
Alfred Meyer (1895–1990) was born and educated in Krefeld, Germany. After considering careers in music and law before serving on the western front in the Great War, he turned to medicine on demobilization. Influenced initially by (Ludwig) Aschoff (1866–1942), Meyer subsequently studied pathology in Munich with (Walther) Spielmeyer (1879–1935) and (Hugo) Spatz (1888–1969); but, being Jewish, decided to leave Germany in 1933 for London where he was welcomed at the Maudsley Hospital by (Edward) Mapother (1881–1940) and (Frederick) Golla (1878–1968). His work with Elizabeth Beck (nk) culminated in the monograph on Prefrontal leucotomy and related operations: anatomical aspects of success and failure (1954). Later Meyer made contributions to the clinical science of temporal lobectomy for the treatment of epilepsy being developed by Murray Falconer (1910–77) at the Maudsley Hospital. In retirement he wrote a scholarly work on Historical aspects of cerebral anatomy (1971), and papers on Dr Thomas Willis (1621–75) with Raymond Hierons (1921–2001).

Professor Meyer and colleagues have previously reported psychiatric and therapeutic results in a series of patients undergoing prefrontal leucotomy; now, they describe the neuropathological findings in 6 of the 10 original cases. That so much material is available does not speak well of the procedure. Not only are there very few studies of anatomical changes that follow lesions of the frontal white matter in man, but the unpredictable location and extent of secondary degeneration make each case a unique experiment, ‘an unqualified boon’. The richness of the opportunity has led to novel observations on the thalamic projection to the cingulate cortex, the premotor region and that part of the fronto-pontine projection known as Arnold’s bundle. Not here included are definitive accounts of the long association fascicule projecting to the prefrontal lobe; those of the prefrontal cortex to the caudate via the subcallosal bundle; and the anatomy of the centromedian nucleus.

A 72-year-old man (Case 3) with agitated depression derives no benefit from prefrontal leucotomy and dies 2 months later from uraemia. The surgical lesion mainly involves the white matter deep to areas 45, 46 and 47, extending rostrally to underlie areas 9 and 8, and caudally to the wall of the lateral ventricle; the orbital regions (areas 11 and 12) and the cingulate gyrus (area 24) are spared. A woman of 50 years (Case 4) with paraphrenia develops a severe frontal-lobe deficit syndrome with restlessness and dies 4 months after surgery from ‘exhaustion leading to thiamine deficiency’. The left hemisphere lesion involves white matter deep to areas 6, 8, 9, 46 and 45, extending into the cingulate gyrus (area 24), rostrally to the middle frontal gyrus and caudally to the lateral ventricle, insula, claustrum, putamen, caudate and internal capsule; the orbital region is spared. A man aged 44 (Case 5) with a long history of destructive schizophrenia dies in status epilepticus 17 months after prefrontal leucotomy that does not modify his psychosis. The left hemisphere lesion underlies areas 9, 10 and the medial orbital region (areas 12 and 11); rostrally it extends to area 32 and caudally to the orbital gyri (areas 47 and 11) and cingulate gyrus (area 24). A woman of 60 years (Case 6) undergoes right frontal lobectomy aimed at removing a basal meningioma causing bilateral optic atrophy; surgery is complicated by pathological sleep and eventual death in coma. The lesion involves areas 8, 9, 46, 45, 47, 11, 12 and 32 with displacement of other structures and softening in the cingulate gyrus (areas 24 and 23). A man of 39 (Case 9) with recent onset schizophrenia dies from pulmonary tuberculosis 2 years after successful prefrontal leucotomy that relieves his hallucinations, delusions and suicidal depression. The lesion stretches from the inferior frontal gyrus (area 45) rostrally to area 46 and caudally to area 44. A woman with a psychopathic personality (Case 10) dies from complications of streptococcal stomatitis and broncho-pneumonia 3 years after prefrontal leucotomy which partially relieves her ‘gross hysterical outbursts’. The lesion extends from the anterior tip of the genu of the corpus callosum to the inferior frontal gyrus (area 45), the orbital region (areas 47 and 11) and the striate body. In total, eight hemispheres are studied, bilateral symmetrical lesions of the same brain counting as one sample but with much variation in the size and distribution of lesions.

First the authors consider secondary changes involving cortical projections from the thalamus. Five hemispheres show retrograde...
degeneration with extensive gliosis and neuronal depletion, or shrunken cells with abnormal morphology, most marked in the medial and ventral parts of anterior thalamic nuclei; the other cases are normal in this respect. Considering the location of the frontal lesions responsible for these abnormalities, the evidence from Cases 4, 5 and 6 favours the position taken by (Sir Wilfrid) Le Gros Clark (1895–1971) who, with others, has argued that fibres originating in the anteriomedial and anteroventral thalamic nuclei project to the rostral and caudal parts of the cingulate gyrus, respectively; and with topographical representation of the individual nuclei and cortical projection zones within these tracts. The authors are less certain whether their work resolves the issue of fibre connections between the anteromedial thalamic nuclei and the orbital surface of the frontal lobe (area 47).

Next they consider lesions of the dorsomedial nucleus of the thalamus, present in all eight hemispheres. In Cases 3, 4 (left and right), 6, 9 and 10 most degeneration affects the parvicellular (Fig. 1), whereas in Cases 5 (left and right) and 6 the magnocellular part is equally or predominantly involved (Fig. 2). In correlating these secondary degenerations with the primary lesions, their view is that the parvicellular part of the nucleus projects to the inferior frontal gyrus (areas 45 and 46); the ventrolateral component to the superior frontal gyrus (area 8); the central portion to the middle frontal gyrus (areas 46 and 9, or 10); and the medial portion to the lateral part of the orbital region (areas 47 and 11). Conversely the magnocellular part projects to the medial half of the orbital region of the frontal lobe (areas 12 and 11). The authors take as their authority the work of (Earl) Walker (1907–95) who has described lamellation with a dorsoventral axis of the prefrontal lobe corresponding to the lateromedial axis of the dorsomedial thalamic nucleus. In this and many other aspects, their work is consistent with Walker’s observations on monkeys; but not with respect to projections of the dorsolateral and ventrolateral portions of the parvicellular parts. Perhaps the differences lie in the relative imprecision of lesions that target white matter rather than direct cortical ablations in monkeys. What can be said with certainty is that the magnocellular-orbital projection is confirmed; and, taken with other connections to this part of the thalamus, a direct link between the hypothalamus and prefrontal region is also established explaining effects of vagal stimulation and autonomic correlates of changes in emotional state.

The submedial nucleus of the thalamus is degenerate in Cases 3, 4 (left and right) and 6. Surprisingly, since Walker finds this nucleus to be intact in monkeys suffering removal of one hemisphere, it must be the case that a new system of connectivity projecting to area 8 of the superior frontal gyrus has been
acquired in humans, perhaps in association with intra-thalamic synaptic connections to the ventrolateral region of the pars parvicularis of the dorsomedial nucleus since this is also invariably affected in these four hemispheres. Case 4 (left and right) shows degeneration only in the anterior ventral and reticular thalamic nuclei. This is consistent with prior evidence that these nuclei project to area 6. The authors’ observations settle an old debate, now considered spurious, that implicates connection between these nuclei and area 8.

Considering the anterior thalamic radiation, all cases show gliosis in the internal capsule, ventral to the caudate nucleus and anterior to the thalamus, which tracks dorsally in the anterior limb of the capsule occupying the upper half anterior to the globus pallidus. This represents the path taken by parvicular fibres projecting from the dorsomedial nucleus to the prefrontal cortex; and an area of ventral gliosis in the anterior sections of the internal capsule is the trajectory for fibres of the magnocellular and medial parvicular origin radiating towards the orbital cortex. A smaller patch of gliosis located in the lateral border of the subcallosal fasciculus of the internal capsule moves to a more dorsal position and ends in the ventrolateral angle of the anteromedial nucleus; this is the fibre tract connecting the thalamus to the cingulate cortex.Taken together, the authors’ observations on the internal capsule indicate that fibres projecting to the orbital region remain within the ventral half of the capsule whereas those radiating to other prefrontal regions shift into the dorsal stream.

In considering the ‘prefronto-pontile’ tracts, the authors draw on evidence from gliosis in the internal capsule to show, in all cases, that the patch of degeneration passes lateral to the reticular nuclei and, at the level of the zona incerta, swings ventrally into the medial segment of the cerebral peduncle close to the subthalamic nucleus, sometimes even entering that structure, and terminating in the dorsomedial nerve cells of the anterior pons. This represents degeneration in Arnold’s bundle. Starting with the work

Figure 2 Diagrams of the primary lesions. Cross-hatching indicates complete loss of tissue; single-hatching represents incomplete loss with nerve-cell or fibre damage. Case 6: the magnocellular part is indistinguishable due to severe degenerative changes. The parvicular part is very cell-poor throughout from the anterior tip of the nucleus to the level of the junction of middle and posterior thirds of the centromedian nucleus and slightly degenerated more posteriorly. The degeneration is at all levels severest in the medial half. (Not all images are reproduced). From Meyer et al. (1947).
of (Sir David) Ferrier (1843–1928) and (William Aldren) Turner (1864–1945: see Brain 2011; 134: 2190–93), the frontal origin of this tract has never been resolved. The authors’ work points to area 10, the evidence from Cases 5 (left and right) and 6 with degeneration and lesions of this region, and Case 3 without either, being especially persuasive. There is better agreement on the termination of Arnold’s bundle in the dorsomedial pontine nuclei, although whether it projects to the substantia nigra is not so clear; and the termination of frontal fibres in the subthalamic nucleus, although proposed by (Santiago Ramon v) Cajal (1852–1934), is equally ambiguous.

Preliminary consideration is given to arrangements of the long association tracts connecting different parts of the cortex based on lesions in these cases undergoing leucotomy. The difficulty is that the degeneration can never be traced across the entirety of any one specimen. The uncinate fasciculus allegedly connects areas 10 and 47 of the frontal lobe with areas 22 and 38 of the temporal lobe. The authors’ observations in Cases 5 and 9 are suggestive of an uncinate pathway running in the external capsule but its frontal origins cannot be stated with certainty. The existence of a cingulate fasciculus seems likely but almost nothing can be said with respect to the putative subcallosal, superior longitudinal, arcuate or inferior occipito-frontal pathways.

Margaret Meyer (nk) considers that there are limitations to this work based on tracking gliosis and secondary neuronal loss which she intends to correct by studying projections from the cortex to the thalamic nuclei using Gleys’ ammoniacal silver impregnation method and Nissl staining in cases with short survival times (7–16 days) after leucotomy. Her starting point is the work of Le Gros Clark classifying these pathways into cortico-striate, cortico-thalamic, cortico-hypothalamic and cortico-pontine. Here she deals with connexions to the globus pallidus, thalamus and subthalamus, posterior hypothalamic and mammillary body. She reports in detail on 4 of 10 available cases; of the remaining six, the lesions are massive and not well placed in three, too small in one, and with fixation artefacts in two others. One hemisphere only is described for each case.

A man of 24 years with paranoid schizophrenia, refractory to electroconvulsive therapy, undergoes bilateral frontal leucotomy after which he is mute and unresponsive, dying on Day 15 from subarachnoid haemorrhage with medullary coning. The lesion destroys white matter deep to areas 6, 8, 9, 46, 32 and 45 and some cortex from areas 9, 32 and 24. Secondary degeneration is most evident in the ventral and medial parts of the internal capsule moving directly into the globus pallidus (Fig. 3). In addition some fibres that pass through the reticular nucleus to enter the anteroventral nuclei are degenerating, whereas those of the anterior nucleus are normal. Fibres entering the submedial and ventrolateral nuclei, the zona incerta and the dorsomedial nucleus are affected. Beyond, there is degeneration of fibres forming part of (Auguste-Henri) Forel’s (1848–1931) field H2 and the prerubral field of (Henry Alsop) Riley (1908–66); those connecting the

![Figure 3](http://brain.oxfordjournals.org/)

Figure 3 The distribution of axonal degeneration is shown by black lines and of terminal degeneration by coarse dots. Case 1: (A) anterior, (B) middle and (C) posterior levels of section through the thalamus and neighbouring structures. From Meyer (1949).
thalamus to the hypothalamus, sparing the posterior and lateral parts, and of the medial mammillary nucleus; and with involvement of the lateral half of the subthalamic nucleus, the substantia nigra and the medial portion of the cerebral peduncle.

A woman aged 38 dies from subarachnoid bleeding and medullary coning 7 days after prefrontal leucotomy carried out for post-encephalitic parkinsonism, complicated by severe behavioural disorder. The primary lesion is hard to assess because of a large frontal haematoma extending into the ventricular system. Secondary degeneration is evident in most of the internal capsule, with relative sparing of dorsal fibres, some passing through an intact ansa lenticularis towards the cerebral peduncle and the substantia nigra; others enter the globus pallidus and sweep into the ventrolateral, submedial nuclei and dorsomedial nuclei, and the zona incerta. Here, there is some damage to fibres connecting the anterior thalamic nuclei. Beyond, there is degeneration of fibres forming part of Forel’s field H2, the prerubral field of Riley, and the red nucleus itself. The subthalamic nucleus is affected and, whereas the hypothalamus is relatively spared, there is extensive degeneration in the medial mammillary nucleus.

A woman aged 65 undergoes prefrontal leucotomy 6 weeks after developing an acute psychosis and dies 16 days later from bronchopneumonia and cerebral coning. There is extensive cerebral haemorrhage and disruption of all prefrontal white matter apart from the posterior orbital region and area 6. There is secondary degeneration of medial parts of the internal capsule extending into the cerebral peduncles and reticular zone of the substantia nigra. In this case, the globus pallidus, mammillary body and thalamic nuclei, apart from the posterior aspects of the dorsomedial nucleus, are intact.

A man aged 73 years with a 3-year history of depression not responding to insulin and electroconvulsive therapy dies on the seventh day following bilateral prefrontal leucotomy. There is white matter damage extending from the anterior part of area 8 to the striate body and the anterior limb of the internal capsule. Secondary degeneration is confined to the medial part of the cerebral peduncle and the dorsomedial nucleus of the thalamus.

Given the imprecise lesioning and confounding factors of post-operative damage, what conclusions can be reached on connectivity of the frontal lobes? A lesion entirely confined to prefrontal granular areas (Cases 3 and 4) leads to secondary degeneration only in the dorsomedial nucleus of the thalamus, and perhaps also the closely associated submedial nucleus. When this extends to agranular cortex (areas 6 and 24) and dysgranular regions (areas 8, 9 and 32), the degeneration involves the mammillary body, other thalamic nuclei (ventrolateral, anteroventral and reticular), the zona incerta, globus pallidus, subthalamic nucleus, Forel’s fields and the red nucleus. Completely spared from secondary degeneration are the parafascicular, arcuate and centromedian thalamic nuclei. The more caudally extensive the lesion, the greater is the damage to the internal capsule and cerebral peduncles. Inferences can be drawn relating to cortical projection patterns for these thalamic nuclei and related structures. The emphasis is on the particular development of area 6. Conversely, the topographical arrangements also implicate projections from areas 6, 8 and 4 to the pontine nuclei. Although fibres approaching the substantia nigra are degenerate, these do not reach the reticular zone and cause neuronal loss. More surprising is the evidence for a direct connection between the frontal cortex and hypothalamus, sparing the posterior region, and with degeneration of the medial nucleus of the mammillary body (Fig. 4)—a structure of unknown function that is especially well developed in man. Others have argued previously that the only pathways connecting the frontal lobe and hypothalamus are indirect. Dr Meyer has not confirmed that there are fibres projecting from the anterior thalamic nuclei to the rostral cingulate cortex although this is not disproved.

As John Garfield emphasizes in ‘Sad psychosurgery’, his review of The lobotomy letters: the making of American psychosurgery by Mical Raz (see page . . .), the fashion for prefrontal leucotomy was brutal, not well grounded in empirical science and soon abandoned. António Caetano de Abreu Freire Egas Moniz (1874–1955)

Figure 4 A series of diagrams through the mammillary body to illustrate the extent and distribution of degenerative changes on the left side of Case 2, representative of all four hemispheres studied. From Meyer (1949).
considered the procedure that he had introduced to be ‘a simple operation, always safe, which may prove to be an effective surgical treatment in certain cases of mental disorder’. Not all Moniz’s patients appreciated his efforts. In the same year that he received the 1949 Nobel Prize in Physiology or Medicine for ‘his discovery of the therapeutic value of leucotomy in certain psychoses’, Moniz was shot in his office by a patient, and spent the remaining 6 years of his life in a wheelchair. Arguably, Moniz’s other contribution to clinical neuroscience, the introduction of cerebral angiography, was more deserving of recognition. But his work did provide an unwelcome opportunity for neuroanatomists working in centres where psychosurgery was used to advance knowledge on the anatomy of the frontal lobe and its connections with deeper structures.

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