Stereotactic lesions for the treatment of psychiatric disorders

A review

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Object. The use of deep brain stimulation (DBS) has recently been expanded to the investigational treatment of specific psychiatric disorders. Much like movement disorders, the targets selected for DBS are based on past experience with stereotactic lesions. A literature review of past studies incorporating stereotactic lesions for psychiatric disorders was performed to provide historical context and possible guidance for current and future attempts at treating psychiatric disorders with DBS.

Methods. Original copies of the proceedings of the second, third, fourth, and fifth World Congresses of Psychiatric Surgery meetings were reviewed, and a Medline search was conducted for studies with the word “psychosurgery” and each of 14 highly prevalent psychiatric conditions identified by the National Institute of Mental Health. Postoperative results for 1145 patients with stereotactic brain lesions targeting various anatomical foci were standardized using a 5-point scale (3 [free of symptoms] to −1 [worse]). Each patient was entered into a database as a unique data point and used for this literature review.

Results. General anxiety disorder and obsessive-compulsive disorder had the greatest reported improvements from anterior capsulotomy, and bipolar disorder, depression, and schizoaffective disorder had the greatest reported improvements from anterior cingulotomy, supporting these areas for DBS investigation. Addiction and schizophrenia showed the least improvement from surgery. Therefore, pursuing the treatment of these disorders with DBS using the targets in these studies may be ineffective.

Conclusions. This study provides retrospective data that suggest which anatomical focus may be effective to lesion or stimulate for the treatment of each of several psychiatric disorders. (DOI: 10.3171/2010.5.JNS091277)

Key Words • stereotactic lesion • psychiatric disorder • literature review

Stereotactic lesions have been used by neurosurgeons since the early 20th century as treatment options for neurosurgical disorders with varying results and sometimes skepticism. For the treatment of movement disorders, stereotactic lesions were first introduced in 1940 by Spiegel et al.46 that targeted the thalamus. Following this, many subcortical targets were investigated, and lesions focusing on the thalamus, subthalamic nucleus, and globus pallidus were shown to deliver the most effective results in the treatment of movement disorders.45 In the 1980s Benabid et al.,7 following initial work by Mundinger,7 demonstrated that high-frequency DBS focusing on these same targets was successful for the treatment of movement disorders.10

The exact mechanism of DBS is unknown; however, it is believed to disrupt pathological networks by affecting nerve cell firing and may act as a functional lesion. Deep brain stimulation is advantageous over lesioning because it preserves the local anatomy, thus making it fully reversible, and it is adaptable to maximize the patient benefit.51 Due to the great successes in the treatment of movement disorders, more recent studies have begun to use DBS for the investigational treatment of psychiatric disorders. Early work in this field has focused primarily on the treatment of severe refractory depression and OCD.24 Both disorders are severely disabling and may be refractory to psychotherapy, pharmacological intervention, and electroconvulsive therapy. These early studies showed considerable promise and prompted Thomas Insel, Director of the NIMH, to conclude, “the same kind of approach that has worked so well in Parkinson’s disease may work equally well—or even better—in depression.”62 However, researchers currently use different anatomical targets for DBS, and they have demonstrated varying degrees of success. For this reason, it would be useful to determine which anatomical targets in the past have demonstrated the most effective treatment of psychiatric disorders with lesions.

The treatment of psychiatric disorders using stereotactic lesions has existed for the greater part of the past century and has shown a great range in the effectiveness of lesioning as a treatment option. The purpose of this
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study is to consolidate available data on stereotactic lesions used for the treatment of psychiatric disorders and evaluate patient outcomes based on these different procedures. This will help determine which procedures and anatomical targets were most effective for the treatment of psychiatric disorders and provide guidance for current and future attempts at treating psychiatric disorders with DBS.

Methods

The materials for this study began with original copies of the proceedings from the second, third, fourth and fifth World Congresses of Psychiatric Surgery meetings,19,20,27,49 The proceedings from the first World Congress of Psychiatric Surgery in Lisbon in 1949 were not published. These texts contained numerous studies on the use of lesions for the treatment of psychiatric disorders presented at the world conferences in 1970, 1972, 1975, and 1978. Twenty-eight articles from these 4 texts contained subject material initially considered for this literature review.

Additionally, a PubMed search was conducted using the word “psychosurgery” and 14 of the most prevalent psychiatric disorders identified by the NIMH in 2006.38 Those search terms were depression, dysthymic disorder, bipolar disorder, schizophrenia, panic disorder, OCD, posttraumatic stress disorder, GAD, agoraphobia, phobias (general), eating disorders, attention deficit hyperactivity disorder, autism, and Alzheimer disease. Searches were limited to include only humans, and no date boundaries were set.

Some of the NIMH’s disorders are defined by the American Psychiatric Association’s DSM-IV-TR2 under the broad headings of “anxiety disorders” or “mood disorders;” however, the inclusion of the specific subheadings has furthered this study’s ability to find applicable data that may have focused on a specific disorder. This PubMed search returned 442 articles initially considered for this literature review (Table 1).

The text and PubMed searches returned 470 articles and studies initially considered for this study. Strict inclusion criteria for the studies were used. Those criteria were that the study must have used focally targeted stereotactic surgeries with 1 or 2 anatomical targets, that patients must have undergone objective pre- and postoperative evaluations by a physician, that the study included lesions for the treatment of psychiatric disorders, and that no prefrontal lobectomy procedures or variations thereof were included. Additionally, data for each group of investigators were included only for the longest patient follow-up, given that many articles were written periodically on the patients as they were monitored for many years postoperatively. Once these criteria had been met, our final materials for this literature review consisted of 1163 patients from 28 different studies who were treated with stereotactic lesions for various psychiatric disorders.

These 1163 patients were then standardized according to a 5-point scale based on postoperative physician evaluations. This scale ranged from 3 to −1, with 3 corresponding to a symptom-free outcome, 2 significant improvement, 1 minimal improvement, 0 no change, and −1 indicating the patient’s disorder became worse after surgical intervention. This scale was used as our dependent variable for this analysis.

Patients were divided into groups according to their disorder. This resulted in 12 groups. Disorders containing fewer than 10 patients were not analyzed due to their low statistical power. This criterion excluded pain (in 7 patients), anorexia (in 2 patients), developmental disorder (in 1 patient), parkinsonism (in 1 patient), and personality disorder (in 4 patients). This left 7 main disorder groups: GAD, OCD, bipolar disorder, depression, schizoaffective disorder, addiction, and schizophrenia. Within each disorder, patients had undergone assorted procedures focused on different anatomical targets, and outcomes varied as a result. Procedures with data on fewer than 5 patients were not included because of the inability to draw meaningful conclusions on such a small sample size. Table 2 summarizes the procedural distribution for each disorder.3–8,11–15,18,21–23,25,26,28,29,31–33,35,36,43,44,47,50,52–54 Either the Mann-Whitney U-test or Kruskal-Wallis test was performed on each of these 7 disorder groups to determine if there was a statistically significant difference in the outcomes from the different anatomical targets.

Results

Our results are presented following DSM-IV-TR group headings for 4 of the 7 psychiatric disorders. These 4 disorders are GAD and OCD, which are presented under the anxiety disorder heading, and bipolar disorder and depression, which are presented under the mood disorder heading. Each disorder was analyzed individually; however, this categorization is a logical way of presenting the results and illustrates the similarities between disorders.

The remaining 3 disorders (schizoaffective, addiction, and schizophrenia) are presented individually.
Anxiety Disorder

Anxiety disorder is a comprehensive term including different forms of atypical and pathologically significant anxiety, fears, and phobias. Consequently, anxiety disorder can be further subdivided into 7 general headings: GAD, OCD, panic disorders with or without agoraphobia, phobias, stress disorders, anxiety disorders due to underlying medical causes, and other forms of anxiety not meeting specific DSM divisions. Each of these disorders, while varying in presentation and symptoms, shares common strains and may be due to pathological changes in similar areas of the brain.30 The available data on stereotactic lesions focused on the treatment of only 2 anxiety disorders: GAD and OCD; hence, our study presents information accordingly.

General Anxiety Disorder

General anxiety disorder is the most commonly diagnosed anxiety disorder, wherein the patient’s intensity, duration, or frequency of anxiety is far out of proportion to the actual likelihood or impact of a feared event. Generalized anxiety disorder may be distinguished from other anxiety disorders because the focus of this anxiety is not confined to an Axis I disorder. Additionally, patients afflicted with GAD have chronic anxiety, oftentimes with or without provocation.2

Our study collected data from 177 patients with GAD; each patient was treated with 1 of 6 different procedures that targeted diverse anatomical regions. Our results suggested that anterior capsulotomy was significantly more effective for the treatment of GAD than anterior callosotomy, cingulotomy, frontal leukotomy alone, frontal leukotomy combined with cingulotomy, and subcaudate tractotomy (innominotomy) (p < 0.005, Kruskal-Wallis). It is important to point out that frontal leukotomies consisted of stereotactic lesions in the medial frontal lobe to interrupt frontothalamic and hypothalamic connections and did not consist of total frontal disconnection.

Additionally, following anterior capsulotomy, there was a high mean postoperative study value of 2.4, and as shown in Fig. 1, almost all patient outcomes fell into the 3 and 2 outcome ranges on the 5-point scale. It is important when evaluating the figures to look first at the relative size of the bars as those show patient numbers, but more importantly to look at the relative distribution of the patient outcomes in the outcome categories for each procedure. As shown in Fig. 1, fewer patients underwent anterior capsulotomy than cingulotomy; however, almost all the patients who underwent anterior capsulotomy were reported to be in the 3 and 2 patient outcome categories. On the other hand, patient outcomes following cingulotomy were distributed among all the outcomes.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is marked by recurrent unwanted and intrusive thoughts or repetitive behaviors. These “rituals” reflect the patient’s anxiety or attempts to control it and can be greatly exasperated in stressful situations.2

Our study collected data from 303 patients receiving stereotactic lesions for the treatment of their OCD. Anterior capsulotomy was more effective for the treatment of OCD with a mean postoperative study value of 2.1, but this was not a statistically significant difference (p > 0.1, Kruskal-Wallis). As is seen in Fig. 2, anterior capsulotomy was reported to be more effective for the treatment of OCD than cingulotomy, frontal leukotomy alone, frontal leukotomy combined with cingulotomy, and subcaudate tractotomy.

Mood Disorder

Mood disorder is a blanket term used to describe disorder subtypes linked by emotional moods distorted or inappropriate to the circumstances. The DSM-IV-TR subdivides mood disorder into 6 groups: bipolar disorder, major depressive disorder (clinical depression), cyclothymia, dysthymia, mood disorders due to an underlying medical condition, and a broad category for those not fitting specific DSM classification. The 2 foremost types of mood disorder, bipolar disorder and depression, were the 2 disorders providing adequate availability of data for analysis on stereotactic lesions.

Bipolar Disorder

The DSM-IV-TR distinguishes between 2 types of

### TABLE 2: Procedural distribution among final study groups*

<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>Total</th>
<th>ACal</th>
<th>ACap</th>
<th>Cin</th>
<th>Cin/FL</th>
<th>FL</th>
<th>ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>177</td>
<td>17</td>
<td>12</td>
<td>60</td>
<td>18</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>OCD</td>
<td>303</td>
<td>0</td>
<td>114</td>
<td>78</td>
<td>46</td>
<td>45</td>
<td>20</td>
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<td>42</td>
<td>0</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>depression</td>
<td>413</td>
<td>0</td>
<td>0</td>
<td>111</td>
<td>12</td>
<td>215</td>
<td>75</td>
</tr>
<tr>
<td>schizoaffective</td>
<td>49</td>
<td>9</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>addiction</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>schizophrenia</td>
<td>139</td>
<td>37</td>
<td>0</td>
<td>83</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

* See callout for Table 2 in the text for the list of the studies included. Abbreviations: ACal = anterior callosotomy; ACap = anterior capsulotomy; Cin = cingulotomy; FL = frontal leukotomy; ST = subcaudate tractotomy.
bipolar disorder. Type 1 is characterized by the occurrence of 1 or more manic or mixed episodes, and Type 2 is characterized by 1 or more major depressive episodes accompanied by at least 1 hypomanic episode. However, the studies used for this analysis did not differentiate these 2 types of bipolar disorder, so general bipolar disorder is presented.

Each of the 42 patients evaluated was either treated with cingulotomy or frontal leukotomy. Cingulotomy was reported as significantly more effective for the treatment of bipolar disorder ($p < 0.01$, Mann-Whitney U-test). As shown in Fig. 3, cingulotomy had the greatest distribution of patients reported to be in the 3 category, symptom-free outcome. Furthermore, following cingulotomy the mean patient outcome by report was 2.8, the highest of any disorder group tested in this study.

Depression Disorder

According to the DSM-IV-TR, and as seen in current practice, depression is subdivided into various groups based on its relative severity. The data collected do not have these specific subcategorizations because the research greatly predates current terminology; however, the majority of the studies acknowledged that all nonsurgical methods to treat depression had been exhausted.

Four hundred thirteen patients were treated with stereotactic lesions for depression. Cingulotomy was reported as being significantly more effective for the treatment of depression than frontal leukotomy alone, frontal leukotomy combined with cingulotomy, and subcaudate tractotomy ($p < 0.0001$, Kruskal-Wallis). Cingulotomy had a mean reported postoperative study value of 2.3 and, as shown in Fig. 4, had the greatest proportion of patient outcomes reported to be in the better outcome categories.

Other Disorders

Schizoaffective Disorder. Schizoaffective disorder itself is perplexing as it involves components of a thought disorder (schizophrenia) such as hallucinations and delusions and of a mood disorder such as depression or bipolar disorder.2 This study has separate categories for schizophrenia, depression, and bipolar disorder; however, schizoaffective disorder was presented independently in the included studies and is presented independently in the current study as well.

For the effective treatment of schizoaffective disorder, cingulotomy was reported to have significantly higher rating than anterior callosotomy ($p < 0.05$, Mann-Whitney U-test). Cingulotomy, shown in Fig. 5, had a mean reported postoperative study value of 2.3 and was shown to produce better outcomes than anterior callosotomy.

Schizophrenia. There are a number of types of schizophrenia depending on the characteristics of the symptoms, but the basic disorder is characterized by symptoms including hallucinations, delusions, disorganized thoughts, incoherent speech, neglected personal hygiene, and disrupted cognitive and social abilities among others. The broad diagnosis of schizophrenia without subtypes was used for this study given the lack of symptom detail reported in the reviewed studies and the need to have broad enough categories for effective analysis.

There was a statistically significant difference in reported outcomes based on the stereotactic procedure performed for schizophrenia ($p < 0.05$, Kruskal-Wallis). As shown in Fig. 6, patients having cingulotomy had the best reported outcomes, followed by frontal leukotomy with cingulotomy, then anterior callosotomy, frontal leukotomy, and finally subcaudate tractotomy. However, the best reported outcome for cingulotomy was 1.6, a poor outcome in comparison with the other disorders.
Addiction. Based on the reported results for addiction, one procedure did not appear significantly more effective for treatment over alternative procedures. Cingulotomy and frontal leukotomy procedures were not statistically significantly different in their reported outcomes ($p > 0.1$, Mann-Whitney U-test; Fig. 7).

Comparison of Outcomes by Disorder

Figure 8 shows a comparison of mean patient outcomes using the most effective procedure for each psychiatric disorder. This comparison was done to illustrate which disorders benefited the most from surgical intervention. As shown, bipolar disorder, with a mean patient outcome following cingulotomy of 2.8, may have the most effective response to surgery. This was followed by GAD and depression. The lowest reported mean patient outcomes were seen in addiction and schizophrenia.

A note of interest in Fig. 8 is that schizoaffective disorder seemed to respond better to surgical intervention than schizophrenia and not as well as depression. This suggests similar trends to those seen in the medical treatment of these disorders.

Discussion

This study relies on research and clinical care conducted over the past 60 years. Although it is necessary to include all data available, outcome measures used in past studies were less rigorous than outcome measures used in modern studies, like the Yale-Brown Obsessive Compulsive Scale. This study does not suggest that DBS focusing on the identified targets will generate as many symptom-free patients as shown in the analyzed studies. However, stereotactic lesion targets that have shown evidence of efficacy may prove valuable in guiding the treatment of psychiatric disorders with DBS.

Anterior capsulotomy, which involves bilateral lesions to the anterior limb of the internal capsule severing connections between midline thalamic nuclei, caudate nuclei, and the orbitofrontal cortex, was reported to be more effective than alternative procedures for the treatment of GAD and OCD. As mentioned previously, these disorders have some common symptoms and a similar grouping. This study suggests that these disorders may share similar pathological pathways and potential intervention targets.

Additionally, anterior cingulotomy, which involves bilateral lesions to the anterior cingulate gyrus, was reported to be significantly more effective than alternative procedures for the treatment of bipolar disorder, depression, and schizoaffective disorder. Both bipolar disorder and depression fall exclusively under the mood disorder heading, and schizoaffective disorder shares common characteristics with mood and thought disorders. As suggested by our study, these 3 disorders may derive significant benefit from procedures targeting a common anatomical pathway. This further suggests similarities among these 3 disorders and provides evidence for the delineation between schizophrenia as predominantly a thought disorder and schizoaffective disorder, which shares commonalities with mood disorders. Cingulotomy was the procedure with the best reported outcomes for schizophrenia; however, the outcomes were far below the outcomes reported for the other disorders.

There is evidence that combining more than 1 target may make the outcomes worse rather than improving them. This is suggested by reported results for depression, where cingulotomy alone was reportedly more effective than frontal leukotomy, and frontal leukotomy when
combined with cingulotomy returned the lowest reported patient outcomes (Fig. 4). This argues against the use of multiple targets and supports the determination of individual effective targets. Furthermore, lesions of the frontal lobes that were popular in early psychosurgery were less effective than procedures focused on other regions of the brain. There are a number of questions regarding the relative benefit to one group of disorders versus another when each undergoes the same procedure. For instance, why did one anxiety disorder, GAD, appear to benefit so greatly from surgical intervention but OCD, a similar anxiety disorder, did not appear to benefit as highly (Fig. 8)? Our study suggests that anterior capsulotomy was significantly more effective than other treatments for both of these disorders, possibly indicating a common pathological pathway.

Interestingly, the few studies reporting effective use of DBS for psychiatric disorders used targets for stimulation that had the best reported outcomes in this study. Several investigators have targeted the anterior internal capsule in the treatment of OCD,1,3,17,32,39–41,44 although other studies have targeted alternative anatomical structures in the region.4,13,26,47,48 There are also recent reports of the successful use of DBS for the treatment of severe treatment-resistant depression, targeting the anterior cingulate gyrus.13,26,34 This preliminary experience with DBS for psychiatric disorders provides limited support for the use of existing data from stereotactic lesion studies as presented in the current study to guide early DBS trials for these disorders.

**Conclusions**

This study provides retrospective data that suggest which anatomical focus may be effective to lesion or stimulate for the treatment of each of several psychiatric disorders. Addiction and schizophrenia had the lowest reported improvements from surgical intervention, suggesting that therapy for these disorders with DBS may be similarly ineffective at these targets. In contrast, GAD, OCD, bipolar disorder, depression, and schizoaffective disorder all showed more sizable reported improvements and may be better psychiatric disorders for DBS investigation.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Leiphart. Acquisition of data: both authors. Analysis and interpretation of data: Leiphart. Drafting the article: both authors. Critically revising the article: Leiphart. Reviewed final version of the manuscript and approved it for submission: both authors. Statistical analysis: Leiphart. Administrative/technical/material support: Leiphart. Study supervision: Leiphart.

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