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Original Article

The impact of subcaudate tractotomy on delusions and hallucinations in psychotic patients

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ABSTRACT

Background: Delusions and hallucinations, hallmarks of the psychotic disorders, usually do not respond to surgical intervention. For many years, the surgical technique of choice for the treatment of refractory aggressiveness in psychotic patients in our Service was amygdalotomy in isolation or associated with anterior cingulotomy. No improvement of hallucinations and delusions was noticed in any of these patients. To improve the control of aggression, subcaudate tractotomy was added to the previous surgical protocol. The main goal of the present study was to investigate the impact of this modified surgical approach on delusions and hallucinations.

Methods: Retrospective analysis of the medical records of psychotic patients presenting with treatment-resistant aggressiveness, delusions, and hallucinations submitted to bilateral subcaudate tractotomy + bilateral anterior cingulotomy + bilateral amygdalotomy in our institution.

Results: Five patients, all males, with ages ranging from 25 to 65 years, followed up by a mean of 45.6 months (17–72 months), fulfilled the inclusion criteria. Delusions and hallucinations were abolished in four of them.

Conclusion: These results suggest that the key element for relieving these symptoms was the subcaudate tractotomy and that the orbitofrontal and ventromedial prefrontal cortices play an important role in the genesis of hallucinatory and delusional symptoms of schizophrenia and other psychoses.

Keywords: Delusions, Hallucinations, Psychosis, Psychosurgery, Schizophrenia, Subcaudate tractotomy

INTRODUCTION

Psychotic disorders, either primary or secondarily determined, are severe and persistent mental disorders causing significant limitations to the social and professional life of the affected individuals.[36] Among the chronic psychotic disorders, schizophrenia is one of the most prominent, affecting approximately 1% of the world population and accounting for 25% of the hospitalizations for psychiatric causes.[31] It seems to adequately represent a viable paradigm for the pathophysiological study of chronic psychotic disorders.

Schizophrenia is clinically characterized by positive (psychomotor agitation, aggressiveness, hallucinations, and delusions) and negative symptoms (blunted affect, social isolation, and poverty of speech),[12,25] being auditory and visual hallucinations present in 80% of the patients.[6] Besides, comorbidities such as anxiety, depression, and obsessive-compulsive disorder are not uncommon.[35]

The therapeutic approach of schizophrenia involves a combination of psychotherapy, psychoactive drugs, and electroconvulsive therapy (ECT).[10,23,30] However, the array of psychotropics currently available notwithstanding, approximately 20% of the patients still remain refractory to the best clinical management.[10]

When aggressiveness is a significant problem and a source of danger for the own patient and/or for those around him/her, surgical treatment for the relief of this manifestation may be contemplated.[7,9,35,39] As per delusions and hallucinations, however, except for a relatively recent study on the impact of anterior capsulotomy on schizophrenia symptoms,[19] it has never been clearly established whether they can be successfully treated by surgery, which turns this issue an open and attractive field.

When we started operating for aggression in chronic treatment-resistant psychotic patients, we elected bilateral amygdalotomy as the procedure of choice. The rates of failure and recurrence were high, though. In 2001, the use of functional neuroimaging studies to determine the best target to treat varied psychiatric disorders was proposed.[38] Using this tool, we observed hyperperfusion in the anterior cingulate gyrus of our patients who failed to respond to amygdalotomy, which led us to consider bilateral anterior cingulotomy in these patients in a second procedure. Da Costa had already reported this combination of targets (bilateral amygdalotomy + bilateral anterior cingulotomy).[9] Although the results showed improvements, the number of failures/recurrences was still relevant. Significantly, no improvements were observed on other positive symptoms such as hallucinations and delusions after amygdalotomy alone or associated with anterior cingulotomy (unpublished data). Once more taking advantage of functional neuroimaging studies, hyperperfusion of the orbitofrontal and/or prefrontal dorsolateral cortex was detected in these patients.[38] Based on these results and on the report of Cox and Brown,[7] we performed bilateral subcaudate tractotomy in those patients who failed to respond to bilateral amygdalotomy + bilateral anterior cingulotomy. The result was a more effective control of this symptom. Eventually, bilateral limbic leucotomy (anterior cingulotomy + subcaudate tractotomy) + bilateral amygdalotomy, in a single stage, became the initial surgical protocol of choice for treating aggressiveness in our Service, which remained for a few years.

The goal of this study was to investigate the impact of bilateral limbic leucotomy + bilateral amygdalotomy on treatment-resistant delusions and hallucinations in psychotic patients undergoing surgery for the control of aggressiveness.

MATERIALS AND METHODS

This retrospective, observational, and qualitative study was approved by the Research Ethics Committees of the Pontifical Catholic University of Goiás (technical report # 239.724) and of the Clinics Hospital of the Federal University of Goiás (technical report # 599.636-0). The primary source of data was the medical records of patients with chronic psychotic disorders operated for aggressiveness at the Goiânia Neurological Institute between September 2003 and December 2011.

The diagnosis was established pursuant to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.[1]

Refractoriness was defined as the presence of frequent psychomotor agitation events associated to self- and/or hetero-aggressiveness, with danger to him/herself and/or to others, despite ongoing optimized treatment with at least three neuroleptic drugs (haloperidol, clozapine, risperidone, ziprasidone, olanzapine, zuclopenthixol, and aripiprazole), in association with benzodiazepines (lorazepam, clonazepam, clobazam, and cloxazolam), nonbenzodiazepine inhibitors of anxiety and impulsivity (propranolol, buspirone, and citalopram), and mood stabilizers (sodium valproate, divalproex sodium, lithium carbonate, topiramate, and oxcarbazepine), all of these drugs in optimal dosages and for a period considered to be adequate, as certified by two independent psychiatrists and one behavioral neurologist. Besides, the disease must have lasted a minimum of 5 years and be the cause of a significant impact on the patient's global functioning and quality of life. Although offered to all patients, ECT was not considered a required criterion for determining refractoriness.

Each patient referred from psychiatric clinics not pertaining to the Goiânia Neurological Institute was submitted to reevaluation by two psychiatrists and one behavioral neurologist to confirm surgical indication. The functional neurosurgeon did not take any part in patient selection for surgery.

An informed consent form signed by the patient or by their guardians was obtained in all cases after meticulous explanation of the technical aspects, risks, and benefits of the surgical procedure. Patient privacy was protected with routine measures to prevent patient and family identification.

During the preoperative period, a neuropsychological evaluation was performed in every case and all the patients underwent magnetic resonance (MR) and single-photon emission computed tomography (SPECT) of the brain. MR or computed tomography (CT) was repeated postoperatively within the first

48 h to determine the adequacy of the position and size of the surgical lesions, and to exclude surgical complications.

The clinical follow-up was done in a systematic manner by at least one of the psychiatrists, the behavioral neurologist, and the functional neurosurgeon. Follow-up visits were scheduled every 3 months during the 1st year, every 6 months during the 2nd year, and, after that, every year or as needed. In the meantime, the patient was also accompanied by his/her referring physician, if he/she was not a member of our institution's staff.

Postoperatively, as part of our protocol, medications remained unchanged for a minimum of 6 months so as to better evaluate the impact of surgery on the clinical features.

To evaluate the changes in quality of life, aggressiveness, psychomotor agitation, delusions, and hallucinations, the authors relied on spontaneous reports from the patients and/or from their close relatives and on their answers to the questions posed by the psychiatrist or neurologist regarding these issues in each follow-up visit.

Surgical technique

The surgical procedure was performed under general anesthesia. Short-term neuromuscular blockers were used only during the induction of anesthesia so as to not interfere with the assessment of motor responses during electrical stimulation. After the placement of the stereotactic frame, CT axial slices were obtained and merged with the inversion recovery axial MR slices obtained on the previous day. Targets' coordinates were determined on these fused images, as follows:

Amygdala

The index target is taken at the most central part of the amygdala, as observed on reconstructed coronal slices. Additional targets are established 3.0 mm superior, inferior, anterior, posterior, medial, and lateral to the index target (five trajectories and seven targets).

Anterior cingulate gyrus

Using reconstructed sagittal and coronal slices, the index target is determined 20.0 mm posterior to the anterior wall of the lateral ventricle (y), 6.0 mm from the interhemispheric fissure (x), and at the interface between the corpus callosum and the anterior cingulate gyrus (z). Two additional targets are established 4.0 mm superior and inferior to the index target. A second mirror trajectory is performed 3.0 mm anterior to the first one (two trajectories and six targets).

Subcaudate area

Using axial and reconstructed sagittal slices, the index target is established at mid-distance between the corpus callosum and the floor of the anterior fossa (z), 7.0 mm from the interhemispheric fissure (x), and 15.0 mm in front of the anterior wall of the third ventricle (y). Four additional targets, 3.0 and 6.0 mm superior and inferior to the index target, are used. A second mirror trajectory, 5.0 mm lateral to the first one (12.0 mm from the interhemispheric fissure), is performed (two trajectories and 10 targets).

Using a 1.27 mm in diameter and 4.0 mm bare tip electrode, electrical stimulation (3.0 V/100 Hz) is performed at all targets. In the absence of adverse motor responses, radiofrequency thermocoagulation is performed with 85°C/60 s.

Inclusion criteria

Psychotic patients with a disease duration over 5 years, presenting with treatment-resistant aggressiveness, associated to refractory delusions and hallucinations, who were treated with bilateral limbic leucotomy + bilateral amygdalotomy, and not submitted to additional further surgery aiming to achieve a broader disconnection of the prefrontal cortex, such as anterior capsulotomy.

Exclusion criterion

Previous surgery for the treatment of aggressiveness.

RESULTS

On reviewing the medical records, the investigators found five patients with chronic psychotic disorder that fulfilled the inclusion criteria. All patients were male with ages ranging from 25 to 65 years (35.4 ± 17.3 years), two of them already treated with several ECT sessions. These patients were followed up by a mean of 45.6 ± 21.38 months (17–72 months) and are summarized in [Table 1].

Preoperatively, all the patients underwent SPECT [Figures 1 and 2]. Unfortunately, the images for one of the patients were not located. The results of these tests are listed in [Table 2].

According to reports given by the patients and their close relatives, four of them presented a significant improvement in the quality of life, in the social relationships, and complete resolution of the delusions, hallucinations, and aggressiveness. The delusional/hallucinatory symptoms initially declined during the first 3 postoperative days and then completely disappeared afterwards. Only a mild improvement was observed in the remaining patient, though.

Recurrence of aggressiveness occurred after 1 year in one of the patients (patient 2), although he remained free from delusions and hallucinations [Table 1]. At that time, a left posteromedial hypothalamotomy was performed, resulting in a complete remission of aggressiveness, except for an isolated episode.

Table 1: Summary of the study subjects.

Patient/ diagnosis	Sex, age	Clinical features	Surgical results	Complications	Progression
01 HS	Male, 27 yr	Hetero- and auto-aggressiveness, delusions, hallucinations (visual and auditory), many suicide attempts	Resolution of delusions, hallucinations, and aggressiveness	Ischemia of the posterior limb of the left internal capsule of unknown etiology + right hemiparesis	Patient resumed his social, family, and professional life
02[a] OSD	Male, 65 yr	Hetero-aggressiveness, delusions, and hallucinations (visual and auditory)	Remission of delusions and hallucinations. Isolated episode of psychomotor agitation and aggressiveness	Bacterial meningitis secondary to infection of the surgical wound	Retired; excellent social interactions
03 ASD	Male, 25 yr	Delusions, hallucinations (visual and auditory), psychomotor agitation, and hetero- and auto-aggressiveness	Remission of hallucinations, delusions, and aggressiveness	None	Persistent general cognitive loss and improved mood, social relationships, and personal care
04 PS	Male, 33 yr	Hetero-aggressiveness, persecutory delusions, and hallucinations (auditory). Committed homicide	Resolution of the delusions, hallucinations, and aggressiveness	None	Resumed family and social life in 3 months and professional life in 1 year
05 PS	Male, 27 yr	Severe hetero-aggressiveness, delusions, hallucinations (auditory), depression, and anxiety. Many suicide attempts	Recurrence of delusions/ hallucinations and aggressiveness 1 and 2 months after surgery, respectively	None	Unchanged

HS: Hebephrenic schizophrenia, PS: Paranoid schizophrenia, OSD: Organic schizophreniform disorder, ASD: Autism spectrum disorder, yr: Year, [a]After 1 year, recurrence of aggressiveness was noticed, but the patient remained free from delusions and hallucinations. At that time, a left posteromedial hypothalamotomy was performed, resulting in a complete remission of aggressiveness, except for an isolated episode.

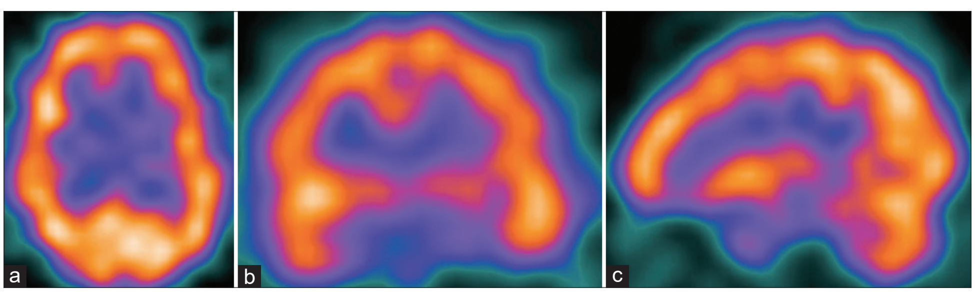

Figure 1: Preoperative single-photon emission computed tomography axial (a), coronal (b), and right side sagittal (c) slices of patient 1 showing hyperperfusion of the prefrontal areas, temporal lobes, right basal ganglia, and right parietal lobe.

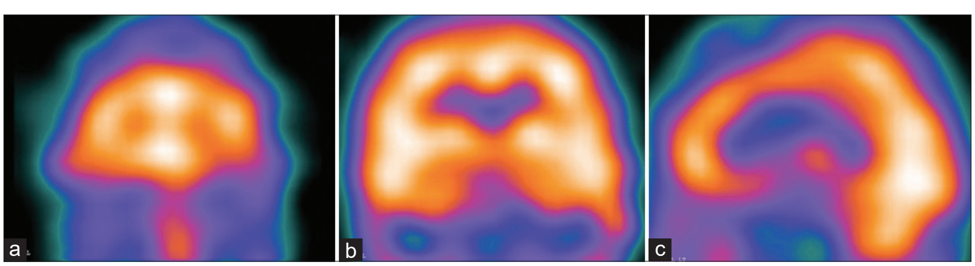

Figure 2: Preoperative single-photon emission computed tomography coronal (a and b) and left side sagittal (c) slices of patient 3 showing hyperperfusion of the anterior cingulate gyri, orbitofrontal cortices, dorsolateral prefrontal areas, temporal lobes, left basal ganglia, and left parietal lobe.

Postoperative MR (four patients) or CT (one patient) was performed within the first 48 h in all patients. The images showed that the location and size of the surgical radiofrequency lesions were adequate in every case [Figures 3 and 4].

Surgical complications are listed in [Table 1].

Table 2: Preoperative single-photon emission computed tomography findings.

Patients	SPECT findings
01	Hyperperfusion in the prefrontal area and temporal lobe, bilaterally, right basal ganglia, and right parietal lobe
02	Hyperperfusion in the orbitofrontal cortex, anterior temporal lobe (R>L), basal ganglia (R>L), and dorsolateral prefrontal area (L>R), bilaterally
03	Hyperperfusion in the anterior cingulate gyrus, orbitofrontal cortex, dorsolateral prefrontal area, and anterior temporal lobe, bilaterally, and in the left basal ganglia and left parietal lobe
04	Images not found
05	Hyperperfusion in the orbitofrontal cortex and anterior cingulate gyrus, bilaterally, and in the left anterior temporal lobe

R: Right, L: Left, SPECT: Single-photon emission computed tomography

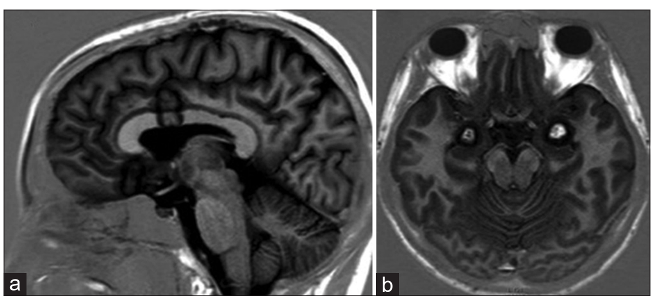

Figure 3: Postoperative inversion recovery MR sagittal and axial images of patient 1 showing the bilateral subcaudate tractotomy + anterior cingulotomy (a) and amygdalotomy (b) radiofrequency lesions.

DISCUSSION

The authors elected schizophrenia as the paradigm for the study of delusional and hallucinatory symptoms, also present in other psychoses.

According to the most accepted hypothesis, the hyperactivity of the mesocorticolimbic dopaminergic system, which extensively modulates the ventromedial and orbitofrontal prefrontal regions, is the determining factor for the appearance of psychosis and other symptoms of schizophrenia.[8,20,24] In untreated schizophrenic patients, the use of neuropharmacological imaging techniques and positron emission tomography (PET) made it possible to demonstrate high levels of D2 dopamine receptors in the ventral striatum, even more so in patients with positive symptoms.[16,28] That fact excludes any drug-related interference in this finding and supports the idea that the mesolimbic dopaminergic system participates in the genesis of schizophrenia symptoms. Other PET and SPECT studies have shown hyperactivity in the prefrontal and temporolimbic areas as well as in the basal ganglia in patients with positive symptoms.[4] Besides, functional MR (fMR) studies in schizophrenic patients with auditory hallucinations showed activation of areas relevant to language processing, as well as of the parahippocampal gyrus, the anterior cingulate gyrus, and the prefrontal cortex.[29]

Another line of evidence derives from the studies of connectivity of large-scale brain networks.[5,15,21,27,32,40] Abnormal network connectivity is increasingly more evident in schizophrenia and other psychoses. Reduced levels of overall structural connectivity were found, particularly in frontal-striatal and temporal-striatal networks.[5] In contrast, studies of functional connectivity of the anterior portions of the default-mode network, that is nuclear to the brain mechanisms of reality monitoring, showed that they are functionally hyperconnected to the orbitofrontal and ventromedial prefrontal cortices.[15,27,32,40] This abnormality might lead to misinterpretation of reality, confusing internally generated information with real perception of the external world, deflagrating delusions and hallucinations.

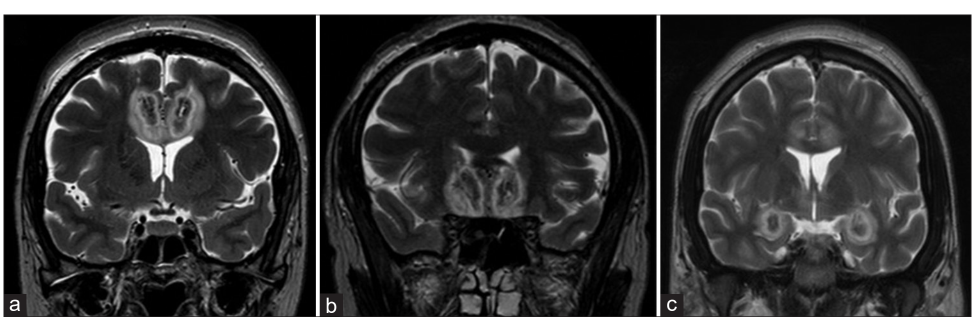

Figure 4: Postoperative T2-weighted MR coronal images of patient 3 showing the bilateral anterior cingulotomy (a), subcaudate tractotomy (b), and amygdalotomy (c) radiofrequency lesions.

Summing up the aforementioned findings, in schizophrenia, the mesocorticolimbic dopaminergic system, which is hyperactive, would over activate the ventromedial and orbitofrontal prefrontal cortices; these areas, in turn, would over excite the anterior portions of the default-mode network, with whom they are functionally hyperconnected, determining the appearance of delusions and hallucinations. Corroborating these observations, the preoperative SPECT, available for analysis in four of our patients, showed hyperperfusion in the prefrontal area in all [Table 2]. Although the surgical indication in every case had been the aggressiveness, to our surprise, the delusional and hallucinatory symptoms were also abolished in four out of five patients.

Previously, in our Service, we had performed bilateral amygdalotomy in isolation or associated to bilateral anterior cingulotomy in 47 aggressive patients, 21 diagnosed as schizophrenics; however, these surgical strategies did not provide alleviation of the delusions and hallucinations in any of those presenting these symptoms (unpublished data).

Taken as a whole, these results suggest that the key element for relieving delusions and hallucinations was the bilateral subcaudate tractotomy, which was associated to bilateral anterior cingulotomy and bilateral amygdalotomy in the five patients reported in the present study. We hypothesize that the subcaudate tractotomy acts by interrupting the efferences from the orbitofrontal and ventromedial prefrontal cortices to the anterior portions of the default-mode network, as well as the dopaminergic input from the nucleus accumbens to those areas.

Obviously, it is impossible to completely disregard the contribution of amygdalotomy and anterior cingulotomy in these results, even more when one considers the prominent role played by the amygdala and the anterior cingulate gyrus in the mesocorticolimbic circuit. In fact, both procedures may have potentialized the effect of subcaudate tractotomy, although, alone, uncapable to alleviate delusions and hallucinations.

One of our patients (patient 5, Table 1) presented only a mild and transient improvement of his positive symptoms (aggression, delusions, and hallucinations). The surgical approach and the location and dimensions of the radiofrequency lesions were exactly the same as in the other four patients. We have no explanation to offer for this discrepant result.

After reviewing the literature regarding the surgical treatment of psychiatric disorders, it was observed that patients with schizophrenia were included in a number of studies.

Cox and Brown reported the results of bilateral limbic leucotomy + amygdalotomy for the treatment of schizophrenia and aggressive states. A significant improvement was observed in the schizophrenic symptoms of 32 patients.[7] Several other studies reporting on the surgical ablative treatment of schizophrenia, among other diseases, have also been published.[2,11,14,17,33] These authors, however, as Cox and Brown, did not mention which manifestations of the disease were alleviated by surgery.

Ballantine reported that delusions and hallucinations may be modified with stereotactic lesions but are seldom abolished.[3] Roeder *et al.* and Vikki reported that bilateral medial thalamotomy and bilateral mesoloviotomy, respectively, can reduce delusions and hallucinations in some patients with schizophrenia.[26,37] Hussain *et al.* operated on nine patients with schizophrenia (bimedial frontal leucotomy in eight patients and stereotactic surgery – technique not specified – in one), two of them presenting delusions; this symptom, however, was not relieved by surgery.[13] Strom-Olsen and Carlisle performed subcaudate tractotomy in five patients with schizophrenia, none of them improving from delusions/hallucinations.[34] Finally, Mitchell-Heggs *et al.* reported on seven patients with schizophrenia or schizoaffective disorder who had undergone limbic leucotomy.[22] Based on their report, we noticed a marked improvement in the intensity of the psychotic episodes in two patients; such results, however, have not been discussed or even pointed out by the authors.

In conclusion, reports of relief (never complete) of delusions and hallucinations in psychotic patients who underwent surgery are sporadic and inconsistent. Moreover, we have not been able to identify any new study on this topic in the English published literature from 1988 to 2013 (pubmed.com).

It is worthwhile highlighting that the surgical techniques used in the aforementioned studies are somewhat different from the techniques currently used. The anterior cingulotomy and amygdalotomy were based on the ventriculography, and the subcaudate tractotomy, essentially, on X-ray images of the skull. In addition, the technique used to create the subcaudate tractotomy lesion normally required implantation of yttrium 90 seeds; the lesion produced was approximately 20 mm long, 10 mm wide, and 5.0 mm high and its medial limit was 7.0–10 mm from the interhemispheric fissure.[3,18,22,33] In our service, as in many others, the target coordinates are obtained from fused images (MR + CT) and radiofrequency thermocoagulation is used to create the lesions. The subcaudate lesion is wider, higher, and shorter, almost inflicting the medial and ventral frontal cortices, making it possible to simultaneously disconnect both the orbitofrontal and ventromedial prefrontal regions. This broad disconnection may have been the determining factor for the complete relief of the delusions and hallucinations noticed in 80% of our patients.

More recently, Liu *et al.*, in a well-structured study, reported their results in 100 schizophrenic patients submitted to bilateral anterior capsulotomy followed up for 2 years.[19] A 71%, 70%, and 82% response rate for hallucinations, delusions, and aggressive behavior, respectively, were obtained. Besides, the negative symptoms of the disease and quality of life were also substantially improved.

Our results, along with those of Liu *et al*., suggest that the orbitofrontal and ventromedial prefrontal cortices play an important role in the genesis of the hallucinatory and delusional symptoms of schizophrenia and other psychoses. To confirm this hypothesis, new and more in-depth structural (tractography) and functional (fMR and PET) neuroimaging studies are necessary. Once confirming this hypothesis, chronic electrical stimulation of the orbitofrontal and/or the ventromedial prefrontal cortex emerges as tentative procedures for the surgical control of these manifestations. In the era of neuromodulation, the benefits thus gained could be substantial, in view of the high prevalence of psychoses and the fact that they are treatment resistant in a significant percentage of patients.

This study presents considerable limitations. Our sample is small, no control group was included, and it was not possible to perform a double-blind study in view of the inherent characteristics of the procedure and of the nature of this study (retrospective). Besides, no formal clinical scales were used to evaluate quality of life, delusions, hallucinations, and aggressiveness.

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Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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