey, between tasks with more purely spatial aspects, and those with more definitely mnemonic components. Instead, one important dimension for additional potential subdivisions in dogs seems to lie in the distinction discussed extensively by Ławicka between the 'spatial' and 'kinesthetic' components of various delayed-response and go left-go right tasks. On tasks with so-called symmetric reinforcement (see Dąbrowska, this Symposium), the dog cannot solve the problems by referring to external landmarks, but only by relying on his own current and previous postures; he has to decide 'which way to turn' from a central position, as Ławicka puts it, and not 'where to go'. This 'knowing which way to turn' is described by Professor Konorski as a kinesthetic aspect of performance, and Dąbrowska's recent experiments, in particular, have strongly suggested that this aspect is selectively affected by certain lateral prefrontal lesions, i.e., those encroaching on what has been called the 'orbital gyrus' in the dog, and not at all by medial prefrontal lesions.

With respect to the more spatial aspect of frontal-lobe tasks, however, the Nencki group evidently finds no cortical focus whose removal would produce a definite impairment in that regard. As the Stępieńs have shown, however, a deep lesion (interrupting fiber bundles in the dorsomedial prefrontal area of the dog) does tend to disrupt performance on tasks that require the animal to make spatial distinctions, i.e., to decide 'where to go'. But the general problem of localizing components of prefrontal syndromes across species is far from solved.

#### *4. Problems of cross-species comparisons*

One of the most puzzling features of cross-species comparisons is the mildness and inconsistency of delayed-response deficits in cats (Warren

et al., this Symposium, *see also* Divac, this Symposium). As Professor Warren pointed out again, at this Symposium, in line with his earlier emphasis at the Pennsylvania meeting, gyrus proreus lesions are considerably less effective in producing delayed-response deficits in cats than in dogs, even though other aspects of the frontal lobe syndrome can be seen quite readily in cats, such as perseverative responding on a variety of tasks, and altered behavior in open-field and in social situations.

Just as surprisingly, it turned out on comparing Myers' results for monkeys with Warren's results for cats that female monkeys with pre-frontal lesions tend to be very bad mothers although seemingly similar lesions in female cats seem to be compatible with excellent maternal performance. The comparison is hampered by the fact that the removals in Myers' monkeys may have been much more extensive than in Warren's cats, but there are true differences between species in reaction to similar frontal lesions; I shall return to this topic when we consider the unsuitability of ordinary delayed-response tests for man. These contrasts may reflect differences in those species-specific behaviors that go into complex activities, such as maternal care of the young. In the same way, certain tasks such as delayed-response may be of quite different degrees of unnaturalness for different species.

Such species differences prompted Professor Warren's plea, supported by Butter, and by Myers, for an increased reliance on more naturalistic and, if possible, ethologic types of observations on frontal-lobe symptoms. This increasing impatience with formal laboratory procedures and their artificiality seemed to reflect a fear that we might be reaching diminishing returns from such tasks as delayed-response or object-reversal learning, or avoidance conditioning; they were seen as methods that were well standardized but also well-nigh uninterpretable, in terms of an animal's natural behavioral repertoire.

In the vigorous discussion stirred up by these assertions, a division appeared between those who felt that these particular laboratory procedures were just as useful now as they had ever been; these methods seemed the only ones, thus far, that had led to reliable parcellations of frontal-lobe syndromes, and had furnished clues as to how our search for underlying physiologic mechanisms might proceed. Others were more impressed with the emotional and social changes seen sometimes in man and quite regularly after orbital frontal lesions in the monkey; they urged that we search for altogether new and different methods of observation and analysis (*see* Butter and Snyder, Myers, Warren et al. this Symposium). On balance, however, it seemed to some participants that much could be gained by retaining the established laboratory procedures and adding more ethologic techniques: the two approaches seemed complementary rather than conflicting. In any case, it remains doubtful

whether the vertical and horizontal gradients of specialization of primate frontal cortex which can guide so much future work would have ever emerged without the invention of special laboratory tasks.

Before leaving these issues we should note that the choice of the term gradient must not be taken as a prejudgment against possibly sharper subdivisions among various sectors of the prefrontal cortex. The double-gradient hypothesis is offered for heuristic purposes since the currently available evidence does not conform to the notion of a functional mosaic. But only the future can tell whether two gradients will suffice, or whether the term 'gradient' is altogether appropriate. Ultimately much of the specificity of function within particular sectors might be found at the single-neuron level, and it may turn out that neurons with differing affiliations are widely interspersed.

##### *5. A parcellation unique to man: right and left frontal-lobe syndromes*

The tracing of a dual gradient of localization in the monkey's prefrontal cortex has been achieved by means of selective, but always bilateral and symmetrical ablations. Little was said at this Symposium about unilateral lesions in monkeys or carnivores (but, see Latto and Cowey 1971ab for the visual and oculomotor effects of unilateral removals from the periarcuate field in monkeys; also, earlier, Bianchi 1895, Kennard and Ectors 1938, Kennard 1939, Welch and Stuteville 1958). Yet it is the analysis of unilateral-lesion effects in man that has led to the other major advance in our current knowledge about questions of 'where', i.e. the parcellation of frontal symptoms.

This work has been almost exclusively in the hands of Professor Brenda Milner and her students, at the Montreal Neurological Institute. Her contributions to this Symposium indicate that the reciprocal specialization that characterizes man's cerebral hemispheres, in contrast to those of monkeys and dogs, can be demonstrated not only for the parietal and temporal lobes, but also for the frontal sector of the human brain. Over the last decade, since her major presentation at the Pennsylvania meeting (Milner 1964) Professor Milner could fully demonstrate that difficulties on certain sorting tasks (Grant and Berg 1948) were not only greater with dorsal than with orbital fronto-cortical removals in man, but somewhat greater and certainly more persistent, with left rather than right frontal resections (Milner 1963, 1964, 1971). Similarly, left-sided removals often produced a marked reduction in verbal fluency e.g., "name all one-syllable nouns starting with 'M' you can think of . . ."). Conversely, right-sided rather than left-sided frontal removals were followed by deficits on certain maze-learning tasks (Milner 1965, 1971).

The results for the left unilateral lesions in man are all the more

impressive because it lies in the nature of Professor Milner's sample (patients with cortical resections for relief of otherwise intractable epilepsy) that the removals from the left frontal lobe are often smaller than those from the right, since the surgeons respect Broca's area on the left. This circumstance, which she has often stressed, render her results especially secure wherever left-sided removals are found to produce greater deficits in a given task than removals from the right.

However, if there had been any doubt about the validity of these differences between man's right and left frontal lobes, they may be dispelled by the most recent experimental results from Professor Milner's laboratory. With her student P. Corsi, she has now obtained evidence for what I like to call "double dissociation of symptoms" (see Teuber 1955): two different kinds of subtle disturbances of memorizing, one after right frontal lesions but not after left, the other after left but not right. Two series of cards, one bearing abstract visual designs (like Mondrian paintings), the other bearing compound words, are presented to the patient. At various points throughout the series, the patient is confronted with test cards bearing two words, or two designs, and he has to tell which of the two words or designs had come earlier and which one last (Milner 1971, Milner and Teuber 1968).

On this kind of task, neither the group with right-sided nor that with left-sided frontal removals exhibits outright failure: both patient groups remember enough about what has been shown to them, during the training series, to be able to decide which of the words and patterns are new and which have occurred before. The trouble comes when either kind of patient has to decide which of two familiar patterns or words has come earlier, and which one last. This selective difficulty with "memory for recency" is, as Professor Milner points out, "material-specific": the patients with right-sided removals show the trouble for abstract visual patterns, but not for words, and those with left-sided removals, for words, but not for patterns.

As so often with disclosures on man, this new finding redirects our attention to those observations in the animal laboratory that have been particularly difficult to interpret in the past: the impression that the bifrontal monkey might have a rather selective defect, not in memory for past stimuli, *per se*, but in keeping track of their proper order, as in rapidly repeated delayed-response trials. The monkey acts as if he did not know which trial came most recently, and which ones before. Such breakdown in the utilization of most recent information (see Gross and Weiskrantz 1964), or in the proper distinction between more and less recent input, may go a long way towards explaining the "parsing effect" described by Pribram and Tubbs (1967) who, following an earlier sugges-

tion by Harlow, were able to show that a bifrontal monkey can solve delayed-alternation tasks, if successive trials are sufficiently spaced out in time. Yet, whatever the functional interpretation, the importance of the Milner-Corsi results for the further parcellation of frontal symptoms in man is clear: they prove a complementary specialization of man's left and right frontal lobes.

#### *6. Differences in behavioral effects of frontal lesions from surface to depth (cortical to subcortical)*

As revealing as the surface gradients (up-down and back-to-front) in monkeys, and the right-left distinction in man, are the many indications of subcortical components in the frontal-lobe syndromes of primates. What is still unclear is whether we are entitled to speak of yet another gradient in this respect — a surface-to-depth gradient of functional specialization, or whether subcortical stimulation or destruction simply replicates what one sees with corresponding manipulations of the frontal cortex.

Originally, Rosvold and Delgado (1956) were able to show that stimulation or destruction of the caudate nucleus was nearly as disruptive of delayed-response performance as was destruction of dorsolateral frontal cortex. At the Pennsylvania meeting, Rosvold and Szwarcbart (1964) specified an entire series of subcortical structures, as well as the hippocampus, as being part of a fronto-subcortical system defined by essentially equivalent losses on delayed-response or delayed-alternation tasks following selective lesions. Rosvold has extended and revised this picture by splitting it in two: he proposes that there are at least two fronto-subcortical systems, in line with the distinction between the dorsolateral and inferior-convexity divisions of the frontal cortex.

The system that pertains to the dorsolateral frontal cortex includes the head of the caudate nucleus, the lateral part of the globus pallidus, and the subthalamic nucleus: lesions in any of these structures produce some degree of impairment in delayed alternation; so do lesions of the hippocampus, although less consistently so. On the other hand, there is a fronto-subcortical system pertaining to the orbito-frontal complex, characterized by impairment on object-reversal tasks, following lesions, and this second system is said to include the ventrolateral caudate, the medial pallidum, and, further, perhaps such thalamic nuclei as the *centre médian*, ventralis lateralis-and ventralis anterior, and possibly, medialis dorsalis. With regard to this last nucleus, the difficulty remains that its circumscribed destruction often fails to mimic prefrontal cortical removals, even though the histologic picture, showing the orderly projections from the mediorsal thalamic nucleus to prefrontal cortex, is clear.

The shift from the notion of a single fronto-subcortical system to a duality of systems, corresponding to the division between dorsolateral and orbital frontal cortex, is certainly cogent, but raises the question of functional interpretation even more forcefully than before. Are we merely dealing with strictly equivalent links in an afferent or efferent chain, so that the identity of symptoms found thus far would reflect the identity of cortical and subcortical function? Or is this identity a false impression, created by the very limited range of tests employed?

Possible distinctions between the functional significance of cortical and subcortical components of frontal-lobe syndromes were discussed, in the course of the Symposium, by Cohen and Divac, among others, but the question remains perplexing. Some subcortical systems, such as the claustrum, with its close affiliation with the neocortex (see the paper by Narkiewicz, this Symposium) cry out for the kind of physiologic and behavioral exploration that is still entirely lacking for that structure. For other subcortical complexes such as the caudate, the situation is almost the opposite: there, we have a wealth of neurophysiologic and even neurochemical data, together with the superb behavioral analyses by Divac (this Symposium) and Rosvold, and their colleagues, indicating that we are dealing with a system that is far from unitary, permitting the production of prefrontal (dorsolateral) types of deficits by destruction of the head of the caudate in the monkey, and symptoms more reminiscent of the inferolateral temporal lobe syndrome by destruction around the tail (see Divac et al. 1967).

But it seemed generally agreed that a still wider range of behavioral tasks would be needed to find out whether there are not after all some important differences in the manifestations of such subcortical lesions as compared with the seemingly analogous cortical ones. A possible additional approach would be to compare the behavioral consequences of cortical and subcortical lesions under conditions where lesions are made very early in an animal's life: are the effects of certain early subcortical lesions more severe than, or qualitatively different from, the apparently corresponding cortical removals? This suggestion brings us to our second major theme, the question of 'when', or the role of time.

#### B. THE QUESTION OF 'WHEN?'

*Critically timed destruction, stimulation or  
recording as tools in analyzing frontal syndromes*

Anyone who has made excursions into the history of brain-behavior studies may have been as bewildered as I was upon first encountering von Monakow's concept of "*chronogenous localization*" (von Monakow

1914): did he mean to express the view that different structures might take on similar functions, at different successive stages of phylogeny and ontogeny? Or that identical structures might assume different functions during the course of evolution and even individual development? Or did he mean something akin to Lashley's still shocking idea that function plays over the cerebral structures successively "like the hands of a pianist over his keyboard"? The trouble with von Monakow's mysterious concept was that he probably meant all these things at once, and this frustrated most of us in our attempts at getting any meaning at all out of his term. This is a pity because this Symposium, in at least three equally important ways, can be interpreted as giving substance to von Monakow's concept of "chronogenous localization", and as carrying out much of the program of research that he vainly had called for, already before the first world war.

We have heard evidence on early vs. late lesions, on serial lesions as against single-stage removals, and on critically timed electric stimulation or recording during acquisition, retention, or performance of certain frontal-lobe tasks. Contributions to each of these topics, at this Symposium, seemed to prepare the ground for considerable advances in our understanding of frontal-lobe physiology.

### *1. Effects of frontal removals as a function of age*

One of the high points of the Pennsylvania meeting had been Harlow's account of the striking contrast between the effects of dorsolateral frontal removals in adult macaques and the virtual absence of effect (at least on delayed response) of similar removals made in the first few weeks of life (Harlow et al. 1964). This important result (first published by Akert et al. 1960) and since extended (by Harlow et al. 1968) has completely held up over the intervening years; it is in line with the earlier work by Margaret Kennard (1938), showing much less severe effects on motor function of early vs. late motor-cortex removals in macaques. In fact, taking this classical work together with subsequent studies of early removals, in kittens, of visual cortex (Doty 1961, Tucker and Kling 1966), somatosensory cortex (Benjamin and Thompson 1959) and temporal-lobe structures (Kling 1962, Isaacson et al. 1968) and of corresponding work with monkeys (e.g., Tucker and Kling 1967), the general verdict seems inevitable: if one must have a brain injury but can pick one's time, the time to have it is as early as possible. Yet I have always had grave doubts about this verdict.

In a number of studies, mostly with Rita Rudel (Teuber and Rudel 1962, Rudel et al. 1966, Teuber 1970) we tried to convey the notion that whether early lesions (at least in man) are really less disabling than

later lesions, or more disabling, or equally disabling, depends on the site of the lesion, and the nature of the task employed. The work on baby monkeys from Rosvold's laboratory, and particularly that of Patricia Goldman and Rosvold (Goldman et al. 1970, Bowden et al. 1971, Goldman, this Symposium) bears our contention out: their results bring the findings on subhuman primates into much closer contact with observations on man.

Harlow's group (Harlow et al. 1960) had shown that capacity, in the normal rhesus monkey, for solving delayed-response tasks appears rarely before the age of 4 months, and that the capacity then grows till the monkey is about one year old. He has proven that there is virtually no effect of dorsolateral frontal lesions on subsequent delayed-response acquisition if the lesions are inflicted at a sufficiently early age, i.e., before the delayed-response capacity would normally appear, nor is there any retardation in the time of appearance of the capacity subsequent to an early dorsolateral lesion. Curiously, the converse is also true: after the capacity has appeared in the normal monkey, its vulnerability to frontal lesions increases, to reach a peak of vulnerability at about one year of age (H. F. Harlow, personal communication).

In confirmation of Harlow's main result, Patricia Goldman (this Symposium) again finds no obvious impairment in delayed response, if the removal of dorsolateral frontal cortex is done in the very young rhesus monkey. In sharp contrast, however, to such escape of dorsolateral frontal function is her report of an immediate and severe impairment after orbitofrontal removals in the very young macaque: these animals huddle when in social groups, and pace restlessly when alone. They are grossly abnormal in their social interactions with other animals, and in their display of affect (Bowden et al. 1970, Goldman, this Symposium).

Such a two-part result may go a very long way towards explaining why some clinical observers of children with early brain damage have minimized the intellectual after-effects of early frontal lesions in man, while others, such as Ritchie Russell (1959) have stressed the grave effects upon affective and social development of such early lesions of the developing human brain. There is still another, and especially intriguing hint in Patricia Goldman's data: so far, at least, it looks as if the effects of early and later lesions depend not only on site of lesion (dorsolateral vs. orbital) and on the tasks employed, but on the age at which the effects are being tested: her monkeys with early dorsolateral lesions, in spite of the initial "escape" of delayed-response capacity, appeared to undergo some belated deterioration of that capacity when they were retested 2 years after the operation. Conversely, the group of monkeys

with very early orbital removals, and immediately manifest deficits, seemed to have outgrown at least part of their handicap when examined 2 years later.

How can all of these observations be brought under a single hypothesis? Patricia Goldman proposes that the consequences of very early lesions differ according to the developmental status of the cortex removed: she suggests that dorsolateral cortex might be relatively uncommitted (a suggestion made more generally for "association cortex" in the past, see Penfield 1966, Teuber 1970). By contrast, orbitofrontal cortex may be relatively committed right at birth, or very soon afterwards, to its principal functions, so that its removal would be noticeably disruptive even at that very early age.

In our discussions following this important communication, much stress was placed on finding ways of identifying some direct structural counterparts of early and late "commitment". There may be differential histologic signs. One could adduce in this connection some as yet unpublished work by Kemper and Caveness, at the Fernald School near Boston, who produced small stab wounds in the motor cortex of newborn monkeys and subsequently compared the area of these wounds, by means of modified Nauta (i.e., Fink-Heimer) stains with a corresponding area of destruction following a stab wound made in the motor cortex of a mature macaque. Their results strongly suggest that the lesions in the very young and in the mature brain lead to quite dissimilar histologic consequences: with lesions inflicted on the neonate, there is a slender cylinder of destruction with very little debris visible beyond the margins of the penetration, whereas with lesions inflicted on the mature brain, a similar cone of destroyed cortex is surrounded by a cloud of degenerating horizontal connections, primarily dendritic elements, which evidently were not transected in the very young because they had not yet had time to form.

Professor Nauta, who has aided some of these studies with his advice, pointed out in our discussions at the present Symposium that the distinction between orbital and dorsolateral frontal cortex in the monkey might, in fact, be reflected in part in a differential rate of postnatal development of dendritic connections with correspondingly different effects of cortical lesions at either site in the very young. In any case, it would seem to be an hypothesis well worth investigating, particularly since it might also help us to understand a further, and at first sight, even more baffling aspect of timing of frontal lesions: the escape of delayed-response capacity in the mature monkey after multiple-stage removals of dorsolateral cortex.

## 2. *Serial versus single-stage removals*

The sparing of delayed-response capacity after early dorsolateral lesions in monkeys has its exact parallel in a similar sparing after seriatim removals in the adult animal (Butters et al., this Symposium). This paradoxical lack of expected symptoms after multiple-stage removals puts serious restrictions upon the interpretation of ablation experiments in general, and those involving the frontal lobes in particular.

The paradox is not limited to the dorsolateral frontal regions in the monkey. In a prototypical experiment, over 15 years ago, Donald Meyer (1958) removed the occipital areas in two stages, first one side, then the other, in adult rats and found that a light-intensity discrimination taught to these animals before the first operation survived the successive removals, even though the habit would have been lost (at least temporarily) after a simultaneous and combined removal of both occipital areas.

The mechanism that underlies such striking escape of function with serial lesions is still utterly obscure; or, perhaps, one should rather say that it is the loss with single-stage removals that now requires explanation, conceivably along the lines of von Monakow's puzzling notion of "persistent diaschisis" (von Monakow 1914). But whatever the explanation, the escape with multiple-stage lesions cannot be attributed in any general way to the circumstances that in most experiments of this type one removes a particular cortical area, first from one cerebral hemisphere and then from the other, allowing for some readjustment in between. That seriatim removals in bilaterally symmetrical instalments can be just as compatible with survival of function, had already been suggested by the extensive serial decortications performed on monkeys by Travis and Woolsey (1956). In the adult monkey even very partial decortications (removing the sensorimotor strip) tend to render the animal incapable of standing and walking. Yet such postural control was preserved in Travis and Woolsey's animals who had undergone near-total decortication but in multiple stages; at each stage, a small bilaterally symmetrical band of cortex had been removed.

Sparing of function appears to occur in analogous fashion with serial removals of somatosensory cortex in rats. Such removals, if performed in a single stage, abolish roughness discrimination (Zubek 1951); in a recent study, Finger (1971) resected a bilaterally symmetrical ridge of tissue from within the somatosensory strip, then waited, and then removed the two parallel bands of remaining somatosensory cortex, without observing any loss in roughness discrimination. There is thus little doubt that the escape of delayed-response capacity after serial dorsolateral frontal removals in monkeys is representative of a much more general phenomenon. But how can it be explained?

A number of approaches to this kind of paradox have been proposed in the past. The role of subcortical structures has been invoked, as has been the possible role of remaining cortex. For instance, it has been postulated that after serial cortical removals, subcortical structures can function vicariously for absent cortex; by contrast, abrupt (single-stage) withdrawal of cortex has been thought to exert a suppressive or disruptive influence upon the subcortical nuclei, in keeping with the notion of long-lasting 'diaschisis'. Unfortunately, neither the idea of vicarious functioning and the reorganization it implies, nor the idea of disorganization by diaschisis, have thus far received much support in the form of physiologic or histologic evidence. Yet such evidence must be sought, if the paradoxical escape of function after serial lesions is to be explained.

There are serious difficulties with the postulated role of subcortical structures in the supposed reorganization of function. In the course of the Symposium, Divac reported that he had removed frontal cortex (gyrus proreus) in cats, and then trained those who had shown losses in delayed-response until they again passed that test. He then destroyed their anterior caudate nucleus but found no return of the initial delayed-response deficit. Such a negative result is important even though there are numerous other subcortical and cortical structures that could be implicated in the apparent escape of function after serial frontal cortical lesions.

There may be a clue in observations made recently by N. Butters (personal communication) who finds that serial removals from orbito-frontal cortex in adult macaques fail to forestall the appearance of those symptoms that are typical for single-stage orbito-frontal destruction. If his preliminary results are confirmed we would have a striking parallel between the initial escape of dorsolateral function after single-stage lesions inflicted very early in life and after multiple-stage lesions inflicted on adults, and there would be a corresponding parallel between the demonstrated breakdown in function after single-stage orbito-frontal lesions in the very young and after serial orbito-frontal lesions in the adult. Could the hypothesis of different degrees of commitment of cortex apply in both instances?

What is obviously needed are histologic and histochemical, as well as neurophysiologic explorations around and below the areas removed, comparing effects of single-stage with those of multiple-stage removals, and looking for contrasts in this respect between orbital and dorsolateral frontal cortex. The reward for such a search might be that we could find what has really never been properly searched for, a structural basis for Monokow's diaschisis. At the same time one should look for possible modifications in the discharge patterns of single units, both in the imme-

diate vicinity of such cortical removals and in some more remote but anatomically related regions. In the case of the dorsolateral frontal cortex these areas might include the cingulate cortex or the mediodorsal thalamic nucleus, or the caudate. The problem is not one of scarcity of possible sites at which to look for signs of diaschisis, or disorganization, or of reorganization, but rather of having too many of such possible sites to consider. But the search is worth-while.

For it cannot be stressed enough that we need a deeper understanding of what ablations mean in terms of the reaction of remaining tissue. Without such an understanding we cannot really offer any firm conclusions about the classical results of apparently total loss of certain functions, nor can we deal effectively, without such knowledge, with the seeming escape of function after very early lesions, or after lesions inflicted at maturity but in successive stages.

Some potential guideposts for such explorations can be found in old and new experiments on electrophysiologic changes in tissue surrounding certain lesions. There is the half-forgotten study of Glees and Cole (1950) who made removals from the primary hand area in the monkey and then studied the edges around the lesions electrophysiologically in the hopes of detecting some possible signs of reorganization of function. There is the recent disclosure (by Wickelgren and Sterling 1969) of drastic changes in single-unit activity in the cat's superior colliculus upon removal of visual cortex (see also Sprague 1966), and the still more recent and unpublished observations in the MIT laboratories by Berman and Cynader, working under Professor Peter Schiller's guidance, who found marked changes in receptor-field characteristics of neurons (e.g., a decrease in modality-specificity) in the superior colliculus of the monkey when the other superior colliculus had been destroyed. What seems to be needed are systematic studies that combine ablation and recording techniques in one and the same preparation.

### *3. The use of critically timed cerebral stimulation or recording in monkeys during acquisition and performance of frontal-lobe tasks*

The puzzling aspects of cortical ablation as a technique make one eager to look at supplemental ways in which the time factor might be exploited in analyzing frontal-lobe function and dysfunction. Such an alternative way of searching for chronogenous localization requires that we take the term in yet another one of its multiple meanings: the sense in which it refers to the successive engagement of different cerebral structures during the performance of certain tasks, or even during their acquisition and retention.

Work on this problem has been pursued systematically, over the

years, by Professor Stamm and his co-workers, and, at this Symposium, John Stamm as well as Shoel Cohen reported on particularly telling applications of this approach. Their techniques have included the registration of transcortical steady-potential shifts during delayed response training and testing as well as attempts at overtaking the cerebral processes presumably involved in delayed response by applying momentary disrupting or facilitating electric stimulation. Only the earliest phases of this kind of work were reported at the Pennsylvania meeting, and many of the requisite techniques, including the recording from single units in the prefrontal region (Bekerman and Encabo, this Symposium, Kubota et al., this Symposium, *see also* Fuster and Alexander 1971, Kubota and Niki 1971) have only been introduced in the last few years.

By recording from indwelling, non-polarizable electrodes, in unanesthetized monkeys, John Stamm had been able to show that there were negative steady-potential shifts that arose over the dorsolateral prefrontal cortex during delayed-response trials. These voltage shifts seemed to reach a peak at the end of the cue presentation and the beginning of the delay period (Stamm and Rosen 1969). Yet, as Stamm pointed out, the crucial task is to define these apparent relationships between local slow-voltage changes and particular aspects of delayed response. For there are rather a number of slow voltage changes that can be recorded from monkey and man under a variety of circumstances and from various cerebral regions.

This work began with the pioneering studies of Köhler and Held (1949) who derived direct currents from the occipital scalp of normal man during the inspection of slowly moving visual patterns. It continued with the discovery of the famous frontal 'expectancy waves' obtained in man during reaction time experiments, as much as 200 msec and more before the overt reaction (Grey Walter's contingent negative variation, Walter et al. 1964; *see also*, for the monkey, Donchin et al. 1971). Similarly, there are various 'readiness' or 'motor potentials', preceding the onset of voluntary movements of eye, head, hand or foot (Kornhuber and Deecke 1964, 1965, Gilden et al. 1966); some of these steady potentials are best recorded from precentral regions. Lastly, there are more diffuse steady-potential shifts during reinforcement on rewarded trials, presumably related to the alimentary reward and not to the consummatory movements, and first described by Rowland for cats in conditioning experiments (Rowland and Goldstone 1963, Rowland 1968). How then can one identify a direct-current shift specific for delayed response in this welter of steady-potential phenomena?

The new findings by Stamm and his colleagues leave little room for doubt: there are three types of steady potential shifts during delayed

response in monkeys, and only one of these seems specifically related to those neuronal events that seem involved in the acquisition of that task. Between trials, and preceding the onset of the cues, the monkey exhibits a typical "expectancy wave" best recorded over the prefrontal regions but not limited to them. At the end of any given trial, and thus following the reward, the monkey shows a "reinforcement shift", apparently rather diffusely distributed over frontal and temporal regions, quite analogous to the reward-related waves in Rowland's cats. Neither the expectancy potential nor the reinforcement potential are in any way related to an animal's mastery of the delayed-response task; they appear irrespective of whether the monkeys is reaching criterion or not. However, there is a steady potential shift recordable from the middle and posterior portions of the sulcus principalis which is clearly related in time to the end of the cue presentation period and to the onset of the delay, and this potential seems to be the only one of the three that is highly correlated with correctness of responses (*see Stamm, this Symposium*). For this reason, Stamm feels justified when he interprets this steady-potential shift as an electric sign of memorization; not the retention or read-out of a trace, but its initial registration, early in the delay period during delayed response trials.

Accordingly, Stamm has now tried with some success to facilitate correct delayed-response performance and its acquisition, by impressing anodal current upon the monkey's sulcus principalis during trials; this experiment attempting facilitation by negative direct current is complementary to the well established disruptive maneuvers that involve the application of ordinary pulsed stimuli to prefrontal regions during delayed response (Stamm 1969, Cohen, *this Symposium*), in line with the classical technique of disrupting delayed response in the monkey by caudate stimulation (Rosvold and Delgado 1956). But what specific process is it that is being reflected in the spontaneous steady-potential shifts at the beginning of the delay period, and susceptible at that time to facilitation or disruption? Is it an increased engagement of kinesthetic analyzers as Konorski suggested (1967)? Or some crucial monitoring of the animal's own motor commands, or a registration of a specific intention as to how to move (which way to turn) after the delay-period is over (Cohen, *this Symposium*; *see also Teuber 1964*)?

It should be clear that we cannot describe the process in the sulcus principalis as memorization *per se*; it seems to be a highly restricted mode-specific form of memorizing, because effects of critically timed stimulation elsewhere in the brain show that different kinds of memorizing are vulnerable to stimulation at sites other than this particular pre-frontal region. Thus, Cohen (*this Symposium*) reported that stimulation

through electrodes implanted in monkeys in sulcus principalis, and in inferotemporal region, as well as in head and tail of caudate, had quite different effects, depending on the kind and the place of stimulation. Confirming earlier results, stimulation of principal sulcus, or head of caudate, disrupted delayed response and did so maximally if the stimulation occurred early in the delay phase, whereas stimulation of inferotemporal cortex or tail of caudate was most disruptive at cue-onset. Presumably, the inferolateral temporal, and posterior caudate stimulation somehow prevented the proper perceptual analysis of the test display, whereas the prefrontal and anterior caudate stimulation interfered with the proper preparation of the subsequent motor response. In fact, Cohen (this Symposium) went further in his own interpretations by suggesting that one should be able to distinguish, eventually, the relative contributions made by prefrontal cortex from those made by anterior caudate; he proposed by means of a bold flow diagram, that both prefrontal cortex and head of caudate participated in the processing of information regarding 'active, self-produced movement' (as suggested by Teuber 1964, 1966, Teuber and Proctor 1964, *see also* Potegal, this Symposium); moreover, Cohen proposed that the prefrontal cortex did so by handling inflow of information, and the caudate by handling outflow.

By his own admission, this bold suggestion will need much more supporting evidence, but without any hypotheses of this sort, the evidence might remain buried in masses of unanalyzed physiologic data. Ultimately, of course, single-unit recording from appropriate samples of prefrontal cortical and from various subcortical neurons will have to be obtained to settle these issues. What is available thus far in this respect is truly tantalizing (Fuster and Alexander 1971, Kubota and Niki 1971). It has of course been known for some time that many cortical neurons increase their rates of discharge during negative surface-potential shifts (*see* Caspers 1963) and also whenever an anodal current is impressed upon the cortex (Creutzfeldt et al. 1962). It is therefore not surprising that there should be such increased unit activity in the sulcus principalis region recordable during the onset of a delay period, on delayed response (Fuster and Alexander 1971), or delayed alternation trials (Kubota and Niki 1971). What is intriguing is the report by Kubota (Kubota et al., this Symposium) that he could identify two different kinds of units in the monkey's sulcus principalis, and the same two kinds in the mediodorsal thalamic nucleus. At both sites, there are neurons (Kubota's D-neurons) that fire at the onset of the delay, on delayed alternation trials, and maintain their discharges, whereas another set of neurons

(Kubota's E-neurons) fire just prior to the motor response. A curious additional observation by Kubota is that the monkey's caudate from which he has also recorded, seems to contain only E-units ('excitatory') but no D-units ('delay' units) at all.

We are calling these results tantalizing because they are obviously full of promise for a closer approach to the 'what' and 'how' of frontal-lobe function, but as Kubota himself underlined, these observations need a great deal of supplementation particularly by detailed monitoring of the animal's behavior during acquisition and performance of delayed alternation. In the MIT laboratories, continuous monitoring of head, eye and hand movements of unanesthetized monkeys held in primate chairs has revealed a great variety of neuronal response patterns in periarcuate and more recently in *principalis* regions of prefrontal cortex (see below, also Bizzi 1968, Bizzi and Schiller 1970). In apparent contrast to Kubota's finding of E-neurons discharging *prior* to the "responses" on delayed alternation, Bizzi and Schiller find large numbers of units discharging *during*, but not before or after, specific eye and head movements. It may turn out that some of the neural events thus far recorded during delayed response tests (Fuster and Alexander 1971), or delayed alternation (Kubota and Niki 1971), need further study under conditions where the eye, head, and hand movements of the animal can be continuously registered, concomitantly with the recording from single prefrontal or thalamic or caudate units. But before turning to these central issues of 'what' and 'how' we should stress a suggestion made by Kubota in the discussions during the Symposium: he believes that his E-units fire before the onset of any given response provided that response is learned; otherwise, they fire, he maintains, during or after the response. In the light of these suggestions, is it imprudent to predict what the next steps in the development of our field might be?

#### C. THE QUESTIONS OF 'WHAT' AND 'HOW'

##### The search for the meaning of frontal lobe syndromes in terms of normal physiology

As we have seen, the questions of 'where' and 'when' lead us inexorably to the still more difficult and yet more important question of 'what' and 'how'. Upon this goal all other efforts converge: to come to know how to interpret the symptoms of frontal pathology in terms of normal function and how to understand these normal functions, if possible down to the single-neuron level. At the Pennsylvania Symposium I proposed (Teuber 1964) that clues to such normal physiologic mechanisms might be derived from studies of man. Accordingly I shall describe, albeit very briefly, how a series of earlier studies from our laboratories

had made us look for a unifying hypothesis about the frontal lobes and their function, and how this hypothesis has fared in relation to the more recent work on animal and man, much of which has been reviewed in the preceding sections of this chapter. After that I shall describe some ongoing physiologic and behavioral experiments that might lead to the much needed crucial tests of our hypothesis.

### *1. Clues from earlier observations on man*

It takes only limited experience with the behavioral consequence of prefrontal lesions in man in order to recognize that there is the bewildering variety in man's reaction even to fairly restricted and non-progressive lesions. Thus one can concentrate one's attention on cases of penetrating trauma of prefrontal structures, as we have done, and exclude frontal-lobe tumors with their invasive and often irritative pathology, and their tendency to exert remote effects upon other parts of the brain. Even then, by focusing on series of cases of fairly stable cerebral lesions from penetrating shell-fragment wounds, or other foreign bodies (see Teuber 1959, 1964, 1969, Semmes et al. 1960, Teuber et al. 1960) one notes that some patients will exhibit continuous and obvious alterations in demeanour, ranging from over-activity and impulsiveness, in certain cases, to an apathetic and seemingly slothful attitude, in others. Yet, for every patient with such obvious changes, there are many others who show at most subtle alterations in behavior, often brought out only in especially contrived laboratory situations.

Presumably, size and site of lesions determine many of these differences in man: orbital lesions, as already mentioned, are more readily followed by evident changes in affect and impulse control, whereas dorsal lesions are likely to produce more complex changes, which may strike an onlooker, in severe cases, as a diminished capacity for making and evaluating plans, and in extreme forms, as a curious inability in the initiation and termination of action. Rarely after trauma but more often with progressive space-occupying lesions, these disorders may culminate in the familiar automatisms of forced grasping and groping (Schuster 1923, Seyffarth and Denny-Brown 1948). Yet even with seemingly identical lesions, there often are quite unaccountable differences in these gross manifestations of frontal-lobe dysfunction, as if patients varied greatly in their tolerance for tissue loss from their frontal lobes.

Faced with such variability of frontal-lobe syndromes in man, one turns to more formal laboratory tasks in the hope of uncovering those mild forms of dislocated functioning that many groups of patients may have in common. If properly designed, such laboratory tasks should help one to uncover what it is that underlies both subtle and gross altera-

tions in behavior; yet the choice of tasks is crucial. It is fairly easy to set down which tasks are not appropriate for this purpose: as we have pointed out, time and again (Teuber 1964, 1969, Teuber and Weinstein 1958, Weinstein and Teuber 1957) ordinary intelligence tests are especially unsuitable; on the other hand, it is equally futile to apply to men with frontal-lobe injuries those laboratory tests that have been found so sensitive to frontal-lobe pathology in subhuman primates.

Quite recently (Corkin and Teuber, unpublished data) we have been able to repeat an earlier study of pre- and post-injury test intelligence (Weinstein and Teuber 1957) in a new group of 121 men with battle injury of the head (*see* Teuber 1969). As in the earlier study, we were able to obtain the pre-injury intelligence test scores in the majority of the cases, and then re-test those patients with an equivalent version of the same test (the U.S. Army General Classification Test) a varying number of years after their injury had been sustained. The group with frontal injury showed little loss, as compared with the group with left parieto-temporal lesions in whom the loss on this kind of test is substantial, even if one excludes all those with persistent signs of language disorder. Yet, just as in the earlier studies (*see*, for summary, Teuber 1969) the group with frontal lesions shared with all other lesion groups a marked impairment on a more general, nonverbal task: the hidden-figure test (*see* Teuber and Weinstein 1956), and those with bilateral frontal penetration were almost as severely impaired on that task as were those with biparietal involvement. As we have said in the past, this test of hidden-figures which requires the detection of particular line patterns embedded and concealed in other line patterns is sensitive to some non-specific effects of penetrating brain injury in man: other tasks are needed to identify those regionally specific changes that coexist with the general non-focal kind of impairment.

It would be simple, if tests specific to various frontal lesions in man could be imported, so to speak, from the animal laboratory. But delayed-response and delayed-alternation tests are not sensitive enough, as one ascends the evolutionary scale beyond the monkeys. As Rosvold has noted, these tests that are so specifically vulnerable to dorsolateral pre-frontal lesions in the rhesus monkey, are only transiently affected by such lesions in chimpanzees (Rosvold et al. 1961). In man, the ordinary delayed-response and delayed-alternation test is quite insensitive to frontal lesions unless the lesion is of a sort that involves more widespread impairment of brain function, as in neoplastic disease (*see* Chorover and Cole 1966).

The insensitivity of such tests as applied to adult man may derive, at least in part, from man's ability to encode essential features of the

test situation in words. We once were startled by a patient, with massive bifrontal trauma, who returned to our laboratory after an absence of five years, and, pointing to a table in a corner, announced: "I recognize that table! That's where you played that game of hiding a penny under one of two cups, and the last time you did it, you had the penny under the cup on the left!" Encoding in words may be one of the reasons for making delayed-response tests less appropriate for man, but Rosvold's observation on the rapid recovery of delayed response capacity in chimpanzees suggests that this role of language may only be part of the story.

As to the tasks that did turn out to be fairly selectively sensitive, in our hands, to frontal, as compared with non-frontal penetrating wounds of the human brain, there are at least four (Teuber 1964, 1966, 1969); all seem to merit, in varying degrees, our old interpretation of being predominantly 'perceptual-motor' or 'spatial' in nature, in the more restricted sense of the term spatial given to it earlier in this chapter when we discussed the signs of periarcuate removals in the monkey. The tasks include the setting of a luminous line to the apparent vertical, with head and body tilted (a visuo-postural conflict situation, as we have called it: Teuber and Mishkin 1954); searching for visual targets in a complex array of such targets, with active eye-and-head movements (Teuber 1964, *see also* Luria et al. 1966, Luria 1971); responding to figures with ambiguous (reversible) perspective (Cohen 1959, Teuber 1960, 1964); locating positions on one's own body in keeping with designated locations on a series of pictures of the human body, showing back and front views in an irregular sequence (Semmes et al. 1963).

These four tasks formed the basis for our earlier proposal that one aspect at least of normal frontal-lobe function in man must involve orientation, not to external landmarks as such, but in relation to one's own standpoint, and shifts of one's standpoint. We postulated that the integrity of certain prefrontal structures might be important in man by permitting him to take his own posture and movements into account, in gauging external stimuli, and this monitoring of movements, we contended, should be anticipatory: it should not merely imply that we can assimilate feedback from the periphery, after the execution of particular motor acts, but that we should be able, by a feed-forward type of mechanism, to predict the anticipated consequences of our actions.

## *2. The hypothesis of a corollary discharge: present status*

These notions add up to our hypothesis of a 'corollary discharge' as the distinctive feature of normal frontal-lobe physiology. The hypothesis states, in its simplest form (*see* von Holst and Mittelstaedt 1950,

Sperry 1950, Teuber 1960, 1964, 1966; for critique see MacKay 1966), that active, 'voluntary' movements involve two sets of signals, rather than one: the classical downward discharge to the effector-organs, and a simultaneous, central discharge, from frontal to more posterior regions of the cerebrum, that pre-sets the sensory system for the anticipated consequences of the motor act. In this way, the hypothetical 'corollary discharge' becomes a physiologic marker for the 'voluntariness' of self-initiated movement, and different degrees of disruption of the corollary mechanism would become manifest as different degrees of compulsiveness, or of abnormally stimulus-bound behavior. Thus, in the case of visually guided reaching, or eye-hand coordination, this kind of disorder would appear in its extreme form as compulsory 'reflex' grasping and groping, in which the patient cannot 'voluntarily' release his grasp, and follows visible objects in a robot-like fashion with eyes and hand, as if drawn by a magnet. In a milder form, the same sort of difficulty might be represented by the curious hyperfixation of Żernicki's cats (this Symposium) with anterior sigmoid or proreal lesions.

From the outset, it was apparent that our broad formulation of the corollary discharge hypothesis went beyond the phenomena on which it had been based. We had less than a handful of tasks, all primarily involving orientation of a restricted visuo-spatial or visuo-motor sort, and if some of these tasks did not involve overt motor output (the reversible figures, the body-scheme tests) then there was at least some virtual motion such as a change of perspective that seemed to be demanded of the patient. Yet the interpretation we offered was made so wide in its implications, in order to move us closer toward three goals: first, to have a framework for functional interpretations of frontal-lobe symptoms that might accommodate experimental findings for subhuman forms as well as for man; secondly, to be able to account for new findings for man, beyond those few upon which the hypothesis was originally based; and, lastly, to provide guideposts for a concerted search for actual physiologic mechanisms of corollary discharge. Some moderate advances along each of these three tracks, since the time of the Pennsylvania meeting, can now be recorded.

The particular tasks for man, on which we had concentrated our earlier efforts, are most reminiscent of those behavioral tests for the subhuman primate that were found to be related to the transitional cortex between precentral and granular prefrontal fields and to structures in the head of the caudate. But our approach could also be extended, fairly easily, to those aspects of the delayed-response and delayed alternation tasks that are 'spatial' rather than mnemonic. Thus, the difficulty of our groups of patients with frontal lesions in the tilted line

task (Teuber and Mishkin 1954) appeared to be neither purely postural (most of these men could adjust their posture quite well to the gravitational vertical when blindfolded in the tilting chair), nor was it purely visual because they did well in gauging the visual vertical as long as their body was upright.

Their trouble, then, was quite analogous to the root difficulty attributed by Ławicka to her dogs with proreal lesions, and their consequent inability to relate exteroceptive to interoceptive cues, or to keep track of external positions in relation to their own (postural) starting point. Such an interpretation of at least one aspect of the difficulty (Professor Konorski speaks of a breakdown in 'kinesthetic analysis') reappears in Potegal's insistence (this Symposium) upon a distinction between egocentric localization and relative localization; he found that caudate lesions, even in rodents, significantly impaired egocentric but not relative localization, just as Łukaszewska could show a diminished reliance on response-produced cues in maze-running by rats with anterior ('frontal') lesions (this Symposium, *see also* Gross et al. 1965 for quite similar results, and Leonard 1969 for the anatomic delineation of 'prefrontal' cortex in rats). It should be noted that soon after the Pennsylvania meeting we were able to prove, with Proctor, that the visuo-spatial task first used for men with frontal trauma (Teuber and Mishkin 1954) was also severely impaired in patients with basal ganglia disease (Teuber and Proctor 1964, and Proctor-Bowen 1969), has since then demonstrated a breakdown in visuo-motor tracking in monkeys with caudate lesions). Equally relevant are the elegant analyses of variations in delayed-response testing for monkeys by Gentile (this Symposium) in which she can make the classical task more readily soluble by requiring her monkeys to develop different degrees of force in lifting the differential cues.

Yet in spite of all of this pleasant convergence of evidence from different species and different test situations, there remains the suspicion that there are important aspects of behavior that were left out of our earlier considerations, and this is suggested most definitely by two tasks that have now turned out to be clearly sensitive to prefrontal lesions in man: the so-called Wisconsin version of a card-sorting test (Grant and Berg 1948, Milner 1963, 1964, and this Symposium), and the Milner-Corsi demonstration of a subtle but undeniable memory disturbance for 'recency'. Beyond that, there is the persistent problem of the orbito-frontal syndromes: can one ever relate the affective changes, predominantly associated with orbital lesions, to the original form of the corollary-discharge hypothesis?

At the Pennsylvania meeting, there emerged a seeming discrepancy

between the results of Professor Brenda Milner's group in Montreal and our own results, in Cambridge, with regard to the applicability of sorting tests to men with prefrontal lesions. Professor Milner had reported that groups of patients with dorsolateral fronto-cortical resections for relief of epilepsy showed definite and characteristic losses on the Wisconsin version of a test of sorting and categorizing (Milner 1963, 1964), whereas our own experience had been that the impairment after frontal lesions on that test was relatively slight, and certainly much less severe than after comparable left parieto-temporal involvement (Teuber 1964).

At that time already, the suggestion was made that this discrepant outcome might be due to differences in the administration of the task. Professor Milner followed the version of Grant and Berg (1948), and gave her patients no warning of impending shifts in the correct principle of sorting from color to form, and from form to number, whereas our own technique had been to give ample warning to our patients about such shifts in categories, before the onset of the sorting task. When our patients were retested with the more stringent technique, however, the differences in results disappeared (Corkin and Teuber, unpublished data). Thus, we can no longer question the existence of a specific difficulty in sorting and categorizing, after prefrontal lesions in man. But how should this deficit be interpreted?

No simple visuomotor or spatial interpretation would seem to be adequate; the patients evidently fail for several other and possibly mutually independent reasons: (i) in some instances they seem to have genuine trouble in discovering the correct principles of sorting; (ii) quite often, they fail by persisting in the application of principles that have been correct but are no longer so, as they move through the sequence of trials, or (iii) they can fail by inexplicably abandoning a correct principle for the sake of another one that has not yet become appropriate within the series of presentations. It is far from satisfactory to say, merely, that there is trouble with induction of principles, and with the sequential structuring of the patient's actions on a complex task; to put matters this way might suffice as a description but fails to uncover the roots of the patient's difficulties. But some clues can be derived from the way in which some patients comment on what they are doing.

We used to be much impressed (Teuber 1959) with those patients who would take one look at the set of cards, at the beginning of the test, and announce without hesitation that the test could be done by "color, form and number". But what follows upon this swift induction of all of the correct principles can be quite different from what one

expects. There is the patient who then proceeds to say (correctly): "You are probably starting with color — so that if I put this card down, it will be wrong? You see — I am right — this one is wrong! And this one — wrong! and wrong again!" He proceeds in this fashion by contradicting in his actions what he can announce verbally as the correct procedure, evidently aware of the contradiction but incapable of avoiding it.

This bizarre kind of behavior has received systematic investigation by Professor Brenda Milner in her analysis of failures on card sorting and of 'rule breaking' on a maze test (Milner 1963, 1964, 1965, and this Symposium). Luria, Pribram and Homskaya (1964) have also commented upon this kind of symptom, but called it a defect in error-evaluation. More recently, Konow and Pribram (1970) have insisted that it involves a failure in error-utilization; these patients often recognize their errors, but cannot act upon that recognition. The symptom, when it does appear, impresses one as a curious mismatch between intention and action, and it is for that reason that we believe it compatible with an extension of our corollary-discharge notion.

Still more tenuous is the possible relationship between our central hypothesis and the important Milner-Corsi results on tests of 'memory for recency', which indicated a definite 'frontal' symptom in man, characterized by a failure to recall the specific temporal order of recent test trials, although each trial can be recalled as such (Milner 1971). It will be remembered that these results were particularly impressive because they carried the further 'local signs' of right vs. left frontal involvement: the trouble with 'memory for recency' seemed more marked for non-verbal (pictorial) material after right frontal lesions, and for verbal material after left frontal lesions (Milner 1971, and this Symposium). As we pointed out earlier, this trouble in man reminds one of those aspects of delayed-response and delayed-alternation difficulties in the monkey that have been interpreted as an inability to keep in mind which test in a series of trials came last, and which one is current (see Gross and Weiskrantz 1964). Or can one assimilate the Milner-Corsi results with the point made by Lawicka (this Symposium) when she ascribes to her dogs with proreal lesions an 'increased conditionability' to actual stimulation, which then keeps them from reacting to a relevant earlier stimulus?

These questions are obviously central to the crucial issue of unity vs. diversity of frontal-lobe syndromes, and the notion of gradients of functional specialization might have to be, once more, invoked. The frontal contributions to the regulation of action may appear under the guise of 'accounting for one's own posture', with more posterior locali-

zations, and under the guise of maintaining intentions over time, and of ordering recent actions in proper temporal sequence, with more anterior localizations along the frontal surface. Yet what is least clear, among all these conjectures, is the possibility or impossibility of extending the corollary-discharge hypothesis to the orbital surface, applying it, so to speak, to what we have called the vertical gradient, from dorsolateral surface to the inferior-convexity of the frontal lobes.

The way in which the emotional changes after orbital lesions present themselves in man is curious, and at least as variable as all the other symptoms after frontal-lobe involvement in man. Rapidly expanding lesions may lead to marked lability of moods, but uncomplicated trauma is more typically associated with persistent mild elevation of mood or its converse, a moderate depression, though future work with fractional lesions might be able to dissociate these kinds of changes. Even in the (rare) cases of 'euphoria' one does not gain the conviction that the patient is truly joyful; and the facetious patient, with his compulsive wisecracking or punning, seems really quite devoid of mirth. What is most frequently seen is either a lack of continuity of emotional reactions or a more general shallowness, the so-called flattening of affect. Could all of these phenomena be interpreted together as an impairment in the proper anticipation and recall of moods?

Professor Nauta (this Symposium) has made a bold attempt at extending the corollary-discharge notion along these very lines: he points out that a normal person, in contemplating and weighing different possible courses of action, might say to himself: the idea of doing such and such 'turns my stomach'. What Professor Nauta wishes to imply is that vicarious, anticipated and remembered internal states, of an autonomic and visceral sort, might function quite crucially in the evaluation of action.

We have little more than straws in the wind, in trying to assess the applicability of these notions to the possible functions of frontal cortex, but we must recall the curious effects of various prefrontal lesions, in animal and man, on their reactions to pain. The superb experimental analyses of reactions to painful shock, in cats and dogs, by Zieliński (this Symposium) make it clear that no simple threshold change can be involved, nor are there any obvious alterations in the autonomic reactions to shock, e.g., in heart rate, as shown by Soltysik, Jaworska and Szafranska-Kosmal (this Symposium). What is affected by certain prefrontal lesions seems to be the latencies of response to shock, and as Zieliński has shown, the more so the longer the interval between conditional and unconditional stimuli (Zieliński, this Symposium). Could this be related to the well-established failure of some patients, after

frontal lesions, to anticipate pain, even though their pain-thresholds are unaltered, and they tend to withdraw their limbs, 'involuntarily', upon venipuncture as much as before their frontal lesions, or actually more so? The relief afforded by various surgical attacks upon the frontal lobes, in cases of intractable pain in man, has usually been interpreted as a loss in the ability to worry about future pain, and not as an alteration in pain sensitivity.

We thus return to our old contention that there is some unity in the diversity of frontal-lobe symptoms, because all of the superficially different symptoms have some family resemblance. Depending on species and localization of lesion, the behavioral pathology after frontal-lobe damage is differently expressed, but across those differences, there are more general features, and these can be traced to our central theme: that the prefrontal cortex, in all of its presumed functions, is neither sensory nor motor, but supports those processes that convey information in the central nervous system in a direction opposite to the classical one: not from input to output but conversely, by corollary discharges that modulate sensory systems in anticipation of future change. But how far have we come in our effort at casting this theoretical physiology into the form of real neurons?

### *3. Direct tests of the corollary-discharge hypothesis: from symptoms to functions*

Work in the MIT laboratories, both before and after the time of the Pennsylvania symposium, has given strong support to the notion that one should look for a direct physiologic proof of corollary discharge and for a special role of the prefrontal structures in this regard. To begin with there has been an accumulating evidence for a profound difference between active and passive movement in mediating sensorimotor adaptation. The prototypical experiments in the MIT laboratories — those by Professors Held and Hein and their co-workers — have been concerned with those critical conditions under which normal man can adapt his perception and his perceptual-motor coordination to a deliberately rearranged sensory input (Held and Bossom 1961, Held and Hein 1963, Held 1968).

In a typical experiment of this sort, a normal adult is fitted with distorting (prismatic) spectacles, so that whatever he sees is systematically displaced from its true location and all lines appear subjectively curved and tilted, in keeping with the distortions imposed by the optics of the prism. After wearing such spectacles for, say, an hour while walking actively about, in a normally structured visual environment,

all of these displacements and distortions are very much diminished. The prism-wearer will no longer misreach for visual objects, and lines appear considerably less curved, and less tilted. Upon abrupt removal of the spectacles, the initial distortions are reinstated to their full extent but with opposite sign: the prism-wearer will transiently misreach in a direction opposite to the one initially induced by the prisms. Thus the extent of this negative after-effect will mark the degree of adaptation.

However, all of these adaptive changes are precluded if the prism-wearer instead of walking actively about is transported passively in a wheelchair. In fact in one version of the basic experiment, two men are exposed to a normal environment wearing identical prismatic spectacles; one walks actively about while pushing the other over the same path in a wheelchair. At the end of the hour the active observer has almost fully adapted, whereas the passive observer has not adapted at all. Under such conditions only active exposure adapts; we would say that only active exposure involves corollary discharge and these discharges are the vehicle of normal adaptation.

Taking his clue from these types of experiments, a former student of Professor Held's, Joseph Bossom, working in H. E. Rosvold's laboratory, has explored prism adaptation in monkeys (Bossom 1965). He found that under conditions of active reaching for visual targets, normal rhesus monkeys will adapt in approximately 8 hr to prismatic spectacles, to which a normal adult man might adapt in less than an hour. Such adaptation by the monkey is not significantly hampered by subtotal lesions placed bilaterally in the occipital, or temporal, or parietal lobes. Only certain bilateral prefrontal lesions have thus far been found to prevent adaptation to prisms.

As one might have expected, one of the effective lesions (and the earliest one to be explored by Bossom) has been the periarcuate field, roughly coterminous with the monkey's frontal eye-fields. More recently, however, Bossom (who is currently at the MIT laboratories) has also implicated sulcus principalis and anterior caudate, with the most effective lesion being one placed bilaterally in the head of the caudate nucleus. Admittedly this support for our corollary discharge notion remains indirect until the discharge itself has been demonstrated on the neural level; some of the most recent work in the MIT laboratories has brought us closer to that goal, although it would be quite premature to say that the goal has been reached.

It should be evident that power of single-unit recording varies directly with one's ability to define an adequate stimulus: the great advance in our understanding of visual-cortex physiology has obviously

come about in that way and the same can be said for the somatosensory cortex (Mountcastle 1957, Hubel 1958, Hubel and Wiesel 1960). But it is in just that respect that the prefrontal cortex remains so refractory. If it is, as we have suggested, neither sensory nor motor, how can we read its neural code?

At the present Symposium, two kinds of approaches to this problem were represented: the work of Kubota, already reviewed (Kubota et al., this Symposium), and that of Bekerman and Encabo (this Symposium). These two approaches are almost polar opposites: Bekerman and Encabo proceed systematically and descriptively, mapping out unit responses in a large number of neurons of the mediodorsal nucleus, elicited by electrical stimulation of various regions of the cat's prefrontal cortex. In contrast, Kubota records boldly from individual neurons in unanesthetized, 'behaving' monkeys, with microelectrodes in the mediodorsal and caudate nuclei, and in prefrontal cortex around the sulcus principalis. He does so during delayed-alternation performance, in the hopes of finding direct correlations between neuronal discharges and different essential aspects of the animal's behavior.

The approach by the investigators at MIT notably Bizzi, and Bizzi and Schiller, can be located between these two extremes: they too record from unanesthetized monkeys but, as we have already pointed out, they are continuously monitoring eye and head movements. The correlations that have turned up are unexpected, and quite fundamental.

Within the periarcuate field in the dysgranular frontal cortex (Bizzi 1968, Bizzi and Schiller 1970), they found a great many units that discharge in relation to active movements of the monkey's eyes or the monkey's head. These relations have an exquisite degree of specificity. Thus a given neuron may tend to fire quite selectively upon rapid (saccadic) eye movements to the left and up by, say,  $15^\circ$ . Another unit may fire only during slow pursuit, and only during such pursuit movements that take the eyes from a particular position, say, in a horizontal direction to the right by  $20^\circ$ . Saccade-related units are silent during slow pursuit, and conversely. In addition there are units related to head movements, and these are silent during movements of the eyes.

The specificity of these arrangements in the frontal dysgranular cortex is astonishing, and almost reminiscent of that found in the occipital cortex; yet there is an important difference in the timing of discharges: the occipital neurons respond to the key stimuli by firing a short time afterward. These frontal units, however, discharge neither before nor after, but during the movements to which they are linked. They are certainly not motor units in the ordinary sense, for if they were

somehow involved in a motor command, their discharges should precede the peripheral action. Nor are these units likely to be sensory or more specifically proprioceptive in function; if they were, their discharge should come with some regularity *after* the peripheral movement, and not *during* that movement as seems to be the rule.

Are these elements then monitoring the ongoing action, not by classical feedback from the periphery but by representing ongoing action to the organism, so that the sensory consequences of the action can be properly evaluated? It is intriguing that most of these Bizzi and Schiller units seem to be inactive when the eye and head movements are passively induced, as by the direct electric stimulation of the brainstem. Is it still too fanciful to say that the activity of such units is a physiologic marker for the voluntariness of voluntary action?

One need not stress that these observations and the conjectures involved in making them represent only the very first steps on our way towards a more complete understanding of the 'how' of frontal cortex function. Nor must we gloss over the fact that the explorations have so far clung to transitional (dysgranular) frontal cortex and that vast regions of granular frontal cortex still remain essentially unexplored. By venturing forward into the *principalis* region, Peter Schiller has recently encountered some units (on the lower lip of the sulcus, midway through its extent) which discharge if and only if the monkey is looking at an object *and* reaching for it. These cells are silent if the monkey looks without reaching or reaches without looking. Is this one of the junction points where one might search for acquired coordinations?

These very preliminary hints gain in potential importance in the context of yet another ongoing experiment in the MIT laboratories: Held and Bauer (1967) have raised stumptail macaques from birth in individual padded chairs which prevent the monkey from seeing his own limbs. After, say, eight weeks, the animal is permitted for the first time to view one of his extremities. The results of this kind of early deprivation appear to be a functional disconnection between eye and hand: the animal keeps gazing at his hand as if it were a strange object, and the hand flails about, helplessly, as long as it is in the animal's view. The moment the eyes are covered, however, the hand is coordinated again and can engage in voluntary reaching movements for objects presented by touch; thus it is only on attempts at visual guidance that the motor control over the limb breaks down.

As we have said elsewhere, it is as if the animal's vision poisoned his motor system. Ordinarily it takes such an animal somewhat over a week of active exploration of his own, previously unseen, arm, with continual efforts at visually guided reaching, until that arm is so-to-

speak 'hooked' into the motor system. It is tempting to suggest that such an animal builds up unit activity that represents a gradual achievement of eye-hand coordination, and experiments tracing such hypothetical changes at the single-cell level would seem to hold great promise.

A complementary and potentially even more hopeful approach would be to deprive the animal, early in development, of some normal motor output, rather than of visual input as such. Some of these experiments have just begun at the MIT laboratories, and it is too early to predict where they might lead, but they hold out hopes for a direct test of some of the physiologic mechanisms that should be involved in our hypothetical corollary discharge. Schiller and Koerner (1971) have prepared monkeys with one eye completely immobilized by resecting all of the ocular motor nerves. When such an animal attempts to move the paralyzed eye, the failure to execute such an action ought to produce a corollary discharge, running off *in vacuo*. We expect this because in patients with an acute paralysis of the extraocular muscles, the patient's impression is not that his eye is paralysed, but that the world moves every time he intends to move his eyes.

Recording from frontocortical, caudate, and perhaps superior colliculus units, in such a monkeys with one paralysed eye, and comparing the neural events with what is happening on visual stimulation and during oculomotor activity of the normal (mobile) eye, might provide us with that direct evidence for or against corollary discharges that we now lack. It may be unfortunate that we end such a long chapter on the present state of the frontal lobe problem with the sight of a monkey scanning the future with one moving and one paralyzed eye, but perhaps this is not altogether inappropriate to the imperfect but enormously promising state of this difficult chapter in brain physiology.

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