J. Neurol. Neurosurg. Psychiat., 1950, **13**, 198.

THALAMIC PROJECTION TO FRONTAL CORTEX IN MAN*

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The object of this communication is to report the present position at the Maudsley laboratory of research on the projection of nerve cells of the human thalamus on to frontal cortex. Previous, more tentative, reports on this topic were published by Meyer, Beck, and McLardy in 1947 and by Meyer, McLardy, and Beck in 1948.

The main material used consisted of 54 cerebral hemispheres with varied leucotomy lesions. A few cases of traumatic and of vascular damage to frontal cortex were also employed. Cortical areas involved in the primary lesions were correlated with the position of retrograde nerve cell degeneration and glial proliferation observed in Nissl-stained serial sections of the thalamus. For the sake of clarity only Brodmann's cytoarchitectural nomenclature is employed in the thalamic diagrams, but the relevant homologues in von Economo's nomenclatures are given in Fig. 1 (*a*).

The main results which have emerged from this study may be summarized as follows.

The whole of the dorsomedial nucleus projects to the granular frontal cortex, with the exception of its most dorso-posterior portion (i.e., the portion left blank in Fig. 1 (*d*)), its most rostral tip, and probably a portion of the pars magnocellularis on its medial border. These three portions appear to be devoid of frontal connexion.

Those nerve cells of the pars magnocellularis of the dorsomedial nucleus which have definite cortical connexions project to granular cortex within the medial half of the orbital region, i.e., essentially to Brodmann's area 11. The pars parvocellularis projects to the remaining granular frontal cortex in the manner indicated by the Brodmann numerals in Figs. 1 (*b*) to 1 (*d*).

It is possible that fibres projecting to the medial half of the orbital cortex travel outside the internal capsule, ventral to the striatum.

There is an antero-posterior axial organization, in that the more rostral cells of the pars parvocellularis are related to the more rostral portions of its cortical projection field, the more caudal to the more caudal; also a general coronal circumferential organization such that adjacent regions in the nucleus project to adjacent areas in the cortex.

The nucleus submedius, when present, projects to the same cortical field as the adjacent part of the dorsomedial nucleus, namely area 8.

The other intralaminar nuclei, including the centromedian nucleus and the parafascicular nucleus, and the midline nuclei, have no projection to the frontal cortex, so far as can be argued from observations on retrograde degeneration after fairly circumscribed damage to the frontal lobe. There is, however, some indication that some of them may possess a diffuse cortical projection.

The agranular area 6 receives projections from dorsal and medial parts of the nucleus ventralis anterior and the nucleus ventralis lateralis and probably also from adjacent parts of the reticular nucleus. There is a dorso-ventral axial organization here.

The agranular area 24 (the anterior cingulate region) receives projections from that portion of the anterior nuclear complex which is probably homologous with the nucleus anteromedialis of lower animals, though histologically indistinguishable from the nucleus anteroventralis in man.

So far there is no clear evidence of any thalamic projection to the agranular area 44, or to that agranular posterior orbital cortex which Beck (1949) has recently delineated in the human brain in regions corresponding to Walker's areas 13 and 14 in the macaque monkey.

Owing to the almost inevitable presence of retrograde degeneration due to the damage related to the region of the leucotome entry-track, it has been impossible to determine quite definitely whether or not there is any thalamic projection to the rostral pole (area 10) or to areas 32 and 12 of the mesial granular cortex. It appears reasonably certain now, however, that area 32 receives no projection from the anterior nuclear complex and that any projection from the dorsomedial nucleus to area 10 must be very weak indeed.

Many of the thalamic nuclei appear to contain small nerve cells of a different order of magnitude from those usually described and studied. They may be intrathalamic in their connexions.

*Paper read at the Fourth International Neurological Congress held in Paris in September, 1949.

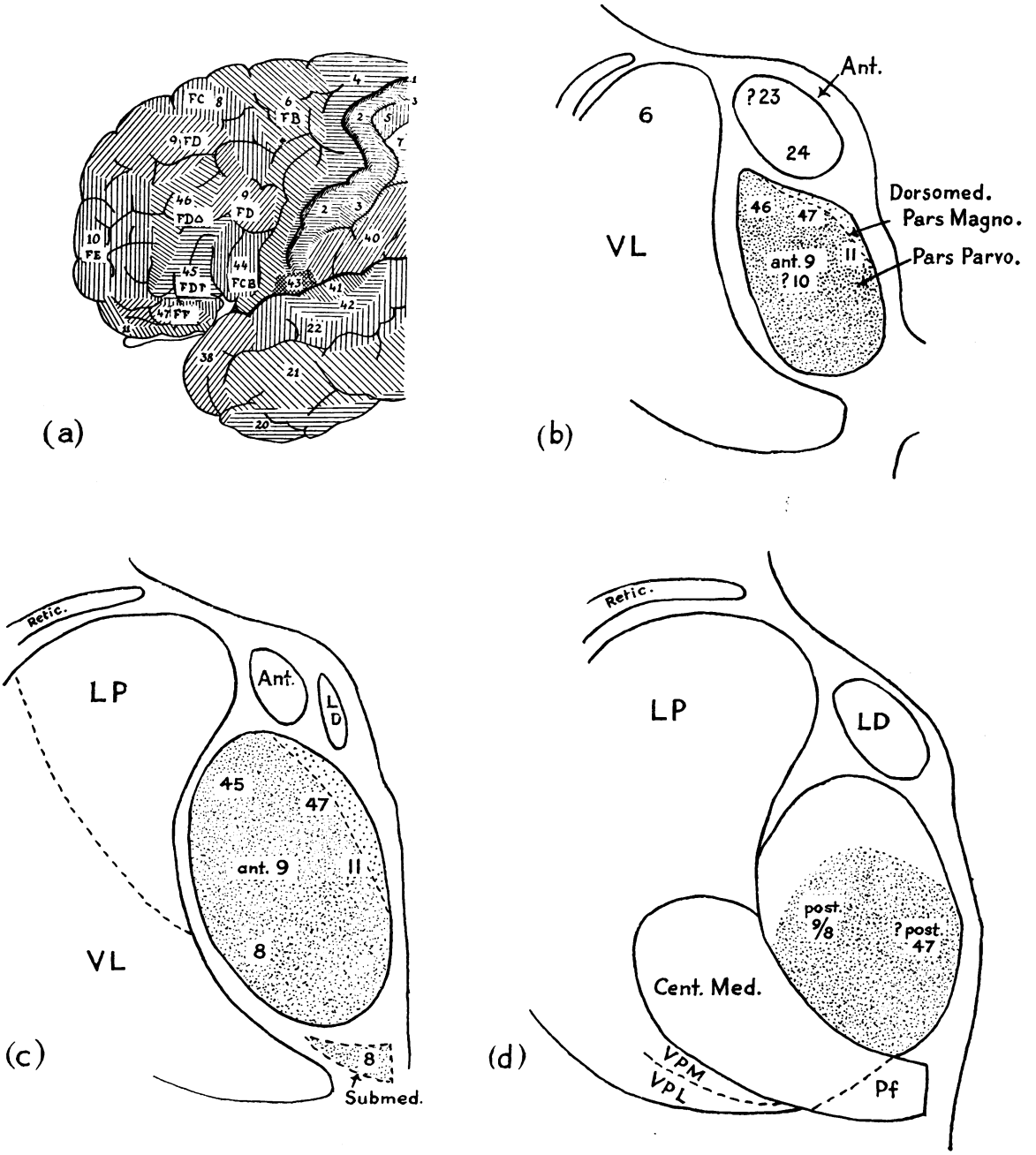

FIG 1 (*a*).—Architectural map of the convexity and orbital surface of the frontal lobe, combining the Brodmann and von Economo terminology.

FIG. 1 (*b*, *c*, *d*).—Coronal sections of the human thalamus at anterior, middle, and posterior levels of the dorsomedial nucleus. The Brodmann areas to which zones of thalamic neurons project are indicated by the numerals. The " blank " area in the posterior part of the dorsomedial nucleus is unstippled.

Ant.=nucleus anterior; Cent. med.=nucleus centrum medianum; LD=nucleus lateralis dorsalis; LP=nucleus lateralis posterior; Pf=nucleus parafascicularis; Retic.=nucleus reticularis; Submed.=nucleus submedius; VL=nucleus ventralis lateralis; VPL=nucleus ventralis postero-lateralis; VPM=nucleus ventralis postero-medialis.

Discussion*

On the whole, the points of agreement with the thalamic parcellation schemes of Freeman and Watts (1947 ; 1948) for man, and of Le Gros Clark and Boggon (1935), Walker (1938 ; 1940 ; 1944), and Mettler (1947) for monkeys, are more numerous than the discrepancies.

Projections of the Dorsomedial Nucleus to the Cortex.—Freeman and Watts relate area 8 to the ventral nuclear complex and not at all to the dorsomedial nucleus as indicated by the present material. Mettler has discussed this difference of Freeman and Watts' observations in man from his own, and from Walker's findings in monkeys, pointing out how variably area 8 has been placed in different cytoarchitectonic maps of the forebrain. The individual variability in the extent of area 8 has been emphasized by Lashley and Clark (1946) in monkeys, and also by Beck, McLardy, and Meyer (in press) in preliminary studies of normal human hemispheres. So far as white matter lesions permit of correct evaluation of the cortical involvement, the present material definitely indicates that at least anterior parts of area 8 are related to the dorsomedial nucleus (and to the nucleus submedius).

The observation that there is a negligible projection from the dorsomedial nucleus to area 10 agrees much more with Walker's (1938) finding in macaques than with Freeman and Watts' relation of this area to an extensive central portion of the nucleus.

In the light of the more abundant and more varied material, the earlier (Meyer and others, 1947 ; 1948) tentative sites within the dorsomedial nucleus which were related to anterior areas 47 and 11 have been reversed. This now brings the position of area 11 into line with that allotted it by Freeman and Watts and by Mettler.

White matter lesions created by leucotomy from the lateral convexity are too gross for correlation with such a small and mesial portion of cortex as area 12, any retrograde degeneration related to this area being obscured by that caused by the damage to more lateral white matter and cortex. In addition, area 12 is cytoarchitecturally very indistinct, if validly separable at all from adjacent areas. It is therefore omitted from the scheme for the present. The same difficulties apply to the determination of any projection to area 32.

The caudal portion of the dorsomedial nucleus is now tentatively suggested by Freeman and Watts (1948) to project to area 13. Walker (1944), who first delineated such an agranular zone of cortex in the posterior orbital region in monkeys (1940), considered that it might receive many fibres from the medial parts of the dorsomedial nucleus, but not from the pars magnocellularis. Von Bonin and Green (1949) concluded that " it receives, at best, a very scarce thalamic projection". Leucotomy lesions of this area have been very few and very small in the present series. Investigation of them certainly does not seem to support the tentative view of Freeman and Watts, whereas there are many cases which would relate caudal portions of the dorsomedial nucleus (Fig. 1 (*d*)) to the most posterior granular frontal areas : ventral area 8, posterior area 9, and posterior, but probably not the agranular part of, area 47. Regarding the " blank " postero-dorsal portion of the dorsomedial nucleus, it is noteworthy that Hassler (1948) in his myeloarchitectural studies of human thalami found no evidence of a projection to the cortex from his " lateral caudal sector ".

Von Bonin and his associates (1947 ; 1949) deny any projection of the pars magnocellularis of the dorsomedial nucleus to the frontal cortex in man and monkey. Freeman and Watts, Walker and Mettler, as well as Le Gros Clark and Russell (1940) and Norman (1945), are all, on the other hand, in accord with the evidence of the present material that at least a portion of it does have cortical projection. None of these authors has delimited its projection so precisely as the present material seems to do, to the medial orbital cortex. That it should ever degenerate completely after lesions limited to the cortex would seem inconsistent with Walker's (1936) demonstration that some of its cells degenerate after certain lesions in the hypothalamus (in monkeys). I have the impression that the whole rostral tip of the dorsomedial nucleus is essentially " magnocellular " and, together with the paralamellar nuclei (which Krieg actually includes in the pars magnocellularis) and the pars magnocellularis, comprises a capsular " grid " around the remainder of the dorsomedial nucleus in a manner reminiscent of the relationship of the reticular nucleus to the entire thalamic nuclear complex (including the geniculate bodies).

An antero-posterior general organization of the projection of the dorsomedial nucleus to the frontal cortex has been found by most observers. Walker's (1940) further observation that the medial part of the dorsomedial nucleus projects to the orbital region, whilst the lateral portion projects to the convexity, is substantiated by Freeman and Watts, as well as by the present material Such niceties as point to point projection are impossible to determine from lesions which involve chiefly the white matter.

*Discussion is limited to findings in primates, except where some general principle has been suggested by observations on lower mammals.

Intralaminar and Midline Nuclei.—Krieg's (1948) observation that the nucleus submedius is inconstant in the human thalamus is fully borne out by my experience. It could be identified, very indefinitely, in about one-third of 65 serially sectioned thalami. Neither its position nor its cortical projection to area 46 as described by Freeman and Watts can be confirmed. It seems, rather, to lie adjacent to and to project to the same cortical region (area 8) as the ventro-lateral portion of the dorsomedial nucleus.

Sheps' (1945) observation that the midline nuclei may be insignificant in man is confirmed by the present material, at least for the majority of these nuclei. That they and the intralaminar nuclei, excepting the nucleus submedius, are spared from degeneration after cortical lesions is agreed by most observers. Le Gros Clark and Russell (1940), however, in their case of hemidecortication, found nerve cells in the midline nuclei surprisingly few in number and I have seen disappearance of the intralaminar nuclei on the affected side in a case of extensive vascular lesion limited essentially to cortex. This might be an indication that these nuclei have a diffuse cortical projection. Again, Le Gros Clark and Russell's (1940) and Norman's (1945) impression that the whole of the dorsomedial nucleus was degenerated in their respective cases of decortication, might be evidence that some neurons even of the main thalamic nuclei project diffusely over the cortex, for the retrograde degeneration in affected parts of the dorsomedial nucleus after leucotomy is never complete. It is important to bear in mind at the same time that it can never be argued conclusively that cells which fail to degenerate have not had their axons cut.

Thalamic Projections to Agranular Cortex.—The present findings are in general accord with Walker's conclusion that the dorsal part of area 6 receives projections, especially from the dorsomedial part of the nucleus ventralis lateralis and the ventral part of area 6 projections from the ventromedial part of the nucleus ventralis lateralis. Walker (1944) also relates area 44 to the ventromedial part of the nucleus ventralis lateralis, but later goes on to say that "in the macaque it receives few thalamic fibres. In the chimpanzee data are lacking, and in man nothing is known of its thalamic connexions". Numerous suitable cases in the present material fail to show evidence of any such projection in man.

This present material also fully corroborates Toncray and Krieg's (1946) observation that there is no discernible distinction between a nucleus ventralis anterior and ventralis lateris in man. There are several cases which confirm Sheps' (1945) finding of degeneration of the entire rostral portion of the ventral nuclear complex in man after extensive cortical destruction, and also Le Gros Clark and Russell's like observation in their human case of hemidecortication. Walker considered that in monkeys, and probably also in chimpanzees, the nucleus ventralis anterior projects to the striatum. Mettler came to the same general conclusion with regard to monkeys, yet he found the whole of the nucleus ventralis anterior to have disappeared in one case after complete decortication (1943, Case 36, quoted in 1947).

No extensive observations have been possible, from the present material, on afferent projections to area 4. Area 13 of the agranular orbital zone has already been discussed.

The Reticular Nucleus.—This nucleus is considered by Freeman and Watts and by Sheps to show no degeneration after frontal lobe damage. Walker and Mettler considered it to be as severely affected as the adjacent ventral nuclear complex. My impression is that its cells are definitely not so severely affected as those of the neighbouring nuclei.

The Anterior Nuclear Complex.—All the material investigated confirms Krieg's (1948) view that in the human thalamus the nucleus anteromedialis is not visually distinguishable from the nucleus anteroventralis.

Freeman and Watts and Mettler related dorsal parts of the anterior nuclear complex to area 24, and ventral parts to area 32. The present evidence of limitation of the connexion of area 24 to the presumptive site of the nucleus anteromedialis agrees with the observations of Le Gros Clark and Russell (1940), Walker (1938), and Kirschbaum and von Bonin (1947) in primates, and of Rose and Woolsey (1948) in lower mammals. There is also some evidence to support Rose and Woolsey's suggestion that the explanation of discrepant findings may lie in the fact that deep lesions in anterior parts of the cingulate gyrus may cut fibres from the nucleus anteroventralis which follow a looped course as far rostrally as the genu of the corpus callosum on their way to the posterior cingulate area 23. There are three clear-cut cases with damage to area 32, and not to area 24, with no retrograde degeneration within the anterior nuclear complex. These findings are in keeping with Walker's view that the anterior nucleus has only a light, if any, projection to the anterior cingulate cortex. The nucleus anterodorsalis has not been noticed to be degenerated in any of the material.

Projection Pathways.—Kirschbaum and von Bonin's impression that the radiation from the

dorsomedial nucleus reaches the internal capsule by streams encircling the lateral nuclear mass both dorsally and ventrally is not at all supported by the present investigations. It would appear that these authors may be misinterpreting either the gliosis extending into the zona incerta which follows lesions involving area 6 or the gliosed fronto-pontile and fronto-nigral tracts before they sweep lateral to, and sometimes through, the subthalamic nucleus into the peduncle. An unexplained gliosed bundle has been observed in some cases passing through the dorsomedial nucleus into the parafascicular nucleus in the direction of the fasciculus retroflexus.

Circumstantial evidence from a considerable number of cases indicates that the radiation from the pars magnocellularis of the dorsomedial nucleus to the medial half of the orbital cortex remains in a ventral position, possibly running ventral to the striatum and never entering the anterior limb of the internal capsule.

Intrathalamic Neurons.—Throughout this discussion the term " nerve cells " has been used to refer to those cells which have been described and defined in the thalamus in some detail by such workers as Sheps and C. and O. Vogt (1941). I have recently observed that under high magnifications most of the main nuclei of the thalamus can be seen to contain additional nerve cells of a different order of magnitude, ranging from two to six times the size of astroglial nuclei. These small neurons do not appear to degenerate appreciably after cortical damage. A fuller description of their distribution and characteristics will be given in a subsequent communication.

Progress in elaborating this parcellation scheme has been slow because, among other reasons, the medial orbital region is very seldom much damaged in the usual leucotomy operation performed in Britain, the mesial cortex is never damaged in even relative isolation, and the exact relation of cortical areas to white matter lesions is often difficult to establish. It would be of the greatest value for a more rapid and precise elucidation of thalamic connexions with frontal cortex if brains on which topectomy has been performed are, in the fullness of time, submitted to neuropathological laboratories for systematic investigation.

Summary

The thalamo-frontal projection has been investigated in some 60 human hemispheres by studying the retrograde degeneration which occurred in thalamic nuclei, especially after leucotomy. The main results are presented in a diagram and are discussed in the light of previous findings in primates by others.

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