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SOME HYPOTHESES CONCERNING THE FUNCTIONAL ORGANIZATION OF PREFRONTAL CORTEX

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Abstract. The paper deals with systematization of the behavioral disorders after partial prefrontal lesions. It is assumed that depending on the localization of lesions two disorders may be discerned: impairment of drive inhibition (meaning by this only preservative but not protective drives) and of motor-act inhibition. The first deficit leads to the disinhibition of no–go responses in Pavlovian differentiation, the second one to the disorder of R_1–R_2 differentiation due to the difficulty of switching from one response to the other. Different parts of the prefrontal cortex are engaged in directional response and nondirectional response differentiation. It is postulated that drive inhibition depends on the limbo-prefrontal system, whereas motor-act inhibition depends on the premotor-prefrontal system for manipulatory responses and the caudate-prefrontal system for locomotor responses.

I. Introductory remarks

Intensive studies carried out in various research centers during the last decade on the functional organization of the prefrontal cortex in animals led to some undoubtful findings which can be summarized in three following statements:

1. On the basis of experimental work in which the animals with prefrontal lesions were trained in a variety of behavioral tasks, we may conclude that the prefrontal cortex participates in controlling a number of these tasks, although they are evidently not mutually correlated. This property may be denoted as *functional heterogeneity of the prefrontal cortex.*

2. On the basis of anatomical studies carried out both by morphological description methods and by retrograde or anterograde degenera-

tions after limited lesions, it may be stated that various parts of the prefrontal region differ from each other both in their architectonics and their interconnections with other parts of the brain. This property of the prefrontal cortex may be denoted as its *morphological fractionation.*

3. Finally, the experimental studies, attempting to specify by ablation techniques fields [1] concerned with particular behavioral tasks, reveal that their performance depends on the integrity of separate fields within the prefrontal region. We may call this property *functional fractionation of the prefrontal cortex.*

Of course, the ultimate aim of our endeavours in studying the prefrontal cortex is to relate its functional fractionation with morphological fractionation, so that we would be able to deduce the functional significance of a particular area from its interconnections with other structures of the brain. Although we are still very distant from this aim, our more modest purpose should be to answer the question of which particular prefrontal fields are responsible for which basic functions involved in various behavioral tests.

Let us clear up this last point. To begin with, it should be stated that, although in our contemporary studies on various behavioral tasks we try to make them as simple as possible, we can hardly reduce them to such a degree that they would represent single unitary functions. On the contrary, willy-nilly each of the tasks we use in our experiments depends on a number of particular unitary functions, the existence of which may even not be clearly recognized.

This statement leads to two important consequences. On the one hand, if the performance of a given behavioral task is impaired after removal of a certain part of the prefrontal cortex, we cannot answer the question which of the components involved in this task is responsible for its deficit. Accordingly, if we happen to find that the performance of a given task is impaired after removal of a number of prefrontal fields, and even after removal of fields situated outside the prefrontal region (as is, for instance, the case with Pavlovian differentiation) this does not mean that these fields are "equipotential" with regard to that task, but rather that different basic mechanisms involved in it depend on different cerebral loci. This principle being self-evident, and even trite, in technology, is still poorly understood in brain physiology. There are, in fact, few studies in which, after discovering that the performance of a given task is impaired after removal of several cerebral fields, the investigator tries to disclose which particular basic function involved in this task is deficient after each of these lesions.

[1] In this article we shall denote as prefrontal fields those parts of the prefrontal region which are supposed to have a definite functional significance.

On the other hand, if a lesion sustained in one of the prefrontal areas impairs the performance of several behavioral tasks, this may mean that either this area is still functionally heterogeneous and should be fractionated, or that all these tasks have a common factor depending on the integrity of that field. Investigations going along this type of analysis are also rather rare in brain physiology.

My aim in the present paper is to analyse from this point of view the impairments of particular behavioral tasks after partial prefrontal lesions, and, on the basis of existing behavioral evidence, find out what is the unitary function depending on the given prefrontal field. Since it is easier for me to carry out such an analysis on the experimental material with which I am closely acquainted, I shall almost exclusively utilize experimental data obtained on dogs in our laboratory in the Nencki Institute. Consideration of data, obtained in other laboratories by means of other methods and on other species, would extend too much the size of this paper, and would also too much increase the effort required for its preparation.

II. Disinhibitory prefrontal syndrome

I shall begin my analysis with a prefrontal syndrome which was first discovered in our laboratory, and has been thoroughly studied on dogs, cats, and in the last years on monkeys, in the Section on Neuropsychology of the National Institute of Mental Health in Bethesda. It is the syndrome of disinhibition of alimentary conditioned reflexes after prefrontal lesions (Brutkowski et al. 1956, Ławicka 1957, Brutkowski 1957, Brutkowski et al. 1963). This problem has been discussed in detail in the Pennsylvania Symposium (Brutkowski 1964), but it has not been dealt with in our present meeting; therefore I shall first remind you the main findings in this field.

1. If a dog has been taught to perform a certain movement in response to a given stimulus (CS_1) by means of food reinforcement and not to perform it in the presence of a similar stimulus (CS_2) by merely not offering him food, then, after removal of the prefrontal cortex, the animal starts anew to perform that movement in response to CS_2, and in intertrial intervals: that is, he turns back to the way of responding he had displayed in the first stages of original training (Fig. 1*AB*). We shall refer to that type of training as Pavlovian differentiation, the cessation of performing the learned movements to the unreinforced stimulus as inhibition of that movement, and its reappearance after prefrontal lesion as disinhibitory effect.

2. The post-operative retraining of the differentiation task leads to the recovery of the inhibitory response to CS_2 and in intertrial intervals

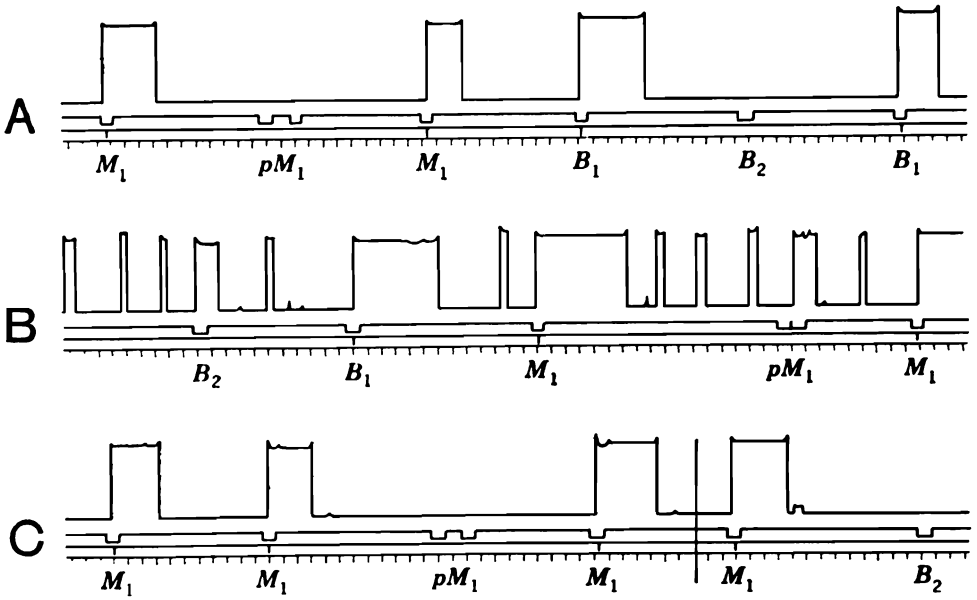

Fig. 1. Pavlovian differentiation in prefrontal dog. Part of experimental session before operation (*A*), early after operation (*B*), and after recovery (*C*). Each record from top to bottom: lifting the foreleg and placing it on the feeder; conditioned stimuli, presentation of food, time marker (5 sec). M_1 and B_1, positive conditioned stimuli; B_2, negative conditioned stimulus; pM_1, conditioned inhibitor followed by positive CS. Note that in *A* pM_1 with 5 sec CI-CS interval as well as B_2 elicits inhibitory response; in *B* many intertrial movements are seen, the responses to B_2 and M_1 preceded immediately by CI, but not to CI itself, are disinhibited; *C* again completely normal responding. The placing of the foreleg on the feeder is always prolonged in positive trials; this is due to the fact that the dog keeps leg on the feeder during the act of eating and puts it down only after the portion of food is consumed. (From Brutkowski et al. 1956.)

(Fig. 1*C*). Resistance to that recovery depends on the difficulty of the inhibitory task, measured by the duration of the original differentiation training.

3. Partial lesions sustained within the prefrontal cortex show that there is a crucial field responsible for the performance of the differentiation task. This is the medial aspect of the prefrontal cortex, the removal of which leads to the disinhibitory syndrome (Szwejkowska et al. 1963, Brutkowski and Dąbrowska 1966, Szwejkowska et al. 1965) (Fig. 2). On the other hand, neither the lateral, nor the dorsal part of this region produces that syndrome. However, as shown by Brutkowski and Dąbrowska (1966), disinhibition is observed after dorsolateral lesions, when the intertrial intervals are shortened from their usual duration of about 1 min or more — to 15 sec.

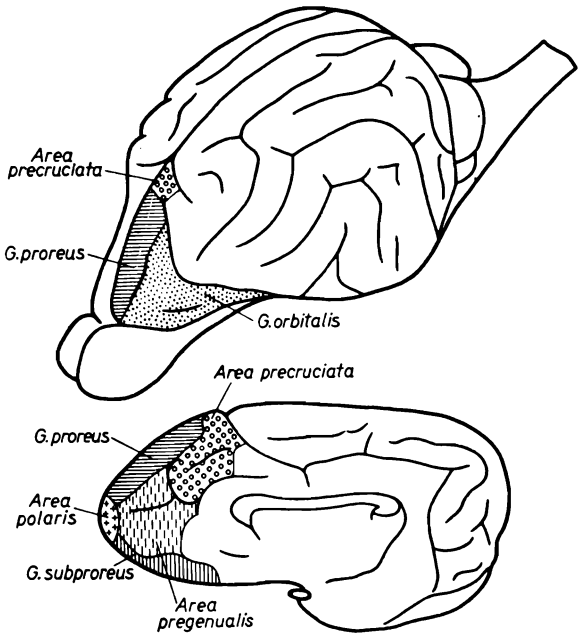

Fig. 2. Dorsolateral and medial aspects of the cerebral cortex of dog to show dorsal (gyrus proreus), lateral (gyrus orbitalis) and medial (area precruciata and pregenualis) parts of the prefrontal cortex.

4. Disinhibitory syndrome after prefrontal lesions is also observed when instrumental CRs are reinforced by presentation of water in thirsty animals (Żernicki 1961). On the other hand, prefrontal lesions do not produce disinhibition in differentiation of instrumental defensive CRs of the active avoidance type (Zieliński, this Symposium).

Let us now turn to the analysis of basic cerebral functions involved in Pavlovian differentiation, which may be impaired after prefrontal lesions.

First, in order to learn differentiation task the animal must distinguish the stimuli used in this training. It might, therefore, be assumed that prefrontal lesion impairs this discriminatory capacity. This supposition is, however certainly not true, because (i) in that case the appearance of intertrial movements would be incomprehensible and (ii) the impairment would affect differentiation of defensive CRs, as well.

Secondly, learning not to perform the trained movement to the unreinforced stimulus similar to the reinforced stimulus, requires the animal's capacity of *suppressing* this movement. Thirdly, since the motive of learning and performance of the instrumental response is provided by drive, in our case by hunger drive, it may be admitted that when the

animal stops displaying this response to the unreinforced stimulus, this is because his hunger drive is inhibited.

Since removal of the medial part of the frontal cortex is followed by abolition of alimentary inhibitory responses, we may conclude that this field is the "center" exerting inhibitory influence upon the hunger drive (Fig. 3). This means that the efferent pathways from this center should

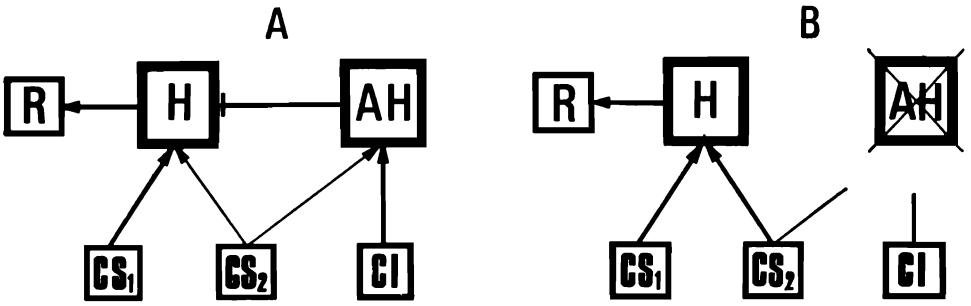

Fig. 3. Mechanism of inhibitory instrumental CRs (*A*) and their impairment after medial prefrontal (in dogs) or orbitofrontal (in monkeys) lesions (*B*). CS_1, positive CS center; CS_2, differentiated CS center; CI, conditioned-inhibitor center (*see* Fig. 1); H, hunger system; AH, inhibitory hunger center situated in the prefrontal extension of the limbic system; R, instrumental response center. Arrows, excitatory connections, stopped lines, inhibitory connections, thin lines denote weak connections. For the sake of simplicity the direct connections between CSs and R are not drawn. Note that only the response to CS_2 is disinhibited, but not to CI, because this stimulus has no connections with the H center.

convey inhibitory messages to the hunger drive centers situated in the lateral hypothalamus and/or medial amygdala, or maybe, to convey excitatory messages to the medial hypothalamus and/or lateral amygdala, both last centers being inhibitory to the hunger drive centers. As is well known, the anatomical studies performed on monkeys have shown that there are pathways leading from the orbitofrontal cortex (which is the functional homologue of the prefrontal medial field in dogs) to the lateral hypothalamus and, through the dorsomedial thalamic nucleus to the amygdaloid complex (Nauta 1964, Johnson et al. 1968).

On the other hand, according to our hypothesis, the medial prefrontal field should receive messages from various gnostic areas of the neocortex (or maybe from some subcortical structures), representing those external stimuli which may become signals of the nonpresentation of food. The long association bundles running from these areas to the prefrontal cortex have also been described (Pandya and Kuypers 1969, Jones and Powell 1970, Nauta 1972).

What is the physiological role of the above described inhibitory hunger center?

In normal conditions of the animal and human existence there are

situations in which food is never available, and there is no way to acquire it. In such situations the hunger drive should become inhibited, otherwise the organism would be doomed to develop it whenever the depletion of nutritive substances in the blood would provide humoral conditions for its occurrence. Of course, such a course of events would be highly maladaptive, taking into account that activation of hunger drive is a potent nervous process inducing the organism to food-seeking behavior and inhibiting all current activities not directed to its satisfaction.

It seems that this interpretation allows us to understand a number of symptoms observed in human patients after damage of the prefrontal cortex. In fact, it may be noticed that the alimentary behavior of some (but not all) of these patients is dramatically changed, showing that their inhibitory feeding reflexes are disinhibted. Thus, they may steal food from the nighttables of their ward-mates, and they will obtrusively ask the ward-nurses for more food. These changes in alimentary behavior may be explained by assuming that our social life has managed to develop many prohibitions based on the formation of inhibitory hunger drive reflexes, which become completely disinhibited after prefrontal lesions.

Now an important problem is bound to arise, as to whether only the hunger drive center is situated in the prefrontal cortex, or whether in this region there are also located centers of other preservative drives, in particular sexual drive. As may be judged from human observations, we know that again some prefrontal patients display sexual disinhibition manifested by courting *coram publico* and indecent behavior towards the female staff in wards. If it be so, we can ask whether the same prefrontal field is engaged in inhibiting all preservative drives, or whether inhibition of particular drives depends on different prefrontal fields.

It seems that this analysis helps us to understand why, to all probability, there is no higher inhibitory control of fear drive belonging to defensive-protective drives manifested by fear. Since the essential source of the protective drives, in contradistinction to preservative drives, lies not in the internal environment of the organism, but in the external agents, the higher inhibitory center is simply superfluous, because there is no humorally evoked drive which should be additionally regulated by the external world. This is why inhibition of avoidance reflexes are not impaired after prefrontal lesions (Zieliński, this Symposium). Why is it that these reflexes are even attenuated after prefrontal lesions is a matter requiring special research.

To end our discussion on the impairment of Pavlovian differentiation caused by prefrontal lesions, it should be noted that the deficit of hunger drive inhibition is perhaps not the only factor to which this im-

pairment may be attributed. It was indicated before, that when the differentiation task is tested with very short intertrial intervals (15 sec), disinhibition is present even after dorsolateral lesions. The mechanism of this defect is still not clear. It may be guessed that it occurs owing to the impairment of another cerebral function involved in the differentiation task, namely the ability of cutting short the excitatory state of a given motor-act center after this motor-act was executed. This property, which may be called anti-perseverative capacity, is ubiquitous in the nervous system, due to inhibitory processes. If the inhibitory process concerning the given type of behavioral acts is impaired, the animal (or man) has a tendency to repeat the motor response again and again, although the stimulus eliciting it has been discontinued. Spectacular examples of such behavior in man after prefrontal lesions were presented by Luria and Homskaya (1964).

Thus we may see that the normal course of the Pavlovian differentiation task depends (at least) on two inhibitory functions: one is hunger drive inhibition, the center of which is localized in the medial prefrontal field, and the other one is motor act inhibition whose centers are localized in other parts of the prefrontal cortex (*see* below). Whereas the hunger drive inhibitory center should exert its influence upon excitatory hunger drive centers located in the emotive brain, the motor act inhibition centers should exert their influence upon the premotor cortex, and the caudate nucleus which may be considered centers programming particular behavioral acts (*see* Conclusions). It should also be noted that whereas hunger drive inhibition is in operation, in experimental conditions, mainly in Pavlovian differentiation and extinction tests, motor act inhibition has much wider application, and therefore we shall meet it in our analysis of the impairment of other behavioral tasks.

Finally, it should be emphasized that the Pavlovian differentiation test is impaired not only after prefrontal lesions, but also after a damage sustained to other cerebral structures, in particular amygdala (Brutkowski et al. 1960) and hippocampus (J. Dąbrowska, unpublished data). Therefore, the question must be raised as to whether the functional role of these structures is a full replica of that played by the prefrontal cortex, according to the principle of redundancy of cerebral functions, or whether some different basic functions are represented by them. This question is so far open to further experimentation.

III. Impairments of motor-act differentiation tasks

The old Pavlovian procedure of food–no food differentiation test, which can be applied both to classical and instrumental conditioning, should be clearly distinguished from another discriminatory test in which,

under food reinforcement, the animal must perform two different motor acts in response to two different stimuli. This test, which may be called *motor-act differentiation*, is clearly different from the previous one in that here the animal, in order to receive food, should *choose* a proper movement depending on which stimulus has been presented, whereas in Pavlovian differentiation he does or does not perform the trained movement, in dependence on whether it is or is not reinforced.

There is good experimental evidence to show that the motor act differentiation task is controlled by the prefrontal cortex, since lesions in this region produce its severe impairment. However, both the problem of the exact localization of fields responsible for this type of task, and the problem of its probable mechanism are much less understood than the localization and mechanism of the control of food–no food differentiation. The study of these problems has been undertaken in our laboratory some years ago by Ławicka (1969*b*) and recently new impetus was given to it by the works of Dąbrowska, and Stępień and Stępień presented in this Symposium. My aim in this paper will be to see which tentative conjectures may be drawn on the basis of these experimental findings.

At the very beginning of this survey the following remarks concerning the classification of various types of motor act differentiation tasks should be made in order to understand our further considerations.

As far as the discriminatory cues utilized in these tasks are concerned, we should distinguish two categories of them, namely those which differ from one another by their location in space, and those which differ only in quality. An example of the first category of cues, called by us directional cues (DC), is provided by two identical tones operating from different places; an example of the second category, which we shall call nondirectional cues (nDC), is when two tones of different frequency operate from the same place.

Analogous distinction may be made with regard to instrumental responses. Here we may distinguish responses which differ in spatial directions (DR) and those which differ in qualitative patterns (nDR). A typical example of a test differentiating two directional responses is the so-called go left-go right task, irrespectively of whether these are walking responses, as in the Nencki test apparatus, or reaching by hand responses, as in Wisconsin test apparatus. A typical example of a test requiring differentiation of nondirectional responses is provided by usual training of house dogs to beg by lifting the paw to one command and bark to another command.

Having at our disposal two categories of discriminative stimuli, and

two categories of responses, we have altogether four possible types of differentiation tasks, namely:

1. DC → DR (directional cue — directional response)
2. DC → nDR (directional cue — nondirectional response)
3. nDC → DR (nondirectional cue — directional response)
4. nDC → nDR (nondirectional cue — nondirectional response).

We shall see in the further text that this categorization of various types of motor act differentiations is indispensable, because they are controlled by different fields of the prefrontal cortex.

Unfortunately, in the experimental work of our laboratory the instrumental responses used in motor act differentiation were not unequivocal, because at the beginning of our work we did not realize the physiological distinction between directional and nondirectional responses. Therefore, when the test of placing the right foreleg on the feeder vs. placing the left foreleg on the feeder was introduced in our laboratory, we simply considered it as R_1–R_2 differentiation, not bothering about the category to which these motor-acts belong (cf. Konorski 1967).

According to our experimental experience it turned out that this task belongs to the category of directional response differentiation, that is, it is equivalent, in the functional sense, to locomotor go left–go right task. The main evidence to show this is provided by the following circumstance. It has been shown by Ławicka (1964, 1969*a*) that the go left-go right differentiation (involving locomotor responses) is established very easily to directional cues (up-down), whereas it appears to be very difficult when nondirectional cues are used, even if the two cues differ considerably from each other (say tone 1500 vs. tone 300 cycle/sec).

Now it has been shown by Dobrzecka and Konorski (1967, 1968) that exactly the same rule applies to left leg–right leg differentiation. In fact, when this task was trained to directional cues operating from behind and from the front of the animal, the task was quite easy, whereas when it was trained to nondirectional cues, even quite dissimilar ones, it was exceedingly difficult. The same rule has been recently observed in monkeys (W. Ławicka, unpublished data).

On the basis of these findings it is reasonable to assume that there is some "physiological affinity" (in the sense of strongly developed potential connections, Konorski 1948) between directional cues and directional responses. If this assumption is true then it may be concluded that our test of placing the left leg on the feeder, vs. placing the right leg on the feeder belongs undoubtedly to the directional motor-act differentiation.

Now, some recent experiments of Stępień and Stępień (this Symposium) have shown that DC → DR differentiation is dramatically im-

paired after a lesion located in the depth of the dorso-medial part of the prefrontal region. On the other hand, as shown by these authors, this test was not affected after a superficial removal of the medial field, nor after superficial or deep removals of dorsal or lateral fields of the prefrontal cortex.

A quite analogous test has been recently used by Goldman and Rosvold (1970) in monkeys with locomotor response: looking up-going left and looking down-going right. These authors have shown that the crucial field for the performance of this test lies inside and around the arcuate sulcus.

We now turn to the differentiation of two responses differing in patterns (nDR). Here our knowledge is even more restricted than in the previous task. In the test used by Dąbrowska (1971, and this Symposium) and called go–no go differentiation with symmetrical reinforcement, two discriminative responses were: to flex the foreleg and place it on the feeder, and to actively restrain from performing that movement. We conjecture that these two antagonistic movements represent precisely the nondirectional category of responses, since it is clear that they have no spatial-directional character. The cues used by the author were nondirectional tones — 700 vs. 1000 cycle/sec. Accordingly, the differentiation task used in her experiments was nDC→nDR.

It turned out that the crucial field for this test is situated in the lateral part of the prefrontal cortex (g. orbitalis). The test is not affected either by removal of the medial or dorsal part of the prefrontal region. Moreover, it is not affected when directional cues are used, that is when the task takes the form: DC→nDR differentiation, although, as shown by Dąbrowska, this task is much more difficult than the nDC→nDR differentiation. By the way, this shows that nondirectional responses have closer affinity with nondirectional than with directional cues.

To sum up, the situation at the present time is this:

The motor-act differentiation utilizing directional cues and directional responses (DC→DR) is impaired selectively by damage of the depth of the dorso-medial prefrontal cortex (Stępień and Stępień, this Symposium).

The differentiation utilizing nondirectional cues and nondirectional responses (nDC→nDR) is impaired selectively by the damage of the lateral part of the prefrontal cortex (Dąbrowska 1971).

The effects of prefrontal lesions upon two other motor-act differentiation tasks, namely DC→nDR and nDC→DR are not yet quite unequivocal. Therefore, we cannot be sure which factor is responsible for the localization of the motor-act differentiation control, whether only

the category of the cue (DC vs. nDC), or the category of the response (DR vs. nDR), or else, both the category of the cue and that of the response. So far the last supposition seems to be most probable, since, according to the preliminary experiments of Dąbrowska (this Symposium), only nDC→nDR differentiation is abolished by lateral prefrontal lesions, whereas neither DC→nDR nor nDC→DR seem to be impaired by lateral lesion.

Turning now to the explanation of motor-act differentiation, we may tentatively assume that the impairment of this differentiation both in DR and nDR procedure lies in the difficulty of switching from one response to the other, namely from flexion of the leg to its extension or vice versa in the nDR differentiation, and from placing one foreleg on the feeder, to placing the opposite foreleg on the feeder in the DR differentiation. This difficulty is supposed to be due to the defect of motor-act inhibition discussed briefly in the preceding section. The fact that the inhibitory mechanism for directional responses is localized in a different prefrontal field than the inhibitory mechanism for non-directional responses may depend on a different localization of centers programming these responses. We have indeed some reasons to believe that the kinesthetic patterns involved in directional responses and those involved in nondirectional responses are represented in different structures *(see* Conclusions).

The above proposed hypothesis explains reasonably well the strong tendency to perseverative responses observed in motor-act differentiations tasks after appropriate prefrontal lesions, as well as the tendency to perform only one "preferential" response, with full neglect of the other one (Dąbrowska, this Symposium, Stępień and Stępień, this Symposium). The last disorder is simply due to the fact that the animal, not being able to solve the problem because of perseveration, easily recurs to the irregular reinforcement strategy, complying with the fact that only a half of all trials are reinforced.

If these considerations are correct the conclusion should follow that the same rules are in operation not only with regard to motor-act differentiation based on alimentary reinforcement, but also to motor-act differentiation based on noxious agent reinforcement, as is the case in active avoidance.

We remember that, according to the data presented by Zieliński (this Symposium), there is no disinhibition of active avoidance in Pavlovian differentiation procedure. This was regarded as due to the fact that the prefrontal cortex is not concerned with inhibitory influence upon defensive conditioned reflexes.

The situation is, however, quite different with regard to motor-act

inhibition, because it does not matter for which master, alimentary or defensive, the given motor-act works. Accordingly, we would predict that if two directional responses, displayed to two directional cues respectively, are displayed to avoid the noxious agent, then deep mediodorsal lesion should be detrimental to this task. On the contrary, if the animal, in order to prevent the occurrence of a noxious agent, must perform two nondirectional movements in response to two nondirectional cues respectively, then the lesion in the lateral prefrontal field should be detrimental.

If we look in this way upon the role of the prefrontal cortex in motor-act differentiation, then we can easily observe that many prefrontal symptoms in man fall exactly into this category of disorders. As a matter of fact, one of the most prominent prefrontal symptoms in humans consists in the difficulty of switching from one response to another, a symptom usually denoted as perseverative tendency (Luria and Homskaya 1964, Milner 1964). Moreover, in human pathology, the difference between the directional locomotor behavior and nondirectional manipulatory behavior is even more pronounced than in dogs. It is well known that both the oral praxis on which speech is based, and the manual praxis involved in skillful movements are represented in the premotor area of the dominant hemisphere. On the contrary, the locomotor and visual spatial orientation is represented in the nondominant hemisphere. Accordingly, we have every reason to believe that verbal and gestural differentiation depends on the dominant prefrontal cortex, while locomotor differentiation on the nondominant one. Beautiful experiments of Brenda Milner reported in this Symposium seem to confirm this expectation.

IV. The role of prefrontal cortex in delayed responses

This problem has been studied in so many research works, and so many various concepts have been advanced to explain it, that it would be both unreasonable and impossible to deal with it in full scope. My purpose will be much more modest: I shall try to see whether it is possible to explain the delayed response deficit after prefrontal lesions by reference to the same mechanism which I tried to utilize in our analysis of the effects of prefrontal lesions on motor-act differentiation. I shall again base my argument on experiments performed in our laboratory on dogs and cats.

To begin with I shall summarize the most important facts relevant to our discussion. Here they are:

1. The impairment of performance of the delayed response tasks following prefrontal lesions is certainly not caused by the deficit of short-

term memory; the decisive proof of this thesis is, among other things, that the animal after making an erroneous run in three-choice situation, very often immediately approaches the correct feeder, showing that he does remember it in spite of the distraction of running to the wrong one (Ławicka and Konorski 1961, Ławicka 1969*b*).

2. The animals exhibit the following abnormal responses in the course of delayed response performance:

a) The tendency to approach that feeder to which the animal is turned in the moment of release (Ławicka and Konorski 1959).

b) The tendency to perseveration which is manifested either by repeating the preceding run (mostly in cats), or by strong preference to approach always one feeder with total neglect of the others (Ławicka and Konorski 1961, Konorski and Ławicka 1964).

c) The tendency to develop "parasitic" instrumental reflexes. This phenomenon is best manifested when the animal is released from the starting platform with no precedence of the preparatory signal (so-called sham trials, Ławicka 1969*b*). Whereas the normal dog simply remains on the starting platform, the prefrontal dog repeatedly runs to one of the feeders, selected according to rules (a) and (b). However, when after a series of sham trials the reflexogenic role of the release is extinguished, and then a normal trial is given, the delayed response is usually correct (Ławicka 1969*b*).

3. The learning of instrumental reflexes is quite normal and locomotor differentiation task to nondirectional stimuli is mastered even more quickly than in normal animals (Ławicka, this Symposium).

4. There is a precisely localized field in the prefrontal region, removal of which causes the impairment of delayed response performance. This is gyrus proreus in dogs (Ławicka et al. 1966) and sulcus principalis in monkeys (Blum 1952, Mishkin 1957, Butters et al., this Symposium).

On the basis of these data, we have stated in the Pennsylvania Symposium that the impairment of delayed responses after prefrontal lesions is due to a loss of proper balance between two behavioral tendencies: one determined by the preparatory signal of the delayed response and the other determined by actual stimuli eliciting definite instrumental responses. Whereas in normal animals the first tendency strongly, though not absolutely, dominates over the latter one, in prefrontal animals the relation is reverse (Konorski and Ławicka 1964).

This loss of balance after prefrontal lesions was supposed to be due to a *decrease* of the motogenic capacity of eliciting the proper response by the trace of a preparatory signal, or to an *increase* of instrumental conditionability connected with increased arousal produced by external stimuli.

Ławicka's further experimental work (Ławicka, this Symposium) spoke in favor of the latter assumption by demonstration that in fact the motor-act differentiation task was mastered more quickly by dogs with proreal lesions than by normals. We may thus assume that the animal is poor in his correct delayed responding simply because he is in the hands of instrumental conditioned reflexes which outweigh the responses based on the trace of the preparatory signal.

As we have seen in the preceding section, the difficulty encountered by the animal with lateral or deep dorsomedial lesions in motor-act differentiation tests, is to switch from one response to the other, in the scope of either nondirectional or directional responses respectively. We have conjectured that the mechanism of this switching capacity lies in inhibition of the excitatory aftereffect produced by each display of the instrumental response. When this inhibition is abolished, the animal tends to repeat the last response, although the stimulus should now elicit the other of the two differentiated responses, or he tends to display always one response to both stimuli.

A similar mechanism can be assumed to operate in the delayed response test. The actual stimulus by which this response is elicited is the releasing of the animal from the leash. This stimulus is connected with three locomotor responses directed to three feeders, the preparatory signal determining the proper response. In a normal animal, after each delayed response performance, the inhibitory mechanism cuts short the excitatory state of the center of the given directional motor-act, and consequently the subject is ready to react adequately in the next delayed response trial. If, however, this inhibitory mechanism is impaired because of the prefrontal lesion, the subthreshold excitation of the center of a given behavioral act outlasts the performance of that act and therefore it is performed in response to the releasing stimulus, either in the successive trial or in a sham trial. However, if by special sham-trial extinction training the parasitic instrumental reflexes are inhibited, the background is cleared for the proper performance of the next delayed response, because it no longer is suppressed by competing responses.

To sum up, what I suggest is that in correct performance of delayed responses, as in other motor-act differentiation tasks, the crucial factor is the suppression of the excitatory process, lingering in the center of a given behavioral act, after this act has been executed. If after lesion in the dorsal prefrontal cortex this suppressive mechanism is impaired, the indiscriminative conditionability of locomotor responses to the feeders is facilitated, and this in turn disrupts even more the correct delayed response performance. Since, according to our earlier discussion, partic-

ular motor-act differentiation tasks seem to depend on particular prefrontal fields, it is no wonder that the delayed response task is impaired after a definite, and to some extent specific, lesion.

CONCLUSIONS

In spite of many new facts which have been gathered in relation to the problem of the functional role of the prefrontal region in the last decade, I still feel that we have no clear idea about how this part of the brain actually works. It is true that we have recently learned a great deal about the behavioral tests which are impaired after removal of particular fields within the prefrontal cortex, but still we cannot find any consistent and convincing concept telling how this region participates in the control of animal and human behavior. Yet it seems to me that in a Symposium devoted to the function and structure of the prefrontal cortex it would be reasonable to make a tentative attempt to present such a concept, being fully aware of its provisional character.

There is general agreement that the prefrontal cortex is composed of two divisions, one being a rostral extension of the limbic system (medial part in dogs, orbital, in monkeys), the other being a rostral extension of the motor system. Our explanation of the functional role of the fronto-limbic region seems to be plausible both physiologically and biologically, and it accounts reasonably well both for experimental data and clinical observations. In fact, the existence of higher inhibitory drive system which adjusts the organism to the environmental factors and checks the omnipotence of humoral factors, seems to be sound.

More difficult is the problem concerning the functional role of the second division of the prefrontal cortex, involved in motor-act differentiation tasks. As indicated in a preceding section we should distinguish differentiation of directional and nondirectional responses, different parts of the prefrontal cortex being responsible for their integrity.

According to the findings of Dąbrowska nondirectional response differentiation is severely impaired after lateral prefrontal lesions. It may be supposed that the lateral area is related to the premotor cortex, which is involved in programming of nondirectional manipulatory movements. Flexion and extension of the foreleg to two different stimuli may be an example of such movements.

On the other hand, directional responses are involved both in go left-go right differentiation task used in Stępień and Stępień experiments and in delayed response type tasks used in Ławicka's experiments. The prefrontal field situated in the proreal gyrus is responsible for the delayed response task, whereas some deeper structures situated beneath the proreal gyrus are responsible for go left–go right task. We suppose

that the directional responses are programmed not in the premotor cortex, but in the caudate nucleus, a structure also involved in the delayed response tasks both in cats (Divac, this Symposium) and in monkeys (Rosvold, this Symposium).

So far — so good. But we are now confronted with the next problem, that of understanding *what* is the exact mechanism of the prefrontal function, or to put it more precisely, what is the way by which the prefrontal cortex fulfils the higher control over both the manipulatory and directional behavior. Among several possible explanations the one which seems now to be most reasonable, is analogous to that proposed with regard to the mechanism of the action of the limbo-prefrontal system, namely that involving inhibitory processes. In the two preceding sections we have emphasized that the tasks of any motor-act differentiation are connected with the capacity of rapid switching from one action to another in the scope of a given category of cues and responses. If this switching is not adequate because of the lagging behind of the given excitatory state after execution of the response, then the subject will commit perseverative errors. Thus, according to this concept, the role of the prefrontal cortex would consist in cutting short the activation of the centers of the given behavioral acts represented in the premotor cortex for skillful movements and in the caudate nucleus for directional (locomotor) responses. Accordingly, it is assumed that the lateral prefrontal field sends inhibitory impulses to the premotor cortex and thus ceases the activation of the centers controlling skillful movements, whereas the dorsal region sends inhibitory impulses to the head of the caudate nucleus to stop activation of centers controlling directional responses.

Our hypothesis seems to explain satisfactorily the fact that the impairment of motor-act differentiation tasks is usually reversible and in certain conditions does not occur. In fact, it should be realized that if a given motor-act differentiation task is firmly established, the tendency to perform the correct response may be stronger than the tendency to repeat the preceding response, particularly if the intertrial interval is sufficiently long.

I should stress, however, once more that I consider the present explanation of the prefrontal syndromes a working hypothesis, the purpose of which is to serve as a guidance for further experimentation.

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