Geoffrey Knight and his contribution to psychosurgery

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This paper retraces the fundamental achievements of Geoffrey Knight (1906–1994), a British neurosurgeon and a pioneer in the field of psychosurgery. His career developed in the 1950s and 1960s, when—following the unregulated practice of frontal lobotomies—strong criticism arose in the medical community and in the general public against psychosurgery. Geoffrey Knight's clinical research focused on identifying new, selective targets to limit the side effects of psychosurgery while improving the outcome of patients affected by mental disorders. Following the example of William Beecher Scoville, he initially developed restricted orbital undercutting as a less invasive alternative to standard frontal lobotomy. He then developed stereotactic subcaudate tractotomy, with the use of an original stereotactic device. Knight stressed the importance of the anatomy and neurophysiology of the structures targeted in subcaudate tractotomy, with particular regard to the fibers connecting the anterior cingulate region, the amygdala, the orbitofrontal cortex, and the hypothalamus. Of interest, the role of these white matter connections has been recently recognized in deep brain stimulation for major depression and anorexia nervosa. This is perhaps the most enduring legacy of Knight to the field of psychosurgery. He refined frontal leucotomies by selecting a restricted target at the center of a network that plays a crucial role in controlling mood disorders. He then developed a safe, minimally invasive stereotactic operation to reach this target. His work, well ahead of his time, still represents a valid reference on which to build future clinical experience in the modern era of neuromodulation for psychiatric diseases.

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THE birth of modern psychosurgery is usually dated to November 12, 1935, when Egas Moniz and Almeida Lima performed the first successful psychosurgery operation by injecting alcohol into the frontal white matter of a 63-year-old woman with paranoid delusions, anxiety, and melancholia.^{7,40,45} The work of Moniz and Lima was preceded by earlier neurosurgical interventions such as topectomies^{5,19} and corticotomies,^{44,45} and by the experimental studies of John Farquhar Fulton, who noticed a lack of emotional expression and frustration behavior after bifrontal resection of the frontal association cortex in animals.^{10,11,45}

Building on these preliminary findings, Moniz and Lima successfully performed their “frontal leucotomy” with the centrum semiovale of the frontal lobes as the main target and published their results in 1936.^{7,40,45} This

led many surgeons in Europe and America to become interested in this field. Fascinated by the ideas of Fulton and Moniz, Walter Freeman started working on frontal leucotomies with his neurosurgical colleague James Watts.^{9,45} They performed their first successful frontal lobotomy on September 14, 1936, on Alice Hood Hammatt, a 63-year-old woman with a history of severe depression, insomnia, and anxiety.^{32,45} After this case, Freeman and Watts performed 20 lobotomies in a series of patients but they soon became aware of a high rate of symptom recurrence after the procedure, along with a non-negligible incidence of complications, including postoperative bleeding (often leading to death), seizures, or frontal lobe syndrome.^{8,45} In an attempt to render his lobotomy intervention less invasive, Freeman rediscovered and modified the transorbital approach described by Amarro Fiamberti and developed

ABBREVIATIONS DBS = deep brain stimulation; SCG = subgenual cingulate gyrus.

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a procedure in which an ice-pick orbitoclast was inserted with a mallet through the orbital roof to a depth of 7 cm and swept laterally by 15°.43,45 Freeman started a cross-country tour to popularize his technique and performed nearly 4000 procedures in the following years. His surgical practice, in the absence of aseptic techniques, anesthesia, and perioperative care, appeared largely deregulated even for the standard of the time. This attracted a growing body of criticism against him, including his former neurosurgical colleague Watts, who became disillusioned with Freeman's lobotomies.^{16,45}

Nonetheless, from 1936 to 1956 a total of 60,000 lobotomies were performed in the US and Europe.⁴⁵ In terms of the number of operations, the United Kingdom saw the second-most operations performed after the US. A contemporary review, analyzing 10,000 standard frontal leucotomies performed in Great Britain between 1943 and 1954, revealed a 6% mortality rate, 1% incidence of seizures, and 1.5% incidence of frontal lobe syndrome. Seventy percent of the patients reported an improvement and 18% could return to a noninstitutional setting.^{45,50}

The Life and Career of Geoffrey Knight

It is in this climate that Geoffrey Knight (Fig. 1) started his neurosurgical career. Mr. Knight was born on October 4, 1906, at Lowfield Heath, Surrey, West Sussex, United Kingdom, the only son of Cureton Hope Overbeck Knight, a produce broker, and Ida Emily Norton. He was educated at Wadham House School, Hove and Brighton College, and qualified in 1930 at St. Bartholomew's Hospital Medical School in London. He subsequently held registrar and chief surgical assistant posts at St. Bartholomew's before being appointed senior surgeon to the West End Hospital for Nervous Diseases in London, and then Consultant Neurosurgeon to the Royal Postgraduate Medical School, Hammersmith. He held various research scholarships awarded by the Royal College of Surgeons, including the Leverhulme scholarship (1933–1936) and the Mecklenzie Mackinnon scholarship (1936–1938). During the Second World War, he was appointed at the "Sector Hospital" for the war-injured in Joyce Green, near Dartford in the South of England, and he was awarded the Order of the White Lion of Czechoslovakia for services to Czech aircrew. In 1950 he returned to London where he established the South East Metropolitan Regional Neurosurgical Centre based at the Brook Hospital. Thanks to his interests in functional neurosurgery and psychosurgery, Knight was able to create a nationally recognized Psychosurgery Unit. His neurosurgical centre at the Brook Hospital will be, together with the Neurosurgical Unit at the Maudsley Hospital, the nucleus of the current King's College Hospital London Neurosurgical Unit.

During his years at the Brook Hospital, Knight was supported by the work of several colleagues, surgeons, and physicians: Mr. John Bartlett, his successor, and Dr. Paul Bridges, his colleague in psychiatry, for his studies on functional neurosurgery; Mr. Gibbs, Mr. Neil-Dwyer, and Mr. Sharr for the studies on the protective effect of nimodipine against secondary cerebral ischemic damage in aneurysmal subarachnoid hemorrhage and for the

FIG. 1. Original photograph of Mr. Geoffrey Knight in his 50s (October 4, 1906–April 2, 1994). "He was a physically large man, greatly talented, innovative, confident, commanding, reassuring and quite unable to tolerate fools in any form."² Courtesy of his son, Martin Knight.

first coiling of intracranial aneurysms in London; and Mr. Northcroft, in the development of postgraduate education and spinal neurosurgery.²

In his works, lectures, and papers, Knight appeared as "Geoffrey Knight, F.R.C.S., F.R.C.Psych." as a testament to his clinical commitment to both neurosurgery and psychiatry. His affiliation read: "Royal Postgraduate Medical School; Surgeon in Charge, South East Metropolitan Regional Neurosurgical Centre, The Brook Hospital, London" often with the specification "Psychosurgical Department," confirming the national recognition and the relevance of the Unit of which he was the "Surgeon in Charge." Among the many awards that he received during his career, he was made Hunterian Professor of the Royal College of Surgeons (United Kingdom) three times, an honor very rarely conceded, and he also held the Vice-Presidency of the International Society of Psychiatric Surgery. After retiring in 1973, he preferred not to engage in clinical practice anymore, but instead "enjoyed many visits to Spain (...) in his elegant Rolls-Royce." He died on

FIG. 2. Schematic representation showing Scoville's operation (left), and the restricted orbital undercutting developed by Knight (right), involving a zone on the inner aspect of the orbital surface. Reprinted from: *The Lancet*, 268, Knight GC and Tredgold RF: Orbital leucotomy; a review of 52 cases, 981–986, Copyright 1955, with permission from Elsevier.

April 2, 1994, survived by his wife, Betty Lydia Havell, and 2 sons who, following in the steps of their father, both embraced medicine.²

Contribution to Psychosurgery

The Basis for a “New Wave” of Psychosurgery

During the 1950s several factors reduced the number of psychosurgery interventions across the world, including the introduction of chlorpromazine as an effective medical therapy, mounting sociopolitical pressure against lobectomies, and the new interest in electroconvulsive therapy for severe depression. In this historical context a new challenge faced neurosurgeons involved in the surgical treatment of mental disorders: identifying more selective targets that could replace extensive and destructive lobotomies, in an attempt to improve the clinical outcome while minimizing complications. In this “new wave” of psychosurgery Geoffrey Knight's research played a crucial role.^{25,41,49,50}

The first step was to develop more selective lobotomies. The orbital undercutting, devised in 1949 by William Beecher Scoville, appeared to represent a new starting point. The idea of limiting the frontal leucotomy to the inferior and medial fibers of the orbital gyri was based on recent clinical observations and more detailed anatomical studies on the connections of the frontal lobes. Walker divided the orbital and medial prefrontal cortex of the *Macaca fascicularis* into several different areas, based on granularity and other staining criteria.⁵¹ Smith⁴⁷ and Livingston et al.,^{35,36} by intraoperatively stimulating the agranular cortex extending from the anterior cingulate gyrus to the posterior orbital gyri, were able to induce autonomic responses in relation to those accompanying emotion, such as dilation of the pupils, erection of

FIG. 3. Illustrations of the restricted orbital cortex undercutting procedure. **A:** Orbital aspect of right frontal lobe, showing Area 13 in cross-hatch and Area 14 in stipple. **B:** Orbital aspect of left frontal lobe, showing site of incision used, 1–8 cm wide, situated 1 cm from midline, extending to 6 cm from the frontal pole. The last 2 cm corresponds to Area 13. Reproduced from: Stereotactic tractotomy in the surgical treatment of mental illness, Knight G, *J Neurol Neurosurg Psychiatry* 28:304–310, Copyright 1965, with permission from BMJ Publishing Group Ltd.

the hair, change of blood pressure, pulse, respiration, and gastric motility, and even vocalization. Ward⁵² confirmed that ablation of these areas produced changes in behavior including loss of fear, diminished aggression, quiescence, and increased tameness. Further anatomical studies by Le Gros Clark and Meyer^{6,31} demonstrated projections crossing in the subcaudate region, directed from the medial orbital surface (Walker's Area 13) to the ventromedial hypothalamic nuclei. Confirmed by studies from Glees et al., the stimulation of the fibers from the anterior cingulate cortex (Walker's Area 24) going into the posterior orbital areas and dividing in the subcaudate region showed those peculiar autonomic responses while their ablation produced tranquility and loss of fear.¹²

The Restricted Orbital Cortex Undercutting

Moving forward from these pioneering studies, Knight devised a more selective orbital undercutting procedure focused on dividing the white matter on the medial aspect of the orbital surface.^{25,30} The modification devised by Knight implied a restriction to the cutting zone, now 2 cm wide, “passing back to a point beneath the anterior limb of the internal capsule at a depth of 5.5 cm from the frontal pole, where the incision was widened to 2.5 cm to catch fibres passing laterally from the capsule”²⁵ (Fig. 2). Knight realized at an early stage the importance of cutting the fibers below the pars frontalis of the internal capsule rather than outlying parts of the white matter toward the inferior frontal gyrus.²⁵ The results of his series of 330 consecutive patients, presented at the Symposium on Orbital Undercutting in 1960, were encouraging. Two hundred forty-eight of the 330 patients were “personally” studied and assessed both pre- and postoperatively, having a complete follow-up. Of these 248 patients, 140 recovered almost completely; 68 improved, to the point of not requiring further psychiatric treatment; 35 were unchanged; and 1 deteriorated. Four patients died and 12 cases of epilepsy were recorded.²⁵ The following step in Knight's research was to localize an even more refined functional target.

FIG. 4. Picture of the original stereotactic device used by Mr. Knight and by his successor, Mr. Bartlett. Courtesy of Mrs. Bartlett.

The Stereotactic Subcaudate Tractotomy

From the results of his “limited” orbital undercutting, he realized that “it was the posterior part of this incision in the substantia innominata which was specially concerned with the best therapeutic effect.”²⁴ Indeed, the terminal 2 cm of the orbital undercutting entered the substantia innominata between the head of the caudate nucleus and the agranular cortex of Walker’s Area 13 (Fig. 3).⁵¹ Lesions within the substantia innominata appeared to interrupt fibers from the anterior cingulate region, isolating the posterior orbital cortex and dividing a projection to and from the amygdaloid nucleus.²³ A selective lesion at this site would influence emotional reactions preserving emotional tone and emotional appreciation, thanks to the sparing of the hippocampus-fornix and most of the thalamofrontal pathways.²⁴

In 1961, Knight devised a stereotactic operation to per-

form a localized lesion in the substantia innominata, using “a destructive agent with limited marginal effects.” The stereotactic device ideated by Geoffrey Knight and his colleagues of the Department of Physics and Radiology at the Postgraduate Medical School was a modification of McCaul’s stereotactic device, with the addition of a needle carrier mounted on a moving vernier scale attached to a perforated plate²⁴ (Fig. 4).

The device was composed of an “implanting needle consisting of a hollow tube with a lateral aperture for the introduction of the seeds and a removable stilette. The needle was fitted with a movable collar containing a millimeter screw adjustment to control the depth of implantation of the deepest seed.”²⁴ The “destructive agent with limited marginal effects” consisted of two rows of 4 seeds of radioactive Yttrium Y90, an element that ensured a short range of beta-radiation with a localized effect no larger than 5 mm. After the first 30 cases, the inner 3 seeds appeared to be sufficient to reach a satisfactory response and, in some later cases, the inner 2 seeds only were implanted with good clinical outcome.²⁴

The operation first included the appropriate skin incision “in a skin crease or concealed in the hair margin” and, after the scalp and epicranium were reflected, bilateral frontal bur holes were performed. Then, the stereotactic device was screwed to the skull and the needle inserted under radiological guidance (with radiographs obtained in the sagittal and transverse planes). The final target was a point situated 5 mm in front of the tuberculum sellae, 11 mm above the orbital roof, and 10 mm lateral to the midline. At this stage of the procedure, a sagittal film was acquired to double-check the final target and to guide the positioning of the Yttrium seeds²⁴ (Fig. 5). Knight noted another important finding: a unilateral implantation lead to a minimal reduction of symptoms, while a marked improvement could be observed once the second implant was placed. Bilateral implants therefore became the standard procedure.²⁴

Knight compared his previous case series of 554 patients treated with restricted orbital undercutting (in part already discussed in the previous publications of 1960 and 1964)^{22,25} and the first 90 cases treated with stereotactic subcaudate tractotomy. The stereotactic procedure demonstrated a better safety profile compared with the orbital undercutting, even in patients with severe comorbidities and advanced age. No deaths were reported (vs 7% for the orbital undercutting series), no postoperative incontinence, no personality changes, and a marked reduction in postsurgical epilepsy were observed.²⁴ Of interest, the good clinical response appeared to be more consistent in patients treated for drug-resistant depression, while satisfactory results were noted in patients with “hysteria,” anxiety, and obsessive-compulsive disorders.

Given these encouraging results, Knight continued to perform his stereotactic subcaudate tractotomy that gradually replaced the orbital undercutting. In the following years, Knight popularized his work, thanks to his prominent role in the Postgraduate Medical School and to a series of publications.^{23,26–29} The number of psychiatric patients referred for surgical treatment continued to increase, and this was remarkable at a time when surgery

FIG. 5. **Left:** Schematic representation of the planning for subcaudate tractotomy, with the target located 5 mm in front of the anterior clinoid and 11 mm above the orbital roof. **Right:** Intraoperative sagittal radiograph, with McCaul's stereotactic device applied to the skull. The Yttrium seeds have been advanced to the target. Note the presence of air to outline the frontal horn of the lateral ventricle (pneumoventriculogram). Courtesy of Mrs. Bartlett.

for psychiatric illness was largely opposed by the general public and part of the medical body.

The work of Knight on subcaudate tractotomy culminated in his 1973 publication, where he reported the results of a consecutive series of 660 patients.²¹ The surgical technique remained unmodified, with the only exception being the introduction of air encephalography to allow better recognition of the midline and visualization of the anterior horns of the lateral ventricles.^{21,23,26,27,29} The clinical outcome was again reported as favorable, particularly for severe depression, with more than 50% of cases free of medical care after the procedure and another 25% significantly improved.²¹ Similar overall good results were observed for patients affected by “obsessional illness” and “anxiety states.”⁴⁹ The safety of the procedure was confirmed, with the almost complete absence of postleucotomy syndrome: 14% of patients were reported to have minor postoperative behavioral or psychological changes and only 2 cases presented difficulty in concentration and memory. One case of operative death in more than 660 operations was reported and attributed to the wrong implantation of the seeds in the striatum. Epilepsy occurred in less than 1% of cases.²¹

With regard to the anatomical structures targeted in subcaudate tractotomy, Knight focused on the connections between the frontal cortex and the hypothalamus. Knight was influenced by the work of Smythies on the association between endogenous depression and depletion of monoamine levels in the hypothalamus:⁴⁸ “It may well be that the effect of operation on fronto-hypothalamic connections exerts an influence either on a reduced production of monoamines in the hypothalamus, or by interruption of the continuous feed-back which increases the seriousness of this deficiency.”²¹

It is worth noting that, while Knight did not conduct basic research himself, he was deeply influenced by the advancements in the field of neuroanatomy (particularly regarding the study of white matter connections), neurobiology, and neurophysiology that constituted the basis of modern neuropsychiatry. He was part of a group of neu-

rosurgeons for mental disorder that focused their attention on selective stereotactic procedures. Foltz and White in 1962 performed the first open anterior cingulotomy. Lars Leksell devised the Gamma Knife in 1968 and the first thermal anterior capsulotomy in 1972, while Desmond Kelly and Alan Richardson attempted and performed the first limbic leucotomy in 1973.⁵⁰

Psychosurgery After Knight

When Knight retired in 1973, the work on psychosurgery at the Brooks Hospital in London was successfully continued by Mr. John Bartlett with the aid of Dr. Paul Bridges, consultant psychiatrist. The psychosurgery unit at the Brooks was renamed “The Geoffrey Knight Psychosurgical Unit,” consisting of a 12-bed ward where 2 surgeries per week were performed. It involved close cooperation between neurosurgeons and psychiatrists, providing a supportive environment for patients who shared a highly specialized treatment. It also offered opportunities for research and for studying postoperative outcome, with resulting improvement in patient selection.³ The stereotactic subcaudate tractotomy originally developed by Knight was continued by Bartlett until the 1990s, with more standardized reporting of clinical results based on the modern classification of psychiatric diseases.^{4,17} This represented an extraordinary example of continuity at the Brooks Hospital, where subcaudate tractotomy was performed continuously over a period of 30 years, involving more than 1300 patients undergoing operations.

A new era in modern psychosurgery has been opened by the advent of deep brain stimulation (DBS). Initially developed in the late 1980s for the management of movement disorders,^{1,46} DBS introduced the advantage of neuromodulation of gray and white matter structures,⁴⁵ gradually replacing lesioning interventions. DBS has been performed with a degree of success by different groups for the treatment of obsessive-compulsive disorders, with the subthalamic nucleus,³⁸ nucleus accumbens,¹³ and anterior limb of the internal capsule⁴² as potential targets.

More recently, DBS of the white matter underlying the subgenual cingulate gyrus (SCG) has been proposed for treatment-resistant depression with promising results.^{37,39} DBS of the SCG has also been proposed for treatment-refractory anorexia nervosa.^{18,34} It is believed that DBS can ameliorate the symptoms of depression and anorexia nervosa by modulating the network of which SCG is a key component.^{15,33,39}

It is interesting to note that there is an overlap between the white matter fibers stimulated by DBS of the SCG and the tracts lesioned in classic subcaudate tractotomy interventions. Studies employing probabilistic tractography to investigate the connections of the SCG in humans^{14,20} demonstrated projections to the cingulate region, nucleus accumbens, amygdala, hypothalamus, and orbitofrontal cortex. Lesion of fibers connecting the anterior cingulate region, the amygdala, the orbitofrontal cortex, and the hypothalamus were hypothesized by Knight in his original works on subcaudate tractotomy.^{21,24} It therefore appears that the target selected for contemporary DBS for treatment-resistant depression is strikingly similar to the classic target identified by Knight in performing subcaudate tractotomy. Of interest, the more satisfactory clinical outcome after subcaudate tractotomy was consistently observed by Knight in patients with severe depression. This contribution of Knight is perhaps the most enduring legacy to the field of psychosurgery. He refined frontal leucotomies by selecting a restricted target at the center of a network of connections that could play a role in controlling mood disorders. He then developed a safe, minimally invasive stereotactic operation to reach this target. His work, well ahead of his time, still represents a valid reference on which to build future clinical experience in the modern era of neuromodulation for psychiatric disease.

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Disclosures

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Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: Marchi, Vergani, Chiavacci, Ashkan. Drafting the article: Marchi, Vergani, Chiavacci, Ashkan. Critically revising the article: Marchi, Vergani, Gullan, Ashkan. Reviewed submitted version of manuscript: Marchi, Vergani, Gullan, Ashkan. Approved the final version of the manuscript on behalf of all authors: Marchi. Administrative/technical/material support: Marchi, Vergani. Study supervision: Vergani, Ashkan.

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