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NEURAL ASSOCIATIONS OF THE FRONTAL CORTEX

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Abstract. Recent anatomical findings in the monkey indicate that the frontal cortex receives associative afferents from the visual, auditory, and somatosensory areas of the cortex. The inferior parietal lobule and the inferior temporal cortex are important way-stations in these cortico-cortical afferent pathways. The olfactory system represents a fourth sensorium having access to the frontal cortex, namely, by way of substantial projections from the piriform cortex and olfactory tubercle to the medial subdivision of the thalamic mediodorsal nucleus. Additional afferents to this nucleus originate from various fore- and midbrain structures implicated in the circuitry of the limbic system; such afferents could well be mediators of information related to the organism's internal milieu. On the efferent side, the frontal cortex is associated with the inferior parietal, temporal, cingulo-parahippocampal cortex, and entorhinal area; it is the only cortical region known to project directly to the hypothalamus and hypothalamus-related structures in the paramedian midbrain tegmentum. The mosaic of origin and termination of the various connections indicates that the convexity of the frontal lobe (especially its caudal half) is reciprocally associated with the parietal and temporal cortex, while the major associations with the hippocampal mechanism originate from two separate areas, viz. the caudal orbitofrontal cortex and a region dorsal to the sulcus principalis, frontal fields from which also the major fronto-hypothalamic connections arise.

INTRODUCTION

The frontal lobe, despite decades of intensive research by physiologists, anatomists and clinicians, has remained the most mystifying of the major subdivisions of the cerebral cortex. Unlike any other of the great cerebral promontories, the frontal lobe appears not to contain a single sub-field that coud be identified with any particular sensory modality, and its entire expanse must accordingly be considered association cortex. It should, perhaps, not be surprising in view of this circumstance alone that loss of frontal cortex, in primate forms in particular, leads to a complex functional deficit, the fundamental nature of which continues to elude laboratory investigators and clinicians alike.

In view of the complex and evasive character of the frontal-lobe syndrome it is appropriate to ask what the nature might be of the neural information normally received and processed by the frontal cortex, and what efferent channels might account for its unique role in behavioral programming. Obviously, nothing short of a comprehensive analysis of the response determinants of single cortical units can be expected to answer the question as to the informational content of neural impulses converging upon the frontal cortex. Studies of this sort recently have provided extremely valuable insights into the feature-extracting mechanisms of the visual, somatosensory and auditory fields of the cerebral cortex. However, the problems encountered in exploring these modality-specific cortical fields are likely to be multiplied many times over in regions such as the frontal cortex which are certain to be associated with more than one sensory modality. Especially the problem of identifying the natural stimuli consistently capable of eliciting responses by a sufficiently large number of cortical units in such regions might prove quite elusive. However that may be, explorations of this sort have not yet provided the data which alone could identify the nature of the information received, and the manner in which it is processed by the frontal cortex. Consequently, little more than anatomical data are currently available from which to draw inferences related to these questions. This anatomical information, as the following account is intended to show, is by no means negligible.

NEURAL CONNECTIONS OF THE FRONTAL CORTEX

1. *Anatomical definition*

The term, frontal lobe or "prefrontal cortex", has come to denote the cortical field that extends forward of the "premotor" area 6 and is projected upon by the mediodorsal nucleus of the thalamus. In primates and carnivores, this large cortical expanse covers the frontal pole of the hemisphere, but in the rat, and probably in other rodent species as well, the corresponding and relatively smaller region is composed of two widely separate sub-fields: one confined to the medial surface of the hemisphere, the other occupying the dorsal bank of the rhinal sulcus, and neither extending forward far enough to cover the frontal pole (Leonard 1969). Apart from such differences of relative size and topography, there is another reason to believe that the prefrontal cortex reaches vastly different stages of development in different mammalian lineages: Only in primates does the larger rostral part of the field exhibit the cytoarchitectural features of a granular cortex. In the cat, dog, sheep, and rat, apparently the only non-primate species in which the prefrontal cortex has been delimited by experimental methods, the field is throughout of an agranular structure; in the rat its laminar pattern is so poorly differentiated that it is nearly indistinguishable from the anterior cingulate cortex with which its medial sub-field is caudally continuous. In fact, on cytoarchitectural grounds alone the existence of a non-primate homologue of the primate prefrontal cortex could be questioned, and it is largely the constancy of its afferent relationship with the mediodorsal nucleus of the thalamus that has allowed a prefrontal cortex to be identified in non-primate forms.

Since the anatomical account to follow is based very largely upon observations in the rhesus monkey, a brief description of the main anatomical features of the prefrontal cortex of this species would seem appropriate. As shown in Fig. 1, the caudal border of the prefrontal cortex is marked by the deep *arcuate sulcus* which delimits it from the agranular "motor cortex" of the precentral gyrus (areas 4 and 6 of Brodmann). Other macroscopic features of importance are: (i) the general shape of the frontal lobe which allows a fairly flat medial surface to be distinguished from the concave ventral (or orbital) aspect and a lateral convexity, and, (ii) the deep *principal sulcus* which divides the lateral convexity into a dorsal and a ventral field.

The cortex forming the most caudal part of the prefrontal region, i.e., the rostral bank of the arcuate sulcus, is structurally speaking something of a transition zone between the agranular "motor cortex" behind it and the distinctly granular cortex that occupies the large rostral remainder of the frontal lobe. This crescent-shaped "dysgranular" zone of the prefrontal cortex, labelled area 8 by Brodmann, is customarily referred to as the "frontal eye field". The justification for this label lies in the fact that electrical stimulation of the region elicits conjugate contraversive eye movements, whereas its ablation is followed by a *transitory* inability of the monkey to turn its eyes to the contralateral side, and a concomitant failure to pay attention to stimuli delivered in the contralateral half of the visual field ("contralateral visual neglect"). Tempting as it would seem to assume that area 8 is the oculomotor area of the "motor cortex", recent findings concerning the temporal relationship between eye movements and the activity patterns of single neurons of

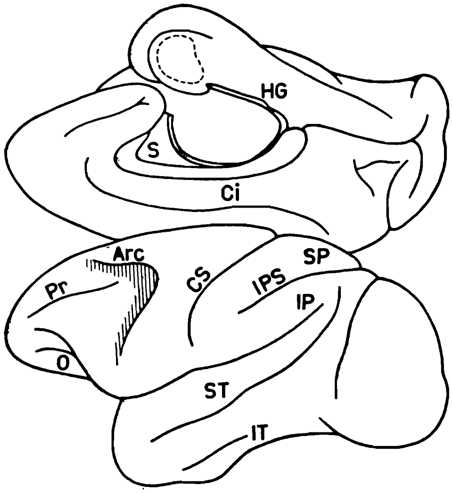

Fig. 1. Line drawing representing the lateral (lower half of figure) and medial aspect of the cerebral hemisphere of a rhesus monkey. The lateral view shows the arcuate sulcus (Arc) which marks the caudal boundary of the region here called "the frontal lobe", and the principal sulcus (Pr) which divides the frontal convexity in a dorsal and ventral half. The shaded region forming the rostral bank of the arcuate sulcus represents the dysgranular area often referred to as "frontal eye field". A small rostral part of the orbital surface of the frontal lobe (O) is visible in the lateral view. The broken line in the upper half of the figure indicates the approximate position of the amygdala, a structure largely hidden from view by the overlying olfactory cortex. Other structures labelled are: Ci, cingulate gyrus; CS, central sulcus; HG, hippocampal gyrus; IP, inferior parietal lobule; IPS, intraparietal sulcus; IT, inferior temporal region; S, septum; SP, superior parietal lobule. (From Nauta 1971).

area 8 flatly contradict such a notion and appear to suggest that the area is involved in some form of monitoring, rather than in the effectuation, of eye movements (Bizzi 1968, Bizzi and Schiller 1970). It is here included in the "prefrontal" rather than the "motor" cortex for the reason that its thalamo-cortical afferents come from the mediodorsal thalamic nucleus (Akert 1964).

The large remainder of the prefrontal region is distinctly granular in type. A varying number of cytoarchitectural subdivisions have been recognized in this large granular territory, but the structural differences have been too subtle to permit anything resembling agreement among individual observers (Akert 1964). Whether or not manifested by cytoarchitectural contrasts, however, a functional parcellation of the region appears virtually certain from the observation that different sub-fields of the granular frontal cortex have markedly different afferent and efferent relationships (*see* below).

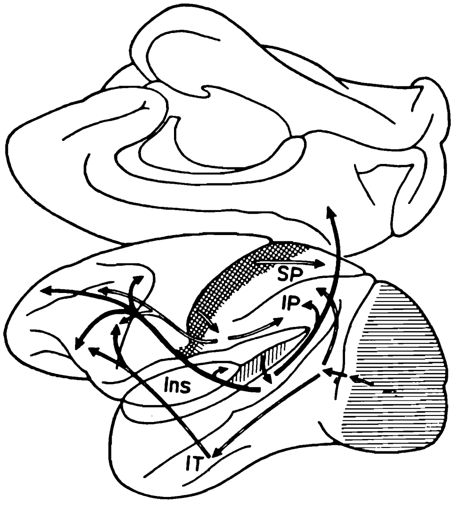

Fig. 2

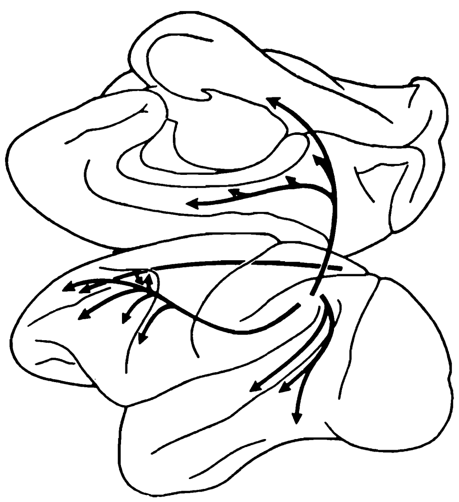

Fig. 3

Fig. 2. Schematic representation of some of the major association pathways extending away from the great primary sensory fields of the cortex. The visual area 17 is indicated by horizontal shading, the auditory area by vertical shading, and the somatic sensory cortex by cross-hatching. Afferents to the frontal lobe presumably conveying auditory information are indicated by solid-black arrows, those conveying visual information, by black and white arrows, and presumably somatosensory afferents by open arrows. Note that pathways representing all of these three modalities also converge upon the inferior parietal lobule (IP). The substantial projections from this parietal region to the frontal cortex are indicated separately in Fig. 3. (From Nauta 1971).

Fig. 3. Schematic representation of parieto-frontal connections originating from the inferior and superior parietal lobules. Those from the inferior lobule can be thought to convey visual, auditory and somatosensory information. Note that the inferior parietal lobule also has substantial efferent connections with the cingulate and hippocampal gyri, and with all of the temporal gyri. (From Nauta 1971).

2. *Afferent connections of the frontal lobe*

Recent experimental findings with respect to the afferent connections of the frontal lobe have combined to suggest that the frontal cortex is a common end-point for generally long neuronal chains that extend away from the primary sensory regions of the cerebral cortex. Some such conduction routes are composed entirely of cortico-cortical links, and could therefore be classified as associative connections throughout. Others, by contrast, involve the mediodorsal nucleus of the thalamus and thus have their last link in the thalamo-frontal projection system.

a) Afferents from the visual, auditory and somatic sensory areas. Associative chains linking the primary cortical fields of the visual, auditory and somatic sensory systems with the frontal cortex have been outlined in a series of recent experimental studies by Kuypers et al. (1965), Pandya and Kuypers (1969), Pandya et al. (1969), and Jones and Powell (1970) in the rhesus monkey. As shown in extremely schematic form by Fig. 2 and 3, in each of these three sensory systems the connection in question initially involves one or more cortical zones adjoining the primary sensory field ("belt zones", for example areas 18 and 19 of the visual cortex), and spreads from there to either or both the inferior parietal lobule and the rostral half of the temporal neocortex. The latter two fields are major sources of direct cortico-cortical afferents to the frontal cortex.

An interesting detail, emphasized in particular by Jones and Powell (1970), is that, whereas virtually no fibers to the frontal cortex appear to originate in the primary sensory fields, some can be traced from the immediately adjoining field (such as area 18 of the visual cortex) and a considerably larger number from the field "next in line" (e.g., area 19 of the visual cortex). It thus appears that the association of each of these three sensory systems with the frontal cortex, although largely organized so as to involve a lineal sequence of intermediate cortical processing stations, includes some additional conduction lines originating in parallel from such intercalated way-stations.

It is remarkable that the direct associative connection of the anterior temporal cortex to the frontal lobe by way of the uncinate bundle is paralleled by a pathway from lower temporal regions (middle and inferior temporal gyri) via the so-called inferior thalamic peduncle to the particular (medial, magnocellular) subdivision of the mediodorsal thalamic nucleus (Witlock and Nauta 1956) that is known (Freeman and Watts 1947, Akert 1964) to project to the cortex covering the orbital surface of the frontal lobe (Fig. 4). The field of origin of this transthalamic temporo-frontal conduction route overlaps that of the uncinate bundle to some extent at least, but whereas the latter, direct connection appears to involve a very large part of the frontal convexity (Pandya and Kuypers 1969), the temporo-thalamo-frontal pathway must be limited in its distribution to the orbital surface. The functional significance of the mediodorsal nucleus as an intermediary in the path to the frontal lobe must for the present remain a matter of conjecture, but it is interesting that the lower temporal gyri share this efferent way-station with the olfactory cortex (see below).

It must be emphasized that the various cortical and thalamic intermediaries in these sensory-frontal conduction routes cannot be viewed as mere "relay stations" along the path to the frontal lobe. There can be little doubt that fundamental input-transformations take place at each step along the way, and there is thus reason to suspect that the information content of the impulse flow arriving at the frontal cortex is little more than a remote derivative of the neural events taking place in the primary sensory areas. Nonetheless, the systematic progression of associative conduction routes toward the frontal lobe suggests that all of the three major sensoria represented by modality-specific areas in the neocortex find some form of re-representation in the frontal cortex, however abstracted or compounded that form may be.

b) Afferents from the olfactory system. It is of interest to note here that the frontal lobe is not the only neocortical region in which association systems related to the visual, somesthetic and auditory systems converge. For example, at earlier stages of cortico-cortical processing a similar confluence, or at least a partial spatial overlapping of these three modalities, appears to take place in the inferior parietal lobule. However, nowhere but in the frontal lobe does this convergence appear to be augmented by an afferent connection from the *olfactory system.* The unexpected evidence of a close relationship of the frontal lobe with the olfactory sensorium came from studies in the rat by Sanders-Woudstra (1961) and Powell, Cowan and Raisman (1965) that convincingly demonstrated a substantial projection from the prepirifom (olfactory) cortex via the inferior thalamic peduncle to the medial, magnocellular subdivision of the mediodorsal nucleus of the thalamus. This olfacto-thalamic connection, schematically illustrated in Fig. 4, implies the theoretical possibility that the posterior orbitofrontal cortex is not more than a few synapses removed from the olfactory receptor neurons. No less interesting is the fact that the projection to the mediodorsal nucleus appears to be only one subdivision of a wider projection from the olfactory cortical formations that includes substantial connections to the lateral hypothalamic region. One could wonder whether perhaps, by these short routes to the frontal lobe and hypothalamus, the olfactory system — no less than other sensoria involved in learning and memory — may be giving us a basic anatomical "flow-diagram" of telencephalic signal-processing, a model which other sensory modalities complicate by the interposition of a series of neocortical processing stations beyond the primary cortical receiving area.

c) Other afferent connections of the frontal lobe. All of the evidence summarily reviewed above suggests the frontal lobe as a neocortical region representing the external environment as reported by all exteroceptive sensoria. But even this encompassing statement may not adequately describe its afferent relationships, for it does not take into account a remarkable diversity of further fiber systems connected to the frontal cortex by way of the mediodorsal nucleus.

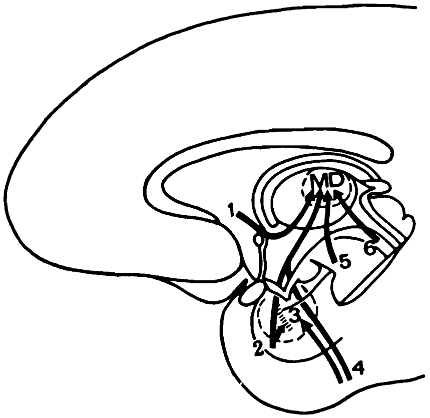

Fig. 4. Schematic drawing indicating some of the subcortical afferents of the mediodorsal nucleus of the thalamus (MD). Arrow *1* represents afferents from the septum; arrow *2*: such from the olfactory cortex; arrow *3* (shaded because of uncertainty mentioned in the text): fibers from the amygdala; arrow *4*: fibers from the inferior temporal region; arrow *5*: fibers from the ventromedial area of the midbrain tegmentum, and arrow *6*: fibers ascending through the dorsal region of the tegmentum. The connections *2*, *3* and *4* are components of the inferior thalamic peduncle. (From Nauta 1971).

Such additional afferents appear to originate preferentially from subcortical structures implicated in the circuitry of the limbic system, and most of those that have been experimentally demonstrated are limited in their distribution to the medial subdivision of the nucleus, i.e. the thalamic gateway to the orbital surface rather than the convexity of the frontal lobe. These afferents include fibers from the septal region and from a ventromedial area of the mesencephalic tegmentum (Guillery 1959), from the interpeduncular nucleus (Massopust and Thompson 1962), and possibly also from the amygdaloid complex[1].

Only sparse data are available with respect to the afferent connections of the considerably larger *lateral* subdivision of the mediodorsal thalamic nucleus, a cell territory known to project to the *convexity* of

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[1] The lingering uncertainty concerning amygdalothalamic connections is due to the efferents from the overlying olfactory cortex that traverse the amygdaloid complex in passage to the hypothalamus and mediodorsal nucleus, and thus are unavoidably involved in lesions of the amygdala. Although, as a consequence, direct proof of an amygdalothalamic projection is lacking, the existence of this connection appears nonetheless likely in the context of current knowledge concerning temporal-lobe efferents contained in the ansa peduncularis and its thalamic extension, the inferior thalamic peduncle. As summarized in Fig. 4, such connections include efferents from both the inferior temporal region and the olfactory cortex to both the amygdaloid complex and mediodorsal thalamic nucleus.

the frontal lobe (Akert 1964, Freeman and Watts 1947). The observation that it receives fibers originating in the intralaminar thalamic nuclei (Nauta and Whitlock 1954) holds little clue-value, for such fibers appear to be distributed widely among specific thalamic nuclei. Neither is much information to be derived from the fact that the nucleus receives numerous thalamic fibers from the frontal convexity: reciprocity appears to be a common, if not indeed universal, property of thalamo-cortical relationships. In a recent experimental study in the rat, however, Chi (1970) has demonstrated a discrete fiber system that ascends beneath the ventrolateral border of the central gray substance of the midbrain, and terminates with dense arborizations in a circumscript region of the more lateral zone of the mediodorsal nucleus. The cells of origin of this well-defined, lemniscus-like fiber system have not been identified, but the position of the bundle in the midbrain suggests that it may be a trans-synaptic continuation of a projection system ascending from the nucleus of the solitary tract, a projection which follows a comparable mesencephalic trajectory (Morest 1967) but appears not to extend into the thalamus directly.

It is difficult to evaluate the functional nature of these various afferents of the mediodorsal nucleus on the basis of anatomical evidence alone. At present, only the projection from the olfactory cortex can be identified in terms of sensory modality. There is nonetheless ample reason to suspect that several at least of the remaining afferent fiber systems mentioned above convey information concerning the organism's internal milieu. Such a relationship would seem likely in particular for the fiber systems originating in the septum and in paramedian zones of the midbrain tegmentum, brainstem regions prominently involved in the circuitry of the telencephalic limbic structures and hypothalamus. It would not seem far-fetched to interpret such conduction systems as conveyors of neural codes related to motivational states and their visceral concomitants.

3. *Efferent connections of the frontal lobe*

Much like most other subdivisions of the cerebral mantle, the frontal cortex has been found to be connected by a great variety of efferent pathways to other cortical regions as well as to subcortical structures. In both categories of connections, indications are found that the frontal lobe is closely associated with the limbic system, but there are other efferent relationships that cannot be so classified.

a) Efferent cortical associations of the frontal lobe. Major cortico-cortical efferents connect the frontal lobe with the anterior temporal cortex, with the inferior parietal lobule, and with the cingulate and parahippocampal gyri (Fig. 5). The two former of these efferent connections to some extent at least appear to reciprocate the prominent afferent association of the frontal lobe with the anterior temporal and inferior parietal regions. The findings of Pandya and Kuypers (1969) suggest that the connection to the inferior parietal lobule originates most massively in the caudal frontal region approximately corresponding to the "frontal eye field", whereas fronto-temporal fibers appear to arise more evenly throughout the frontal convexity and are organized topographically in such fashion that the dorsal half of the convexity (i.e., the field dorsal to the principal sulcus) projects to the superior temporal gyrus, the ventral half to the dorsal bank of the middle temporal gyrus. It is important to note that a substantial projection to the amygdaloid complex arises from the inferior temporal region (Whitlock and Nauta 1956) (Fig. 4). The fronto-temporal connection could therefore be thought to permit the frontal cortex to modulate not only the activity patterns of the temporal cortex but also those of the amygdala.

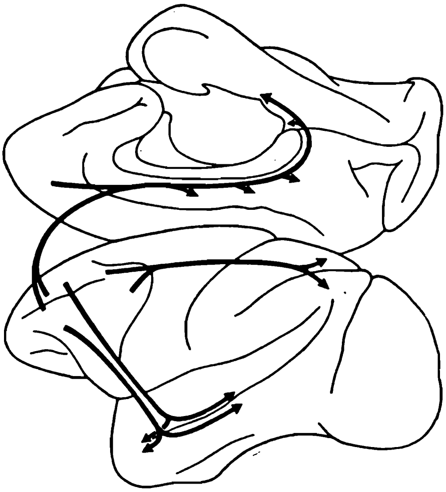

Fig. 5. Schematic representation of efferent connections of the frontal lobe with both parietal lobules, upper and middle temporal gyri, and cingulate and hippocampal gyri. This figure is based in parts on reports by Pandya and Kuypers (1969), in part also on personal communications from Dr. D. N. Pandya. (From Nauta 1971).

A major system of frontal efferents to the limbic cortex (cingulate and parahippocampal gyri) appears to originate largely from dorsal convexity cortex, and there is evidence (D. N. Pandya, personal communication) that the field of origin has its center in the dorsal bank lining the middle one-third of the principal sulcus. This fronto-limbic association is established by a fairly compact fiber bundle that follows the white matter of the cingulate gyrus caudalward, issuing fibers to the overlying cortex throughout its extent. The longest fibers curve around the splenium of the corpus callosum into the hippocampal gyrus, and are distributed in this region as far as the presubiculum hippocampi.

Very recently, a second pathway linking the frontal lobe to the hippocampal formation has been identified (Dr. G. Van Hoesen, personal communication) in the form of a direct projection from the caudal orbitofrontal cortex to the entorhinal area, a region of the uncus cortex that has long been known to be the source of a massive fiber system (Cajal's perforant pathway) to the hippocampus.

By virtue of these fronto-limbic connections the frontal cortex may stand in very close relationship with the hippocampal formation, but it must be emphasized that the frontal lobe is not unique in this regard, for Pandya and Kuypers' (1969) study has demonstrated that substantial direct projections to the cingulate and parahippocampal gyri originate also from rostral temporal regions and from the inferior parietal lobule. The conclusion can be drawn from these observations, that neocortical projections to the limbic (cingulate and juxtahippocampal) cortex originate largely at least from three interconnected cortical regions among which the frontal cortex appears to occupy a central position.

b) *Subcortical projections of the frontal cortex.* Nowhere more explicitly than in its subcortical connections does the frontal lobe declare its close association with the limbic system. This relationship is expressed most clearly by the substantial projections that have been traced from the frontal cortex (De Vito and Smith 1964, Nauta 1962, 1964) to the preoptic region and hypothalamus and, beyond these diencephalic structures, to a paramedian zone of the mesencephalic tegmentum that includes the ventral half of the central grey substance, the ventral tegmental area, and the nucleus centralis tegmenti superior of Bekhterev. Together with the septal region, these subcortical structures and their interconnections compose a highly differentiated meso-diencephalic continuum that also is a major distribution zone for projections arising in various components of the limbic telencephalon, the hippocampus and amygdala in particular (Nauta 1958, 1961).

By entertaining subcortical projections in such extensive overlap with those of the limbic forebrain, the frontal lobe distinguishes itself sharply from all other regions of the neocortical mantle. It must be noted, however, that this unique neocortical projection apparently does not arise from all subdivisions of the frontal lobe equally. A frontal projection to the lateral preopticohypothalamic region, for example, has been traced from caudal regions of the orbital surface (Nauta 1962) whereas a second projection, apparently originating dorsal to the principal sulcus, distributes itself not only to lateral regions of the hypothalamus, but also to the so-called dorsal hypothalamic area and to the posterior hypothalamic nucleus, central grey substance, ventral tegmental area, and Bekhterev's nucleus (personal, unpublished observations). In a recent article Johnson et al. (1968) have described an additional projection passing from the dorsal bank of the principal sulcus to the septum. Few if any comparable projections appear to arise from convexity cortex ventral to the principal sulcus. It must be noted, however, that the fronto-hypothalamic and fronto-mesencephalic projections have not yet been analyzed in adequate detail with respect to either origin or distribution.

Besides these projections to the hypothalamus and associated brainstem structures, the frontal lobe has been found eo emit fibers to the striatum, to the subthalamic region, to a region of the mesencephalic tegmentum lateral and dorsal to the red nucleus, and to a medial zone of the pontine grey matter. The fronto-striatal projection involves a rostroventral part of the caput nuclei caudati as well as certain regions of the fundus striati (i.e., the zone of confluence of the caudate nucleus and putamen).

Any particular functional significance of the fronto-striatal connections must lie hidden in its topographic characteristics, for all or nearly all cortical regions project to particular zones of either the caudate nucleus or putamen, or both. No functional mosaic of the striatum appears to be known at present, but it may eventually prove significant that, in the cat, extensive lesions of the general region of the caudate nucleus receiving the frontal lobe projection have been found to cause a peculiar hyperkinetic dyskinesia (Liles and Davis 1969) that has been compared tentatively to athetosis. The functional implication of the fronto-subthalamic and fronto-tegmental projections are obscure except for the obvious likelihood that the frontocortical mechanism, by virtue of these connections, can affect general activity levels.

DISCUSSION

In hindsight it is possible to argue that, even in the absence of any but elementary physiological knowledge, the general functional associations of many cortical regions could have been inferred from anatomical relationships. Such a statement would be not at all presumptuous in reference to the sensory areas or the sensorimotor cortex, and perhaps not even much so if it were made with respect to certain associative areas such as the parietal cortex. Whether it can be applied to cortical regions functionally as complex as the frontal cortex remains to be considered. In any event, in attempting to elucidate a unique functional attribute of a given cortical region, it would seem appropriate in a first approach to look for unusual features in the anatomical relationships of that region.

The unique feature of the neural circuitry outlined in the foregoing account is, that it places the frontal cortex in a reciprocal relationship with two great functional realms, namely: (i) parietal and temporal regions of the cerebral cortex involved in the processing of visual, auditory and somatic sensory information, and (ii) the telencephalic limbic system and its subcortical correspondents, in particular the hypothalamus and meso- and diencephalic structures associated with the hypothalamus. The reciprocal nature of both of these two relationships deserves particular emphasis, for it entails a need to view the frontal lobe at once as a "sensory" and as an "effector" mechanism.

Thus, on the basis of its cortico-cortical connections the frontal cortex could be interpreted not only as a high-order processing mechanism for visual, auditory and somesthetic information, it could also be capable of modulating earlier stages in the processing of such information. By the same token, because of its reciprocal connections with the limbico-hypothalamic axis the frontal cortex could be viewed at once as a modulator of hypothalamic mechanisms and as a cortical region receiving information concerning the functional state of the limbic system and hypothalamus, a state in turn determined in large part at least by neural and humoral factors representing the organism's internal milieu.

Judged by anatomical data, a re-representation of both external and internal environment would seem to be a major characteristic of the frontal cortex, but such convergence is not likely to be an attribute unique to this particular cortical expanse. The cingulate cortex appears as another region where association pathways from multisensory cortical fields (in particular the inferior parietal lobule, *see* Fig. 3) converge with the projections of a thalamic cell mass implicated in the circuitry of the limbic system — in this case the nucleus anterior. It would therefore seem unlikely that loss of frontal cortex, even when complete, would prevent the cerebral cortex from receiving interoceptive information. Neither would a thalamic lesion localized to the mediodorsal nucleus of the thalamus be likely to detach the frontal cortex completely from such impulse afflux: some interoceptive information could in such a case still reach the frontal lobe by way of afferents from the cingulate region. However, comparable as the frontal and cingulate cortices are with respect to the neural circuitries of which they form part, important differences nonetheless appear to exist between these two contiguous cortical fields. Apart from cytoarchitectural contrasts which suggest that the intrinsic cortical mechanisms are not exactly alike, the two regions appear to have fundamentally different subcortical relationships. Notable in the latter category is the circumstance that the frontal cortex maintains direct projections to the hypothalamus and associated mesencephalic structures whereas no such connections appear to arise from the cingulate or, for that matter, from any other region of the neocortex. This difference suggests that one of the unique features of the frontal lobe may lie in its capacity to project panmodal neural codes directly to meso-diencephalic structures centrally involved in visceral and endocrine effector functions as well as in the neural mechanisms underlying affect states.

In past decades, a direct fronto-hypothalamic connection would likely have been interpreted as evidence of a cortical "control" over hypothalamic effector mechanisms. Within the frame of more contemporary notions, however, a somewhat different interpretation would seem possible in which the relation between frontal lobe and hypothalamus is expressed in terms of information rather than control of "higher" over "lower" levels. It could be asked, for example, if loss of the frontal cortex could perhaps entail the loss of a channel whereby neural codes representing perceptual or ideational processes in the cerebral cortex are conveyed to the hypothalamus, and by which the latter, in turn, can report to the frontal lobe any changes in its functional state, whether resulting from such cortical afflux or from neural and humoral signals emanating from the organism's viscero-endocrine periphery, or from both.

Up to this point in the discussion, the frontal lobe has been dealt with as if it were a homogeneous structure. There is, however, ample evidence that the input–output relationships of the monkey's frontal cortex vary considerably from one subregion of the field to the next, and some of these variations have been noted in the anatomical account. To recapitulate, it seems certain that those afferent associations likely to convey visual, auditory and somesthetic information primarily affect the caudal half of the monkey's frontal convexity, and particularly the region of the frontal eye-field. Olfactory information, by contrast, would seem to be distributed via the mediodorsal nucleus entirely to the orbital aspect of the lobe, and the same is probably true of the transthalamic afflux of impulses here interpreted as representing the internal milieu, except for that part conveyed through the mesencephalon by way of the lateral division of mediorsal nucleus to a yet undisclosed region of the frontal convexity. Further "interoceptive" afferents to the frontal cortex are likely to come from the cingulate cortex, but their distribution remains to be determined. As to the efferent connections of the frontal lobe, it is remarkable that both the fronto-hypothalamic connection and the frontal projection toward the hippocampal formation appear to originate largely from two widely separate fields: the caudal orbitofrontal region and some region dorsal to the sulcus principalis. By contrast, the efferent association with the amygdala by way of the temporal cortex is more likely to arise from ventral convexity areas, while the "feedback" association with the multimodal processing areas of the parietal lobe arises largely in and near the frontal eye-field. This anatomical mosaic suggests a great functional differentiation of the frontal region, a suggestion that has begun to be borne out by observations made in the course of some recent behavioral studies in the monkey. Since the authors of several such studies are with us, we may expect to hear of their findings later in this conference.

This paper is an abbreviated and modified version of an earlier publication (Nauta 1971).

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