Long-Term Follow-Up of MRI-Guided Bilateral Anterior Capsulotomy in Patients with Refractory Schizophrenia

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Key Words
MRI-guided capsulotomy · Refractory schizophrenia · Mental disease

Abstract
Aim: To determine whether there is a long-term benefit of MRI-guided bilateral anterior capsulotomy in the treatment of refractory schizophrenia. Methods: 116 patients (16 patients did not complete the follow-up evaluation) who underwent capsulotomy were included. The treatment effect was evaluated using a series of international rating scales. Evaluations were performed at baseline, 3 weeks and 24 months after surgery. Results: The rate of effectiveness was 74% according to the Clinical Global Impression evaluation, and there was an obvious improvement based on the statistical analysis for Positive and Negative Symptom Scale (baseline vs. 24 months after surgery, 6.86 ± 8.12, 10.70 ± 8.70 to 26.65 ± 4.85, 21.66 ± 7.19), Brief Psychiatric Rating Scale (14.75 ± 13.21 vs. 44.97 ± 9.36), Activities of Daily Living Scale (18.06 ± 6.58 vs. 24.61 ± 8.95), Social Disability Screening Schedule (6.69 ± 6.12 vs. 15.06 ± 3.18) and Global Assessment Scale (74.35 ± 12.75 vs. 48.74 ± 9.18). Among all the symptoms of schizophrenia, aggressive behavior (82% response rate), hallucination, (71% response rate) and delusion (70% response rate) showed the best response. Conclusion: Our research indicates that capsulotomy is a relatively safe and effective intervention for patients with refractory schizophrenia. It could be an alternative therapy for those patients with chronic and severe schizophrenia. But there must be strict inclusion criteria considering the complications and irreversibility of this procedure.

Introduction
Schizophrenia is a chronic, severe and disabling mental disorder which is among the most economically costly medical conditions in the world [1]. The symptoms associated with schizophrenia have been divided into three domains: positive symptoms (i.e. hallucinations, delusions, racing thoughts), negative symptoms (i.e. apathy, lack of emotion, poor social functioning), and cognitive symptoms (i.e. impairment in attention, memory and executive function). Symptoms of schizophrenia typically emerge in adolescence and early adulthood, with a global lifetime prevalence of about 0.30–0.66% [2, 3]. Schizophrenia does not only affect mental health but also causes a lot of damage to the physical condition. Patients with
schizophrenia die 12–15 years before the average population, and this mortality difference has been increasing in recent decades [1].

Medicine has been the first choice of treatment for patients with schizophrenia and normally include [4, 5]: (1) first-generation antipsychotics, such as haloperidol, perphenazine, and chlorpromazine; (2) second-generation antipsychotics, such as risperidone, aripiprazole, clozapine and olanzapine. The superior effects of second-generation antipsychotics are still controversial; however, the second-generation antipsychotics such as clozapine and olanzapine are being increasingly used as they have lower complication rates [6–8]. Although there is still controversy over the higher rate of effectiveness of second-generation antipsychotics, the use of drugs such as clozapine and olanzapine has increased due to fewer side effects. In addition, clozapine proved to be beneficial in medical treatment-resistant patients; however, only 30–50% of patients experience clinically significant symptom improvement with clozapine treatment [9–11]. In addition, clozapine has proven to be beneficial in the treatment of patients who are resistant to medicine; however, only 30–50% of cases have a significant reduction in symptoms. Medication usually shows good results in the treatment of positive symptoms of schizophrenia, while negative symptoms are generally less receptive to the treatment by medicine. Besides the medication, family therapy, supported employment, skill training and other psychosocial interventions may be helpful in the treatment of schizophrenia [12–15]. But there are still about 20% of schizophrenia cases which do not respond well to any treatment mentioned above [16]. Electroconvulsive treatment could be a viable option for medication-resistant schizophrenics as it has been shown to relieve acute symptoms such as aggression and suicidal behavior as well as enhancing the effectiveness of antipsychotics. Currently, there is limited use of electroconvulsive treatment in China, mainly due to misunderstanding of the treatment as well as poor therapy compliance.

With the developments in neuroimaging techniques, there is more and more evidence supporting that schizophrenia is associated with the frontal-subcortical neuronal circuits, especially the orbitofrontal circuit and anterior cingulate circuit [17–21]. Based on these theories of brain circuits, stereotactic neurosurgery (psychosurgery) was used more and more as a treatment option for psychotic diseases. The modern psychosurgery is quite different from the old practiced by Egas Moniz, Walter Freeman and Gottlieb Burckhardt. In the past, surgery was performed without accurate target, which resulted in an unacceptable level of complications. Although frontal lobotomy initially grew in popularity during the 1960s in the United States, its popularity waned due to serious adverse effects and its potential abuse to control violent behavior. In modern psychosurgery, coordinates of the target area are determined by preoperative MRI which has a high resolution [22]. Many modern MRI-guided procedures were used to treat mental diseases, such as frontal lobotomy, anterior cingulotomy, subcaudate tractotomy, limbic leukotomy and anterior capsulotomy [23–25]. Following a variety of studies, a general conclusion was reached that significant improvements are observed in approximately 70% of patients with refractory obsessive and compulsive disease (OCD) who undergo capsulotomy [26–29]. The success of capsulotomy achieved in OCD stimulated researchers to extend its application to other mental diseases [30–32].

To the best of our knowledge, no paper has been published about MRI-guided capsulotomy used in schizophrenia patients. In this study, we treated patients with schizophrenia by MRI-guided capsulotomy and assessed the therapeutic effect and safety in a long-term follow-up study.

Method
Participants
A total of 116 patients (62 males and 54 females) with schizophrenia underwent bilateral anterior capsulotomy between October 2008 and September 2011 at the Department of Stereotactic and Functional Neurosurgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 100 of which (55 males and 45 females) finished the 2-year follow-up study. All patients were assessed individually by a group of psychiatrists, neurosurgeons and neurologists according to the inclusion criteria before the operation. Additionally, each case was strictly reviewed by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine in accordance with the Declaration of Helsinki. Patients were assessed by our psychiatrists using the Chinese version of the MacArthur Competence Assessment Tool-Treatment first. Our results showed that more than half of patients with refractory schizophrenia (58/100 patients) were competent to provide consent. For these patients, a detailed explanation of the procedure in the form of a Power Point presentation was given by the treatment group (including a neurosurgeon, a psychiatrist, and a psychologist). The informed content was signed by the patient only after he/she had a full understanding of the procedure. Less than half of patients with refractory schizophrenia (42/100 patients) were unable to provide consent. Their representatives who were able to consent were informed in detail about the process of the surgery, and only after the representatives of the patients had a full understanding of the surgery, was the informed content signed by them according to the mental health law in China.
The inclusion criteria were as follows: (1) Patients were diagnosed with schizophrenia in the Department of Psychiatry by independent psychiatrists according to DSM-IV. Refractory schizophrenia patients were confirmed by the team of psychiatrists, neurosurgeons and neurologists which proposed neurosurgical treatment. In our study, the refractory schizophrenia was defined as follows: (a) illness severity was ensured by restricting inclusion to subjects with a score of ≥35 on the 18-item Brief Psychiatric Rating Scale (BPRS, score 1–7) and Clinical Global Impression (CGI) >4; (b) at least three periods of treatment in the preceding 3 years with neuroleptic agents (at least two different chemical classes) at doses ≥500 mg/day of chlorpromazine for a period of 8 weeks, each without significant symptomatic relief; (c) the duration of mental disorder was more than 3 years, and there was no period of good function. (2) The age of the patients was between 18 and 60 years. (3) The disorder severely affected the quality of life of the patient, preventing participation in normal activities such as work or study. (4) Patients or their representatives have the ability and willingness to give informed consent and have the support of their family.

The exclusion criteria were as follows: (1) patients with obvious encephalotrophy caused by Alzheimer’s disease, tumor, and trauma, which was confirmed by MRI; (2) pregnant women; (3) patients with any contraindication to MRI; (4) patients with severe heart diseases or other organic problems who could not undergo neurosurgery; (5) less than 18 years or more than 60 years of age; (6) refusal to sign the patient information and consent form, or refusal to take part in this study.

Surgical Procedure
The procedure of capsulotomy was described in our previous study [33]. Briefly, a Leksell stereotactic frame (Elekta Inc., Stockholm, Sweden) was mounted on patient’s head under local anesthesia or mild sedation. Once the frame was placed, the patient was taken for preoperative MRI scan (1.5 T; General Electric, Madison, Wisc., USA) immediately. The target was identified with the visualization of the internal capsule on stereotactic MRIs. Usually, the target lies at 15–17 mm anterior to the AC, 15–17 mm lateral to the midline, and 2–4 mm under the AC-PC line. After calculation of stereotactic target coordinates and measure of the trajectory angle, bilateral burr holes were made anterior to the coronal suture based on measured entrance trajectory. After dural opening and cauterization of the pia-arachnoid, a 2 mm in diameter and 2-mm uninsulated tip radiofrequency electrode (Radionics, Burlington, Mass., USA) was employed for impedance measurement, followed by stimulation test and lesioning. The radiofrequency lesions were made at 80 °C for 60 s. The first lesion was located 3–4 mm below the AC-PC line and extended up to 10 mm above the AC-PC line. During lesioning, neurological testing was carried out to ensure that there was no impairment of motor or sensory functions. After adequate cooling, the electrode is withdrawn 2 mm, and the ablation procedure was repeated 4–5 times to ensure the complete ablation of the target. Finally, a lesion 4 mm in diameter and 10 mm in length along the contoured target was produced (fig. 1).

Clinical Evaluation
All patients were evaluated by a group of experienced psychiatrists who used a series of international rating scales. We have two independent teams of psychiatrists (team A and team B). The team of psychiatrists who recommended the surgery was not the team that evaluated the results. If the patient was recommended the surgery by team A, team B evaluated the results after surgery to reduce the bias. The rating scales (Global Assessment Scale, GAS; CGI; BPRS; Positive and Negative Symptom Scale, PANSS; Social Disability Screening Schedule, SDSS; Activity of Daily Living Scale, ADL; Mini-Mental State Examination, MMSE) were employed to evaluate the clinical symptoms, social functions and mental status of the patients with refractory schizophrenia. The CGI was divided into five grades: (1) full recovery; (2) obvious improvement; (3) improvement; (4) no change; (5) condition worsened. 1, 2 and 3 were classed as effective, 4 and 5 were classed as not effective.

Statistical Method
All quantitative data are presented as means ± SD. The differences of scales before and after surgery were made by using paired-samples t test. A value of p < 0.05 was considered to be statistically significant, and all statistical analysis was performed using commercially available statistical software (SPSS 16.0; SPSS Inc., Chicago, Ill., USA).
Results

Participants
A total of 116 refractory schizophrenia patients approved by the Ethics Committee of the Ruijin Hospital were referred for neurosurgery and underwent bilateral anterior capsulotomy. 16 patients were excluded from the study because of the failure to follow up within the stipulated time. Figure 2 shows the process of patient selection for the study. 100 patients (86.21%) completed the 2-year follow-up, and their data were analyzed. The age of the patients ranged between 18 and 59 years (mean ± SD: 28.92 ± 7.59 years). Of the 100 patients enrolled in the study, 89 suffered from hallucination (auditory hallucination: 86; visual hallucination: 17; olfactory hallucination: 2; tactile hallucination: 1), 96 suffered from delusion (delusion of reference: 26; delusion of grandeur: 8; delusion of loved: 3; delusion of persecution: 84), 94 had aggressive behavior, 54 suffered from affective flattening, 76 suffered social withdrawal, and 48 had difficulties in integrating thoughts, feelings and behavior. Consistent with other studies, persecutory delusion is the most common type of delusion among patients with schizophrenia. Overall, the most common persecutory behaviors were chasing-capturing (40%), physical attack (25%), angry thoughts (21%), and murder (14%). The patients’ demographic data are summarized in Table 1.

Effectiveness Measures
In total, 116 patients with chronic schizophrenia underwent bilateral anterior capsulotomy, and 100 (86.21%) completed the 2-year follow-up. Of the 100 follow-up patients, 11 were classified as fully recovered, 25 showed obvious improvements, 38 showed improvement, and 26 showed no change according to the CGI evaluation. The effective rate was 74%. Both the positive and negative symptoms showed obvious improvement according to the PANSS evaluation. Among the symptoms, aggressive behavior showed the best improvement after the surgery (54 patients showed obvious improvement, 24 patients...
improved, 16 patients showed no response). Additionally, suicide behavior (n = 15) or self-destructive behavior (n = 3) disappeared completely after surgery. Most of the obsessive and compulsive behaviors (n = 13) vanished too. Symptoms of schizophrenia reappeared in 8 patients, and the effect of drugs was unsatisfactory. Before enrollment into the study, none of the patients could work and all needed others' help in their daily life due to the severity of their illness. Following the surgery, 40 of the patients were able to return to work, and 34 were able to complete housework without the assistance of others; there were still 26 patients who remained the same following the surgery and still needed to be cared for by others. Statistical analysis of PANSS, BPRS, ADL, SDSS and GAS score showed significant differences (table 2) between the baseline results and the results obtained after surgery and at 2-year follow-up. Concerning the MMSE score, no significant difference was noted between the baseline and follow-up results (p > 0.05).

Comparison of Drug Doses Taken before and after Surgery
The dose of medications decreased gradually in all patients 6 months after the surgery. At 2-year follow-up, 11% of the patients stopped taking medicine completely; 32% of the patients took only half of the regular dose; 34% of the patients took one third of the regular dose; 5% of the patients took one fourth of the regular dose; 17% of the patients took the same dose as that before operation, and 1% of the patients needed to have the dose of the medications increased.

Complications
The most common short-term complications were urinary incontinence (n = 18), disorientation (n = 4), sleep disorder (n = 12) and fatigue (n = 10). These symptoms usually disappeared within 2 weeks after the operation. A few patients experienced long-term complications which included bulimia (n = 9), memory loss (n = 7), personality changes (n = 6), lazy behavior (n = 5) and hypererotism (n = 4). The occurrence of intracranial hemorrhages, infections, seizures associated with surgery was 1, 0, and 1%, respectively. One patient had slight bleeding after the surgery and recovered without reoperation. No patient had wound infection. One patient had a seizure and was controlled with antiepileptic medication (sodium valproate: 200 mg/t.i.d.). The occurrence of surgical complications was similar to other stereotactic neurosurgeries [34, 35]. There were no fatalities during our study (table 3).

Discussion
Cingulotomy and capsulotomy are the best-established current treatment options for mental disorders. However, capsulotomy has rarely been applied in schizophrenia, and as a result there is no long-term follow-up research [36]. To the best of our knowledge, this is the first long-term follow-up study about the MRI-guided capsulotomy in schizophrenia. In our study, 100 patients with refractory schizophrenia received MRI-guided capsulotomy, and a 2-year follow-up was performed. Our re-

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Table 1. Demographic characteristics of the subjects based on age, gender, mean duration, therapy and clinical manifestation at the time of surgery (n = 100)

<table>
<thead>
<tr>
<th>Test</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>2 years after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>28.92 (18–59)</td>
<td>28.92 (18–59)</td>
<td>28.92 (18–59)</td>
</tr>
<tr>
<td>Males/females</td>
<td>55/45</td>
<td>55/45</td>
<td>55/45</td>
</tr>
<tr>
<td>Mean duration of illness, years</td>
<td>8.93 (3–40)</td>
<td>8.93 (3–40)</td>
<td>8.93 (3–40)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication alone</td>
<td>88</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Medication + psychotherapy</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Medication + behavior therapy</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Delusion</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Suicide behavior</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Self-destructive behavior</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>OCD</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Body form obstacles</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate range.

Table 2. Evaluation of patients with refractory schizophrenia before and after bilateral capsulotomy (n = 100)

<table>
<thead>
<tr>
<th>Test</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>2 years after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS positive</td>
<td>26.65±4.85</td>
<td>6.21±8.43*</td>
<td>6.86±8.12*</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>21.66±7.19</td>
<td>10.25±9.46*</td>
<td>10.70±8.70*</td>
</tr>
<tr>
<td>BPRS</td>
<td>44.97±9.36</td>
<td>14.64±13.78*</td>
<td>14.75±13.21*</td>
</tr>
<tr>
<td>SDSS</td>
<td>15.06±3.18</td>
<td>6.42±6.10*</td>
<td>6.69±6.12*</td>
</tr>
<tr>
<td>ADL</td>
<td>24.61±8.95</td>
<td>17.65±6.54*</td>
<td>18.06±6.58*</td>
</tr>
<tr>
<td>GAS</td>
<td>48.74±9.18</td>
<td>73.05±12.37*</td>
<td>74.35±12.75*</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.29±0.72</td>
<td>28.32±0.68</td>
<td>28.29±0.70</td>
</tr>
</tbody>
</table>

Significance test results are all compared with results before surgery (paired t test). * p < 0.001.
Results indicated an effective rate of 74% according to the CGI evaluation and an obvious improvement based on the statistical analysis for PANSS, BPRS, ADS and GAS score in a long-term follow-up.

Besides lesions, neuromodulatory strategies such as deep brain stimulation (DBS) are well accepted now because of their reversibility and minimal invasion [37, 38]. However, we did not use DBS in our study due to several reasons. Firstly, DBS consists of the implanted pulse generator, the lead, and the extension, all of which require long-term maintenance. Schizophrenia is a more complex disorder with psychotic features; therefore, it will be extremely challenging considering the long-term management of the DBS. MRI-guided capsulotomy is a well-established and relatively safe procedure. It is a kind of procedure which does not require a lifelong commitment to regulating the stimulation devices, fixing hardware failures, or changing exhausted batteries [34]. For patients who do not want regular device programming and maintenance, capsulotomy would be an optional choice. Secondly, there are case reports indicating the possible effects of bilateral anterior capsulotomy in schizophrenia. Jimenez et al. [39] reported that combined bilateral anterior capsulotomy and cingulotomy successfully reduced aggressive behavior and improved clinical evaluations in 23 schizophrenia patients. Lastly, the anterior limb of the internal capsule (ALIC) serves as a relay route between cortical structures (such as prefrontal cortex, PFC) and the thalamus; the dorsolateral PFC region of the frontal lobe is involved in attention, affect and working memory, all of which are reported to be abnormal in schizophrenia [40, 41]. Therefore the PFC, striatum, and the connective fibers (such as anterior limb of internal capsule) between functional regions play an important role in schizophrenia, and neuroimaging results confirm the conclusion [42–44]. All this evidence indicates the critical role of ALIC in the occurrence of schizophrenia. Therefore, lesions targeting ALIC were performed in our study.

In our study, both positive and negative symptoms showed obvious improvement after the capsulotomy (tables 4, 5). The positive symptoms of schizophrenia are proven to have a close relationship with the dopamine...
system. Dopaminergic neurons originated from the substantia nigra and ventral tegmental area (VTA). There is evidence indicating that PFC, amygdala, VTA, and nucleus accumbens all share critical functional connections. Some of these connections have important implications for dopaminergic regulation of cortical-subcortical emotional regulatory processes, which is critical for the onset of the positive symptoms in schizophrenia patients. The improved positive symptoms after capsulotomy in our study are consistent with the hypothesis of dopaminergic regulation in schizophrenia. It was reported that serotoninergic system plays an important role in negative symptoms of schizophrenia. Serotonin neurons from the dorsal and median raphe project to the PFC, and the PFC sends projections back to the raphe nuclei, which provides the feedback control of cortical 5-HT release. Serotonin could stimulate the 5-HT2A receptors in PFC, which inhibits the activity of DA neurons in this area, thus disturbing the serotonin circle by lesions in the ALIC which could regulate DA release in the terminal area. This might be a mechanism by which the capsulotomy improved negative symptoms in our study.

In addition, accompanied symptoms such as obsessive and compulsive disorders disappeared in most of the patients (13/16). The memory and cognition of most patients with schizophrenia were stable before and after the operation as assessed by the MMSE. Eleven patients who were assessed as fully recovered stopped taking medicine gradually and found a job, thus gaining financial independence. The majority of patients reduced the dosage levels of their medication following the operation (n = 71), although the reasons for this are still unclear. One of the possible reasons may be that the patients’ symptoms had improved sufficiently as a result of the surgery and so they no longer needed a high dose of medication, but since the detailed mechanism is still unknown, it will require further studies to explore this.

In our study, a relapse of schizophrenia was observed in 8 patients. Sudden drug withdrawal and life changes such as failure in love, divorce and unemployment play a critical role in the relapse. The most common short-term complications were urinary incontinence, disorientation, sleep-disorder and fatigue. These symptoms usually disappeared within a few weeks after the operation. However, long-term complications such as bulimia, memory loss, and personality changes are problems which cannot be ignored [45]. Although the accurate positioning before operation could decrease the complications, the exploration of precise mechanism of schizophrenia should be the key point to eliminate the complications.

There are limitations to our study. Firstly, the present study is not a randomized trial because of the lack of a control group. When treating lesions, it is difficult to set up a control group, but the problem could be solved by research of DBS. Secondly, our investigation is a single-center study with a relatively short follow-up time. Data of the same procedure in schizophrenia from other centers would need to be collected to verify the persistence of the surgery.

All in all, our data primarily showed that capsulotomy is an optional invasive and effective procedure with relatively less side effects and complications in refractory schizophrenia patients. However, this procedure is still an invasive method, and the lesion is irreversible. Therefore, we must keep in mind that surgical therapy should only be considered as a complement of the medical treatment, and the inclusion criteria must be strictly carried out; in addition, this must be accompanied by an appropriate psychological rehabilitation plan and family-social support program to help the patients recover.

Conclusion

In our study, we treated 100 refractory schizophrenia patients with MRI-guided capsulotomy and found obvious improvements in the clinical symptoms of schizophrenia based on scale evaluation during the 2-year follow-up. Our research indicates that MRI-guided capsulotomy is an optional intervention for patients with refractory schizophrenia. However, candidates for this invasive procedure must be selected according to strict criteria considering the complications and the irreversibility of this procedure.

References


