The Significance of the Frontal Lobe Connections in Mental Diseases

BY P. GLEES[1], Oxford

Introduction

Research on frontal lobe connections and functions has been unexpectedly stimulated by the surgical procedure performed by MONIZ and LIMA in 1936. To improve mental illness by a surgical operation of the brain seems, at first sight, a crude and almost childish procedure, however the results observed in cases of frontal lobe removal or frontal lobe lesions in cases of severe mental illnesses are so gratifying, that it is justified to consider these operations for treatment and analyse with scientific methods their anatomical and physiological consequences.

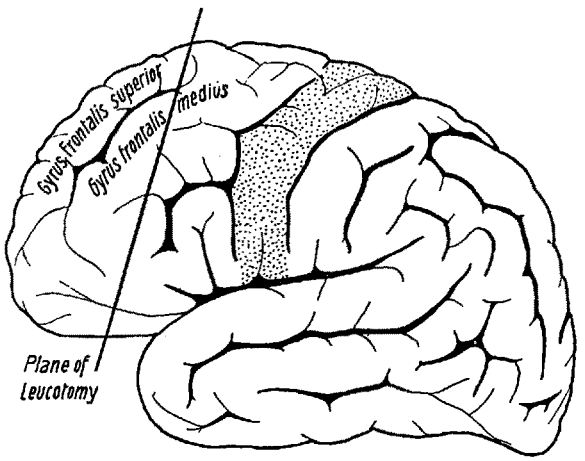

Fig. 1.

Fig. 1 and 2. Lateral and medial views of the human cerebral cortex. The dotted area shows the extent of the motor cortex or electrically excitable cortex. The black line indicates one of the customary planes in which prefrontal leucotomy is surgically performed. (Some cases will of course show a more anterior or even more posterior plane).

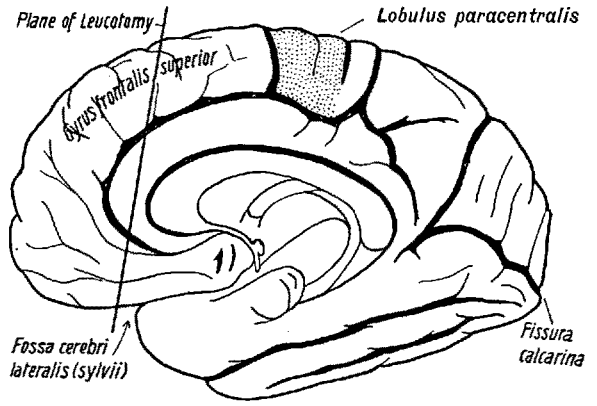

Fig. 2.

[1] University Laboratory of Physiology, Oxford, England.

Historical review

FULTON[1] gives a short historical note on the events leading to frontal lobe surgery. When FULTON and JACOBSON communicated their observations on frontal lobotomy performed on two chimpanzees to the International Neurological Congress in London in 1935, Professor MONIZ, a Portuguese neurologist, participated in the discussion of their paper and remarked that if after frontal lobe removal, an experimental neurosis no longer developed, would not this be an ideal operation for human beings suffering from persistent anxiety states. But the discussing parties agreed that such a procedure would in humans be a major operation, and was therefore unlikely to be performed. Howevèr MONIZ invented a special instrument, "The Leucotome", which could be inserted through a small hole in the skull into the brain of a patient under local anæsthesia, thus avoiding a major operation. Since this procedure has been made known, similar operations on a great number of cases have been performed in America and England, and a great deal of information resulting from them is being studied.

Foremost workers in this field are FREEMAN and WATTS in America, CUNNINGHAM DAX, RADLEY-SMITH, MCKISSOCK, and ROSS in England, who have communicated numerous cases which prove the success of an operative procedure for modifying mental symptoms.

FREEMAN and WATTS[2] have gone so far in their operations for relieving mental symptoms as to term their operative procedure "psycho-surgery". They define this ambitious term as an operation upon the anatomically intact brain for the purpose of relieving mental abnormalities. Their description of the operative procedure is quoted from as follows:—"Prefrontal lobotomy is carried out with the patient under local anæsthesia so that his conversation can be recorded. The response of the patient to the initial stages (incising scalp, drilling holes) varies. Some patients are restless and apprehensive, others are calm either with the tenseness of facing death, with their preoccupation still dominant or even in a catatonic state. Some are easily led to a discussion of their emotional difficulties and are not distracted by the operation. This discussion can be continued with perfect co-operation after the incisions in the frontal lobes are completed on either side, or after incisions which are made symmetrically in both upper or both lower halves of the two frontal lobes. (The upper and lower halves are usu-

[1] J. F. FULTON, Acta med. Scand. suppl. *196*, 617 (1947).

[2] W. FREEMAN and W. WATTS, Ann. Rev. Physiol. *6*, 517 (1944); Proc. Roy. Soc. Med. *39*, 445–447 (1946).

ally referred to as quadrants.) When the third quadrant is sectioned, there is a notable falling off in the length of their replies and in the display of emotion connected with them. When questioned, the patient with three quadrants incised is found to be well in contact with his environment and his voice still has a certain liveliness, indeed some patients with severe depression and retardation begin to speak more freely at this stage than before. When the fourth quadrant is sectioned the patient usually becomes unresponsive, his face is expressionless and his orientation is lost, he may even deny he is being operated upon. Any pre-existing nervous tension is lost with corresponding effects upon pulse rate and blood pressure. When the incisions are closed the patient is in a state resembling sleep. The patient is not asleep, however; when sufficiently stimulated he opens his eyes, smiles at relatives, gives his hand in greeting but then sinks back into his former completely indifferent state."

The patient recovers after a few days and slowly renews his contact with the outside world. In fortunate cases hardly any symptoms of his previous mental illness can be noted, or if they are still present, they do not distort his personality any more. If suitable rehabilitation is applied to the successfully operated patient an almost complete return to normal can be achieved, and the patient can return as a working member to his family. Less fortunate cases may improve sufficiently to be much more easily nursed, or to be able to be fitted into the regime of an ordinary convalescent home, or similar institution. (The exact percentage of recoveries are stated in original publications on the subject by FREEMAN and WATTS, and other authors—see Proc. Roy. Soc. Med. 1946).

Mental abnormalities treated by frontal leucotomy

COOK[1] is of the opinion that leucotomy is of greatest value in relieving states of morbid emotional tension and distress and disrupting the behaviour patterns dependent on them. He believes that there is no specific remedy for any particular mental disorder. Suitable cases for this treatment are placed by him in four groups—depressive psychoses with severe agitation and apprehension, obsessive compulsive states, some florid schizophrenic reactions with hallucinations and delusions, long-standing violent conduct disturbances (e.g. aggressive psychopaths).

Since leucotomy has been introduced clinical, psychological and electrophysiological studies have further contributed to observations and research on prefrontal leucotomy[2].

From an anatomical point of view, the study of cases who died at various intervals after prefrontal leucotomy have been most carefully examined by MEYER[1] and his collaborators. The number of his cases so far investigated is over twenty[2], and a great many interesting anatomical details have been revealed by his studies. In addition his observations have made it possible to compare the amount of damage to the central nervous system with the mental state after operation, so that one can say that only after his papers can a more critical evaluation of the leucotomy problem be attempted and positive or negative conclusions be drawn. Similar studies on fever cases have been published by FREEMAN and WATTS[3].

Functions of the frontal lobe

Investigations to gain more insight into the effects of frontal lobe operation can be divided into two categories—observations of frontal lobe function in the human (e.g. war injuries) which on the whole suffer from the great disadvantage that no anatomical controls are as yet available to any great extent, and secondly frontal lobe experiments on primates. The questions at once arising from these two points are—what are the functions of the normal frontal lobe, what is the truth about a frontal lobe syndrome, how far can animal observations on frontal lobes be related in any way to the brain functions of man? It cannot be my task to go into the normal functions of the frontal lobe or into the definition of frontal lobe syndrome. Extensive studies on this point have been made recently by GÖSTA RYLANDER[4] and published in 1939.

RYLANDER was able to show that a quite distinct frontal lobe syndrome could be demonstrated in his clinical material. Most of his patients had emotional changes such as diminished inhibition of affective responses and signs of euphoria or depression. Intellectual changes involved only the higher faculties of mental processes.

HEBB and PENFIELD[5], however, believe that bilateral frontal lobe removal can be carried out without any effect on intelligence and personality.

MEYER[6] believes that bilateral lesions of the frontal lobe and particularly the orbital involvement results in syndromes of euphoria (Witzelsucht) and general disinhibition.

Assuming that the primate frontal lobe has in the main an anatomical organization similar to the human, experiments on the frontal lobe provide a basis for studying frontal lobe connections which subsequently help in understanding their function. A detailed study

[1] L. C. COOK, Proc. roy. Soc. Med. *39*, 449 (1946).
[2] H. KRAYENBÜHL, Schweiz. med. Wschr. *36*, 965 (1947).
[1] A. MEYER, E. BECK and T. MCLARDY, Brain. *70*, 18 (1947).
[2] Personal communication. (Number includes published and unpublished cases).
[3] W. FREEMAN and J. W. WATTS. J. comp. Neur. *86*., 65 (1947).
[4] G. RYLANDER, Personality changes after operations on the frontal lobes. Oxford University Press, 1939.
[5] D. O. HEBB and W. PENFIELD, Arch. Neurol. and Psychiat. *44*, 421 (1940).
[6] A. MEYER and E. BECK, J. ment. Sci. *91*, 411 (1945).

of the primate frontal lobe has been carried out recently by METTLER[1], illustrating the current problems. Furthermore our experiments on the macaque frontal lobe have convinced us of the existence of a frontal lobe syndrome in the monkey, and it seems justifiable to use the monkey brain as a simplified model of the human. Anatomical, physiological, and psychological conclusions forthcoming from these experiments can be applied to the human frontal lobe problem if necessary caution is taken. This line of research has been followed up in Oxford for the past few years in collaboration with Dr. R. FREUDENBERG[2] and two young psychologists, FOSS and WILLIAMS[3], and for two months with Dr. OBRADOR[4,5].

Before this work on monkeys was begun however, more general investigations about the mode of the terminating fibres in the frontal lobe were carried out (GLEES, MEYER, MEYER[6]).

For the experimental work on monkeys *Macaca mulatta* has been used. The monkeys were operated on under Nembutal, the identification of the cortical areas was greatly facilitated by using electrical stimulation to reveal the motor area.

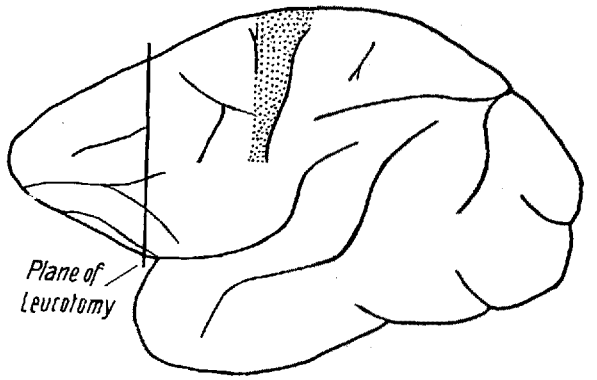

Fig. 3. A lateral view of the brain of *Macaca mulatta* illustrating one of the planes of leucotomy employed by Dr. FREUDENBERG and myself.

Different types of section were used for the prefrontal leucotomy in monkeys (vertical and horizontal leucotomies were performed). The animal's behaviour after operation was closely studied by our team and it could be observed that the behaviour varied according to the plane of leucotomy performed on a particular animal. Characteristic signs of leucotomy in monkeys were that originally very fierce aggressive animals became completely tame and docile, whilst others became extremely restless.

After a suitable survival period, the brains of the experimental monkeys were studied with modern methods of neuro-histology (GLEES[1]). These studies revealed that the most obvious signs of degeneration could be detected in the dorso-medial nucleus of the thalamus (in accordance with the findings of MEYER and MCLARDY[2], WALKER[3], LE GROS CLARK and RUSSELL[4]). We could show further that the dorsal aspect of the frontal lobe is mainly connected with the lateral half of the dorso-medial nucleus, and the orbital areas of the frontal lobe with the medial or mainly magnocellular portion of the dorso-medial nucleus of the thalamus.

Our experiments show that there is not only a projection from the dorso-medial nucleus on to the frontal lobe, but also fibres which originate there and terminate within the thalamus. Lesions in the dorso-medial nucleus of the thalamus convinced us that the fibres from this nucleus travel by a slightly different route than those originating from the frontal lobe. Previous experiments by GLEES, MEYER and MEYER[5], have shown that afferent fibres to the frontal lobe terminate in the third and fourth layer which seem to be the main receptive layers of the frontal cortex.

However, how far the individual areas of the frontal lobe as they have been mapped out by CAMPBELL, VOGT and BRODMANN are connected with separate fields of the medial nucleus has to be studied in greater detail. Unfortunately, LASHLEY and CLARK'S[6] severe criticism of cortical architecture throws grave doubts upon the value of previously published brain charts.

Whether the mental improvement in the human patient after leucotomy is really due to, or partially due to the interruption of the thalamo-frontal circuit has to be seen. Attempts have also been made by OBRADOR[7] to perform a leucotomy of the temporal lobes. However, his results up to now and the small number of cases do not as yet allow any conclusions to be made.

It can be generally stated that frontal lobe removal or prefrontal leucotomy does not cause any intellectual deterioration; it is mainly the reactions towards emotions which are changed. It is quite natural, therefore, to assume that prefrontal leucotomy interrupts

[1] F. A. METTLER, J. comp. Neur. *86*, 119 (1947).
[2] Netherne Hospital, Surrey.
[3] Inst. exp. Psychol., Oxford.
[4] R. FREUDENBERG, P. GLEES, S. OBRADOR, B. FOSS and M. WILLIAMS, The effects of frontal leucotomy and lesions in the basal ganglia and thalamus in the monkey. (Demonstration of histological material and psychological tests.) Int. physiological Congress, Oxford. July 1947.
[5] Now in Madrid.
[6] P. GLEES, A. MEYER and M. MEYER, J. Anatomy *80*, 101 (1946).

[1] P. GLEES, Brain. *66*, 229 (1943); J. Neuropathy a. exp. Neurol. *5*, 54 (1946); Nature *160*, 194 (1947).
[2] A. MEYER and T. MCLARDY, Proc. Roy. Soc. Med. *40*, 141 (1946).
[3] A. E. WALKER, The Primate Thalamus. University of Chicago Press, 1938.
[4] W. E. LE GROS CLARK and D. S. RUSSELL, J. Neurol. and Psychiat. *3*, 123 (1940).
[5] P. GLEES, A. MEYER and M. MEYER, J. Anatomy *80*, 101 (1946).
[6] K. S. LASHLEY and G. CLARK, J. comp. Neurol. *85*, 223 (1946).
[7] S. OBRADOR, J. Neuropath. and exp. Neurol. *6*, 185 (1947).

at some level the balance between the cerebral cortex and the hypothalamus. The focus for this connection may be the dorso-medial muscles of the thalamus, which projects upon the frontal lobe cortex. However, definite proof of this has still to be brought forward.

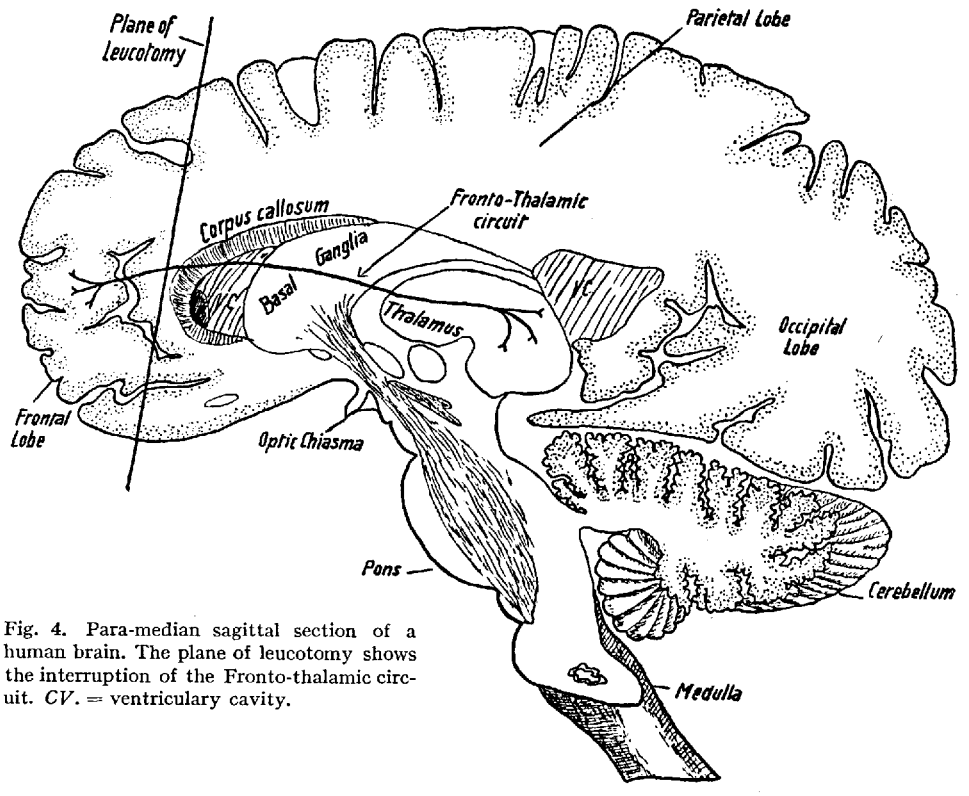

Fig. 4. Para-median sagittal section of a human brain. The plane of leucotomy shows the interruption of the Fronto-thalamic circuit. *CV.* = ventriculary cavity.

Further research on these points has to be done, and is already in progress, and we can safely expect that the publications of the next few years will not only show great interest in this delicate problem but also real progress in the understanding of the human mind.

I am indebted to the Doctors mentioned in this paper for their collaboration, and to Miss SMITH and Miss SIMMS for technical help.

Zusammenfassung

Seit der Einführung der prefrontalen Leukotomie oder dem frontalen Hirnschnitt[1] sind mehr als 10 Jahre vergangen. Trotz anfänglicher Bedenken der Hirnchirurgen und Psychiater hat sich jetzt die Mehrzahl der Fachärzte in der angloamerikanischen medizinischen Welt entschlossen, diese Operation zur Behandlung von Geisteskrankheiten mit heranzuziehen. In England sind mehr als 1000 und in USA. mehr als 2000 Fälle hirnchirurgisch behandelt worden. Die Operationsmethode besteht im Durchschneiden der weißen Substanz des Frontallappens auf beiden Seiten rostral der motorischen Region, um keine Lähmungen zu verursachen. FREEMAN und WATTS sind die amerikanischen Autoren, die die größte Erfahrung auf diesem Gebiete haben und deren Publikationen genaue klinische Informationen und Literaturübersichten bieten, während die Auffassungen und Erfahrungen englischer Autoren in einem Sitzungsbericht der «Royal Society of Medicine» 1946 zusammengefaßt wurden. FREEMAN und WATTS führen die Leukotomie nicht nur bei Psychosen aus, sondern auch in Fällen von unerträglichen Schmerzen, die durch Karzinommetastasen oder Tabes dorsalis verursacht werden. In England wird der frontale Hirnschnitt bei Schizophrenien, depressiven Psychosen und ernsten Zwangsneurosen vorgeschlagen. Wichtige neuroanatomische und pathologische Beobachtungen von einer großen Anzahl von Fällen sind von MEYER (Maudsley Hospital, London) veröffentlicht worden, die eine kritische Analyse der Operationen ermöglichen.

Im Physiologischen Institut Oxford werden in den letzten Jahren zusammen mit Dr. FREUDENBERG, Psychiater am Netherne Hospital, Surrey, experimentelle Untersuchungen an Affen durchgeführt, um die anatomischen, physiologischen und psychologischen Grundlagen des Hirnschnittes zu erforschen. Ein Teil der Ergebnisse konnte auf dem internationalen Physiologenkongreß (1947) in Oxford demonstriert werden. Wir konnten feststellen, daß die prefrontale Leukotomie beim Affen charakteristische Symptome verursacht, die je nach der Ebene, in der die Leukotomie vollzogen wird, verschieden sind. Intelligenzverluste ließen sich bei den Affen nicht feststellen, während neurotische Reaktionen, die vor der Operation experimentell erzeugt waren, verschwanden (Foss und WILLIAM).

Anatomische Untersuchungen zeigten eine Verbindung vom dorsomedialen Thalamuskern zum Frontallappen und vom Frontallappen zum Thalamus. Der dorsale Teil des Frontallappens steht mit dem lateralen Teil des dorsomedialen Thalamuskernes in Verbindung, ebenso der orbitale Anteil des Frontallappens mit der medialen Hälfte des dorsomedialen Kernes des Thalamus. Die Vermutung liegt nahe, daß die Verbesserung eines krankhaften Geisteszustandes darauf beruhen kann, daß die nervösen Bahnen zwischen Frontallappen und Thalamus durch den Hirnschnitt unterbrochen werden. Diese Vermutung wird dadurch noch bestärkt, daß die emotionelle Qualifizierung nach der Operation eine andere wird. Da der mediale Teil des Thalamus eine innige Beziehung zum Hypothalamus hat, hat diese Vermutung eine gewisse Berechtigung, obschon ein Beweis bis jetzt noch nicht erbracht ist. Aus diesem Grunde ist es wichtig, auch andere nervöse Mechanismen in Erwägung zu ziehen.

Die Arbeit auf diesem klinisch und theoretisch so wichtigen Gebiete ist darum auch hier und in anderen Forschungslaboratorien in vollem Gange.

[1] Diese Bezeichnung wird als deutsche Übersetzung vorgeschlagen, da eine wörtliche Übersetzung der etwas unglücklich gewählten englischen Bezeichnung dem Wesen der Operation nicht entspricht.