

Patients with Huntington's disease pioneered human stereotactic neurosurgery 70 years ago.

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Introduction

It is well known that stereotactic functional neurosurgery, using ablative procedures or deep brain stimulation (DBS) is used mainly in the surgical treatment of Parkinson's disease (PD), essential tremor (ET) and dystonia. These are also the only established indications for functional stereotactic neurosurgery. What is less well known is that the first stereotactic operation ever was performed 70 years ago was for treatment of Huntington's disease. This historical account will review the birth of human stereotactic surgery, and its very first applications.

Stereotaxis (from the Greek stereo meaning solid or spatial, and taxis meaning arrangement) is a surgical method first described for experimental animal use by Sir Victor Horsley and Dr. Robert Clarke in a paper in 1908 published in *BRAIN* with the title "The structure and functions of the cerebellum examined by a new method" (Horsley and Clarke, 1908). It took almost 40 years before this method was applied in humans.

Birth of Human stereotactic surgery.

Human stereotactic neurosurgery saw the light 70 years ago at Temple University in Philadelphia when neurologist Ernest Spiegel and neurosurgeon Henry Wycis (Figure 1) published a paper in *Science* in 1947, entitled "Stereotaxic apparatus for operations on the human brain" (Spiegel et al, 1947) describing the first stereotactic frame for use in humans and its potential clinical applications. They stated in that paper that the impetus to develop a stereotactic frame for human use was to allow psychosurgical procedures based on precise focused ablations of subcortical structures, instead of the crude lobotomy procedure commonly used at that time.

However, according to several accounts by early pioneers of stereotactic surgery, including one of them, Philip Gildenberg, who was a fellow of Spiegel and Wycis, the first stereotactic intervention was for a patient with Huntington's disease. Gildenberg wrote in his "The birth of stereotactic surgery: a personal retrospective" (Gildenberg, 2004): "Although "stereotaxic" surgery (as it was then spelled) was conceived for psychosurgery, the first patient had Huntington's chorea."

In a historical vignette published the same year in the same journal, another grand old man of stereotactic neurosurgery, Blaine Nashold from Durham, North Carolina wrote: "It has been more than 55 years since Spiegel and Wycis operated on a patient with Huntington's chorea; with the use of a stereotactic instrument, they injected alcohol into the pallidum to relieve

jerking of the head and limbs. The patient improved and lived for 15 years. Dr. Wycis performed the postmortem examination and paid for the funeral” (Nashold, 2004) Medial thalamotomy, targeting the specific dorsomedial nucleus of the thalamus that has projections to the orbitofrontal cortex via the anterior arm of the internal capsule, was also used “to sedate this chronically agitated patient” (Gildenberg, 2003).

Why Huntington’s disease and not Parkinson’s disease.

It seems peculiar that a stereotactic apparatus initially designed for psychosurgery was first used for a movement disorder. And it is even more peculiar that it was Huntington’s chorea rather than Parkinson’s disease that was the first “movement disorder” condition treated by stereotactic surgery, and this in a period during which Parkinson’s disease was the most common movement disorder to be operated on with open non-stereotactic surgery. So why Huntington’s chorea? Ernest Spiegel himself gives the answer: “ I confess that I was initially reluctant to produce lesions of the pallidum or its efferent fibers, since I was under the spell of Foerster’s doctrine that pallidal lesions induce not only hypokinesia but also rigidity. I recommended, therefore to Wycis that we should try first to place small lesions in this ganglion in a condition characterized by hyperkinesia and hypotonia, namely, Huntington’s chorea... After we became convinced that such lesions were able to reduce or abolish the choreatic hyperkinesia without producing even on long-range observation, the dreaded rigidity, it seemed to us justifiable to place lesions in the pallidum and ansa lenticularis in parkinsonian patients” (Spiegel, 1966).

At the age of 84, Ernest Spiegel published a book titled “Guided brain operations”, summarizing eloquently the field of stereotactic surgery since 1947. (Spiegel, 1982) In the chapter about Involuntary Movements (page 59) he shed more light about why he was reluctant to implement stereotactic surgery first on Parkinsonian patients. He wrote: “It is an old experience that conditions inducing extensive, although not exclusive, pallidal lesions such as CO poisoning are associated with hypokinesia. This experience induced Spiegel and Wycis to attempt a control of choreiform movements by pallidal lesions. Of 9 cases with such movements, definite improvement was obtained in 4 (3 Huntington’s chorea, 1 postencephalitic chorea) and a slight improvement in 2 patients with Huntington’s chorea.”

The original papers of Spiegel and Wycis on surgery for chorea.

On April 22, 1949, Spiegel and Wycis presented at the meeting of the Philadelphia Neurological Society the results of their surgery on Huntington’s disease

patients, including motion picture demonstrations. Motion pictures were presented again at the meeting of the American Neurological Association in June 1950. Subsequently the authors published three articles between 1950 and 1952 about their experience. The latter one, titled “Thalamotomy and pallidotomy for treatment of choreic movements” (Spiegel and Wycis, 1952) gives details about four operated patients, and the rationale for performing a double target surgery on these patients: the authors explain that for treatment of choreic and athetotic movements, electrolytic lesions were placed in the region of the dorsomedial nuclei (thalamotomy), or in the region of the globus pallidus (Pallidotomy)”. The rationale for the former was that “afferent stimuli and emotional reactions are able to accentuate choreic and athetotic movements” and it “seemed worthwhile” to use that target in Patients with Huntington’s disease. However, that procedure (dorsomedial thalamotomy) was efficient in reducing the choreic movements in only one out of the four patients. The authors added 1 drop of 50% alcohol into the globus pallidus, but “there was no change of the involuntary movements or of muscle tone, apparently because the pallidal lesion was too slight in order to produce a definite hypofunction”. Therefore the authors produced electrolytic lesions of the pallidum and wrote: “Nine months following the second operation, the patient's improvement has been sustained. The only residual is a mild weakness of the left lower limb. The choreic movements have not returned despite the known progressive character of the disease.” The authors concluded that “lesions of the pallidum are able to eliminate nearly completely violent choreic movements on the side opposite the operation.”

Contemporary stereotactic surgery for Huntington’s disease

In the last two decades, DBS has been the dominating method for functional neurosurgery in movement disorders even if pallidotomy and thalamotomy are still used occasionally. By far the main indications are Parkinson’s disease, essential tremor and dystonias (Hariz and Hariz, 2013). Regarding the latter illness, the target of choice for DBS or for lesion is the globus pallidus internus. Further applications of pallidal DBS have been in patients with Lesch Nyhan disease and Gilles de la Tourette syndrome. Among the over 150 000 patients worldwide who have received DBS, patients with Huntington’s disease constitute a microscopic minority. The literature on DBS contains only 19 articles totalling 36 patients (with some overlapping) (Wojtecki et al, 2016). The general results of these papers, describing mostly single open label cases, indicate that the pallidum is the main target, that chorea can be more or less improved even at longer term, that bradykinesia can get worse on stimulation requesting a lowering of the frequency of the electrical current, and that the

patients who would benefit most of DBS are those with dominant choreic phenotype, younger age, shorter disease duration and relatively preserved cognitive abilities.

Conclusions

The year 2017 marks the 70th anniversary of the birth of human stereotactic neurosurgery. The first procedure was a pallidotomy for Huntington's disease, demonstrating efficacy on hyperkinetic movements. Today, 70 years later, the pallidum, especially its sensorimotor part remains the target of choice for stereotactic ablation or for DBS in parkinsonian patients with levodopa induced dyskinesias and in patients with dystonia, as evidenced by the wealth of literature on this subject. Among all movement disorders treated by stereotactic surgery (PD, essential tremor, MS tremor, dystonia, etc), one condition is barely considered for surgery: it is Huntington's disease, the very first application of functional stereotactic neurosurgery some 70 years ago. Indeed two of the hallmarks of Huntington's Disease are gait disturbances and early cognitive decline, which are the two conditions that are not amenable to treatment by stereotactic lesional surgery nor DBS. In many patients, these symptoms would affect the quality of life of the patients more than the chorea. Nonetheless, the movement disorders community would do well to read the old publications of the pioneers of stereotactic neurosurgery in order not to forget that stereotactic surgery may be of some benefit for patients with Huntingtons' disease who are not severely cognitively impaired and who suffer from medication-refractory chorea.

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LEGEND FOR FIGURES:

Figure 1:

Portraits of neurologist Ernest Spiegel (left) and neurosurgeon Henry Wycis, who pioneered human stereotactic neurosurgery in 1947.