In The Matter Of:

Mary Lou Zimmerman, etc. v.
The Cleveland Clinic Foundation

Ali Rezai, M.D.
April 2, 2001

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IN THE COURT OF COMMON PLEAS
CUYAHOGA COUNTY, OHIO
MARY LOU ZIMMERMAN, Etc.
Plaintiis,
JUDGE BURNSIDE
-vs- CASE NO. 399411
THE CLEVELAND
CLINIC FOUNDATION,

Defendant.

Deposition of ALI REZAI, M.D., taken as if upon cross-examination before Katherine A. Koczan, a Notary Public within and for the State of Ohio, at the offices of The Cleveland Clinic Foundation, 9500 Euciid Avenue, Desk S-80, Cleveland, Ohio, at 2:50 p.m. on Monday, April 2, 2001, pursuant to notice and/or stipulations of counsel, on behalf of the Plaintiffs in this cause.

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On behalf of the Defendant.

ALI REZAI, M.D., of lawful age, called by the Plaintiffs for the purpose of cross-examination, as provided by the Rules of Civil Procedure, being by me first duly sworn, as hereinafter certified, deposed and said as follows:

CROSS-EXAMINATION OF ALI REZAI, M.D.

BY MR. LINTON:

Q: Dr. Rezai?

A: Yes.

Q: Good afternoon, my name is Bob Linton and I'm one of the lawyers representing Mary Lou Zimmerman and her husband, Sherman Zimmerman, in a lawsuit that's been filed against the Cleveland Clinic.

We are here today to take your deposition. Have you ever been deposed before, doctor, have you been through this process before?

A: No.

Q: Okay. Did you have a chance to meet with Mr. Malone to prepare for your deposition?

A: I had some discussions with Mr. Malone, yes.

Q: Did you have a chance to actually meer with **him** face to face?

A: Yes.

Q: Did you have a chance to meet at all with his

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not have much time.
Q: Would it have been less than an hour?
A: Definitely.
Q: Less than a half-hour?
A: Most likely. I can't recall.

(Thereupon, a discussion was had off the record.)

Q: All right. I want to review now what you did for your deposition. You had the two meetings with Mr. Malone, and you did not meet with nor discuss preparing for your deposition with anybody else, is that correct?
A: That's correct.
Q: Have you reviewed anything to prepare for your deposition today?
A: No.
Q: Have you reviewed at any time any of the medical records relating to Mary Lou Zimmerman?
A: No.
Q: Have you discussed Mary Lou Zimmerman's case with Dr. Barnett or any other person at the Cleveland Clinic?
A: No.

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Q: Have you done any research of the medical literature to prepare for your deposition?
A: No.
Q: Have you reviewed any medical literature to prepare for your deposition?
A: No.
Q: We have now covered everything you've done to prepare for your deposition today?
A: Right.
Q: Fair enough. You've handed us what I've marked Exhibit 1, that is your current curriculum vitae, is that correct?
A: Yes.
Q: Are there any additions or subtractions that need to be made to bring it up-to-date?
A: Let's see. I gave several talks in the past couple weeks, but no, I think this is pretty much it. Yes, that's significant enough, yeah.
Q: Any of those talks relate to the issue of psychosurgery or surgery for psychiatric conditions?
A: I have talked about surgery for psychiatric conditions at those talks, yes, but that was not the major focus of the talk.
Q: Would that have been talks you gave that are not

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listed on your resume?
A: Yes.
Q: Okay. And what talks have you given that would have included doing surgery for psychiatric conditions?
A: Talks on pacemakers for the brain, and a component of that involves implantation of pacemakers for psychiatric disorders.
Q: Does that include for OCD?
A: Yes.
Q: Who did you give — was it more than one talk that you gave?
A: Yeah, it was more than one talk.
Q: That was not in your resume?
A: Yes, let me just see here quickly. Okay. If I remember when was the last time I revised my resume. Yes, it is. It was.
MR. MALONE: You got March 6, 2001 on here.
A: Yeah, it was a couple of talks subsequent to this. That's not included here.
MR. MALONE: Okay.
Q: And how many talks have you given that were not, that are not reflected in your resume?
A: Two talks.

Q: When were those given, to the best of your memory?

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hasn't beer, here in over three years.
MR. LINTON: It may have relevance, I don't know till I get an answer.
MR. MALONE: Unless it's somehow calculated to getting stuff that's reasonable.
MR. LINTON: It absolutely is, Jim.
MR. MALONE: How is it reasonably calculated to lead to discoverable evidence.
MR. LINTON: In all fairness, I don't need to explain it to you.
MR. MALONE: If you want answers, you're going to have to give me some basis to go into this never-never fantasy land.
MR. LINTON: If you feel it's inappropriate, you can instruct the witness not to answer at any time.
Q: Doctor, the center, when was that formed?
MR. MALONE: We are going to go a little bit further with this and then we are going to stop. Go ahead and answer that one.

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A: At the same time, January, February, around that time, I can't recall exactly.
Q: And how many neurosurgeons works in that center?
A: At this time, it's only myself.
Q: How many staff people support you?
A: Can you clarify that question? What do you mean by staff?
Q: Anybody that's not a physician.
A: Oh, okay. Staff means physician here.
Q: Thank you for that clarification.
A: Let's see. Probably at least 20 that I can think of at the top of my head.
Q: How many physicians staff are in your section?
A: At the center?
Q: No, you said —
A: My section?
Q: In your section.
A: I'm the only one that does functional neurosurgery. So one at this time.
Q: And how many staff people?
A: One. Oh, staff?
Q: Nonphysician staff.
A: Nonphysicians. Seven.
Q: Where do you perform surgery for psychiatric conditions, is that all done at the center or is it also done elsewhere?
A: I only operate at the Cleveland Clinic.
Q: The center that you talked about, that's here at the Cleveland Clinic as well?
A: Yes.
Q: Does that contain the surgical suites where you perform surgery?
A: Yes, they're all part of the same area, yes.
Q: And where is that housed?
A: In the main hospital.
Q: What building?
A: Oh, main OR's, H, I think it's H Building. I'm not sure. I'm not sure.
MR. **MALONE:** Then don't guess.
Q: What are your research responsibilities as the section head?
A: Understanding the mechanisms underlying movement problems, movement disorders like Parkinson's, chronic pain and psychiatric disorders.
Q: What responsibilities do you have for quality control in your section?
A: If there are any complications, they are reported to the departmental quality controller, and all records of all complications are kept.
Q: Who is the quality controller of your department?

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A: I don't know the exact person, but it's administrated through Marc Mayberg.
Q: Is there any other department outside of your section here at the Cleveland Clinic that is currently doing psychosurgery or surgery for psychiatric conditions?
A: I'm not sure.
Q: Well, weren't you brought in here to consolidate functional neurosurgery?
A: But I'm not sure if anybody else is doing it. I don't keep a record of all the ORs. There's over 70 ORs here. To the best of my knowledge, I'm the only one that's doing psychosurgery at this time.
Q: Do you have any working relationship with Dr. Barnett relative to psychosurgery since you've come here?
A: I have discussed some patients with him that have been referred to me.
Q: Okay. Has he assisted with surgery since you've come here?
A: No.
Q: Are you familiar generally with the term psychosurgery as it's defined in the neurosurgical literature?

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performed?
A: I am not sure a hundred percent because I don't know the details.
Q: Okay.
A: So —
Q: Do you know if surgical outcomes are tracked in the computer?
A: I don't know.
Q: Okay. Have you made any efforts since you came to the clinic to try to obtain that information regarding your own surgical cases?
A: I have obtained information as far as the types of surgeries and number of surgeries.
Q: But no additional information?
A: No additional information.
Q: Have you tried to obtain that information regarding any other neurosurgical procedures performed by other people here at the Cleveland Clinic?
A: No.
Q: How many neurosurgical procedures do you do a year, you personally?
A: I don't know my numbers for the last year, but at least a hundred.
Q: Okay. Is that full capacity?

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MR. MALONE: For who?
Q: For yourself.
A: What is, a hundred?
Q: Yes.
A: No, it can be more. I'm not sure of the exact number I do.
Q: Okay. But do you have — obviously you're coming in, there's a transition period before you get out —
A: Right.
Q: — and have your plate completely full?
A: Right,
Q: What do you **expect** to be the total number of surgical cases you'll eventually be doing?
MR. MALONE: Really, where does this go? You've got to help me.
MR. LINTON: It may go to qualifications, I don't know, Jim.
MR. MALONE: He didn't operate or even see your client. He wasn't even an employee of the Cleveland Clinic when your client was here.
MR. LINTON: I understand.
MR. MALONE: His qualifications are not at issue. His expectations for

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future surgical volume can't possibly be an issue in this case. I'm sorry if I'm really dense and dumb and missing something.
MR. LINTON: I'll be happy to tell you about it.
MR. MALONE: Go ahead, I'm listening.
Q: Dr. Rezai —
MR. MALONE: Will you tell me about it or not?
MR. LINTON: No, I'm going to continue to ask questions until you tell him not to answer and we'll address it with the court later.
MR. MALONE: Try again.
Q: Doctor, you are presently doing, you did last year about a hundred surgical procedures. Assuming you have a full caseload, what do you expect the number of procedures to be, approximately?
A: Anywhere from 150 to 200.
Q: Now, how many of the procedures that you've done so far here at the Cleveland Clinic have related to psychosurgery for OCD?

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A: I have not done any yet here.
Q: Have you done any before coming here?
A: Yes.
Q: How many have you done, psychosurgeries for OCD?
A: Probably, I can't recall the exact number, at least ten.
Q: Your best estimate at this point would be at least ten, is that correct?
A: Yes.
Q: And would those be ten that you did as the attending, or does that also include ones you assisted with during training?
A: During training.
Q: Would all the ten be assisting during training?
A: Almost all, yes.
Q: Can you recall any that you would have done as the attending physician?
A: Yes.
Q: How many of the ten?
A: One or two, probably one. I can't remember exactly.
Q: Again, your best memory at present would probably be one?
A: At least one, yeah.
Q: And when would that have been performed?

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assist with there?
A: Gamma knife capsulotomies.
Q: Do you remember if the cases in Sweden were for **OCD** or for **OCD** and depression?
A: I don't recall.
Q: Were you involved at all on any long-term follow-up care for those patients?
A: No.
Q: Do you know the follow-up care for those patients in terms of a long-term basis?
A: No.
Q: What was the procedures that you, the other procedures that you performed in psychosurgery?
A: Radiofrequency cingulotomies.
Q: And can you say how many of those were for **OCD** versus OCD and depression?
A: No.
Q: Did you follow those patients on a long-term basis?
A: Some.
Q: What would be the longest out you would have followed any of the patients?
A: I would say at least six months.
Q: I assume it would not have been longer than a year since you were only training for a year

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there?
A: Most likely, yes.
Q: Would you agree that they are, the research shows that one can still have improvement following psychosurgery for a year or longer after the surgical procedure?
A: It can, yes.
Q: Have you personally been involved — do you need to take that call?
Have you personally been involved in any scientifically reliable studies relating to the surgical outcomes for the patients in which you personally were involved in?
A: Rephrase that. The ones — can you rephrase that question?
Q: Sure, I want to focus now just on the psychosurgery cases that you had been involved in.
A: Okay.
Q: Have those been the subject of any scientifically reliable research studies?
A: Some, some of them, yes.
Q: Which patients and which studies?
MR. MALONE: You can't name patients.

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Q: And I'm not asking for patients' names.
MR. MALONE: You just did.
Q: No.
MR. MALONE: You said which patiems. I don't know how you answer that without giving the patient's name. Come on.
Q: Which studies have involved any patients that you've performed psychosurgery on or assisted in psychosurgery?
MR. MALONE: Without naming patients, if you can answer.
A: I don't remember the patients, first of all.
MR. MALONE: Well, good.
A: Surgery for Gamma knife, surgery for deep brain stimulators, and outcome studies for regular radiofrequency surgery.
Q: Okay. Have all of your ten patients been involved in research studies?
A: I don't know.
Q: Do you know how many of your ten patients?
A: No.
Q: Do you know which of your ten patients?
A: I can't recall.
Q: Can you name a study that has involved any of

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your patients?
A: There are no published reports yet of these patients that I know of.
Q: Is any currently in the works?
A: *Yes.*
Q: And are those being authored by you?
A: I am involved in them, yes.
Q: Okay. Who is the primary author?
A: Hasn't been decided yet.
Q: What is the primary purpose — strike that.
Who's on the team?
A: The team involves groups from Belgium, from Brown University and Cleveland Ciinic.
Q: Who is the lead surgeon from Belgium?
THE WITNESS: Do I have to answer all that, these questions?
MR. MALONE: Is that, I mean —
THE WITNESS: What's the relevance?
MR. MALONE: I don't know how — it's not published yet, I assume?
THE WITNESS: No.
MR. MALONE: It's being worked on.
A: There's confidential studies that are being developed.

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A: I don't know of it, I don't know any data in the past.
Q: Do you know, does the study — strike that.
Do you expect to include surgical outcomes in that study?
A: In this current study?
Q: Yes.
A: Yes.
Q: Will it include a comparison between the success or the efficacy of one type of procedure versus another?
A: No.
Q: So there will be no — strike that.
Give me a ballpark, if you can, of the number of surgical procedures you would be involved in up to the present time, total number of procedures you would have been involved in in both your training and your job as an attending.
A: I can't tell you that.
Q: More than 500?
A: Definitely.
Q: More than a thousand?
A: Most likely, yes. Definitely, yeah.
Q: I want to make sure I'm correct in my understanding. You have not performed any

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psychosurgery on a patient yet here at the Cleveland Clinic, correct?
A: Correct.
Q: Have you evaluated any patients for psychosurgery yet at the Cleveland Clinic?
A: Yes.
Q: Okay. How many patients have you evaluated?
THE WITNESS: Do I have to answer that?
MR. MALONE: The number,
A: I can't recall the number, but several patients.
Q: Several meaning? Give me a range.
A: Meaning, I would say at least five.
Q: Did you recommend surgery for any of those five cases?
A: Yes.
Q: And how many of the five?
A: I don't recall.
Q: Okay. Were they OCD patients?
A: For the most part, yes.
Q: What psychosurgery did you recommend for the OCD patients?
A: Eirher a cinguloromy or a deep brain stimulator.
Q: Is a cingulotomy radiofrequency or is it Gamma?
A: Radiofrequency.

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Q: And do you know why those patients did not have surgery?
A: Rephrase that question.
Q: Sure. You said you evaluated five. Do you know why those patients did not have the surgery you recommended?
A: Oh, it's complex reasons. There are many different issues involved with these patients.
Q: Okay. What is an orbitomedial lesion?
A: Spell that, orbito.
Q: O-r-b-i-t-o-m-e-d-i-a-l.
A: It's probably historical origin in terms of lesions, I don't think anybody does orbitomedial lesions.
Q: Okay. That's a separate lesion than what is performed for either a cingulotomy or capsulotomy, is that correct?
A: Yes.
Q: You did not perform any orbitomedial lesions in your training, did you?
A: No.
Q: The cingulotomies that you have performed, have those been Gamma Knife or have those been radiofrequency?
A: Radiofrequency.

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Q: To your knowledge, aside from the study that's in the works here at the Cleveland Clinic, have there been any scientifically reliable studies performed on psychosurgeries here at the Cleveland Clinic?
A: I don't know.
Q: You're not aware of any?
A: I'm not aware of any.
Q: Have you ever requested that information?
A: Have I — no.
Q: As the section head of the, that type of surgery, would you expect you would have learned about that if, iii fact, such a study had been done here at the Cleveland Clinic?
A: Not necessarily.
Q: Have you ever performed or assisted in the performance of a combined capsulotomy and cingulotomy?
A: I can't recall.
Q: Do you know —
A: Most likely.
Q: Okay. Why do you say most likely?
A: Because we have done both.
Q: Okay. Maybe I need to clarify. Have you ever been involved in a combined capsulotomy and

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Q: Would you agree that the more procedures an institution performs, generaliy the lower the complication rate?
A: Don't a hundred percent agree with that.
Q: Would you agree that the more procedures a specific surgeon performs, generally the better the success rate?
A: Cannot say for sure. These are, there's really no hard and fast rules about these statements.
Q: The same concerning risks of complication?
A: Yes.
Q: Have you yourself ever published anything in the literature that relates to success rates for psychosurgery?
A: Yes.
Q: Where's your CV? Can you identify what literature?
A: Okay. Let's see where I have this. Page 17.
Q: And what specific literature are you referring to that reports a success rate?
A: Number 34 in particular, CNS Spectrums.
Q: And is CNS Spectrums the — strike that.
Is there any other literature that you have authored or co-authored that addresses the success rate of psychosurgery?

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A: There's another paper which is not published yet.
Q: Has it been submitted for publication?
A: Yes.
Q: And where has it been submitted?
A: It's a Psychline article.
Q: Psych?
A: Psychline.
Q: Is that a journal?
A: It's a journal.
Q: Is it a peer review journal?
A: Yes, although this is by invitation by the editor for me.
Q: Who invited you?
A: The editor, one of the editors.
Q: Who is that?
A: Dr. Dujoveny.
Q: Can you spell that, please?
A: D-u-j-o-v-e-n-y.
Q: When do you expect that will be published?
A: I don't know.
Q: Sometime within the nest year?
A: Possibly, yeah, possibly.
Q: Do you refer to or rely on any different data for your success rates in the Psychline article as compared to the CNS Spectrums article?

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A: The data is basically a review of the literature for psychiatric disorders.
Q: And what did you do so that you were able to report on the results of that review for publication?
A: Rephrase that question again.
Q: Sure. What literature did you review so that you could accurately report that in Psychline?
A: A variety of previously published reports.
Q: So did you review the literature that you felt was reliable —
A: Yes.
Q: — and accurate in order to come up with success rates for that submitted article in Psychline?
A: Yes.
Q: And do you currently have a file that contains that information?
A: Yes.
Q: What do you call that fiie?
A: What do I call the file?
Q: If you had to tell your secretary or someone to go pull the file for you, what would you ask them to pull?
A: Under psychosurgery.
Q: And what under psychosurgery, just pull your

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psychosurgery file?
A: Yeah.
Q: Is that a computer file or a hard file?
A: Both.
Q: Do you have broken down in either of those files the specific data you reviewed for the Psychline article?
A: Should be, yes.
Q: How do you have that classified, how can you identify what is for Psychline?
A: I have to check.
Q: Okay. Is there a subfile or —
A; There should be.
Q: — subcategory for that?
A: I don't recall the exact breakdown.
Q: But you could look at that and determine what you relied on for the Psychline article —
A: Yes.
Q: — is that right?
A: Yes.
Q: And is one of the ways you can determine what you relied on looking at the footnotes that you referenced in the journal article?
A: Yes.
Q: Is that typically what you do when you publish an

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MR. LINTON: Jim, I assume you have this.
Q: This is Exhibit 2, doctor. Is that a copy of the article you referenced on your CV setting forth the success rates for psychosurgery in CNS Spectrums?
A: Yes.
Q: You were, in addition to being co-author of that article, you were also the guest editor for that volume of CNS Spectrums, is that correct?
A: Yes.
Q: And did you read — I assume you've read that, the volume, since it has been published in October of 2000?
A: Yes.
Q: Did you read — you know Dr. Jack M. Gorman?
A: Yes.
Q: And who is Dr. Gorman?
A: He's one of the editors.
Q: Okay. And I assume that you read what I'm handing you as Exhibit 2A, his greetings that were contained in Volume 2?
A: Did I read this?
Q: Yes.
A: Yes.

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statement that our readership is broad, almost every psychiatrist and neurologist in the United States receives CNS Spectrums?
A: I don't know the exact answer to that. But it's written there.
Q: You don't have any reason to dispute that, do you?
A: I don't have information to dispute that, no.

for publication that this was a very well-respected journal that was read by neurologists and psychiatrists in the United States, correct?
A: From my understanding, yes.
Q: Doctor, handing you what is Exhibit 2B, does the highlighted portion state the success rates as you reported them for cingulotomy?
A: From the references, yeah, it's what it says.
Q: Okay. The reference — strike that.
Earlier I asked you about where the success rates were published and you referenced this article?
A: Right.
Q: The specific page that includes the success rates

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are what I highlighted on page 26, correct?
A: Yes, for cingulotomy.
Q: Okay. We can agree that the — strike that.
Different neuropsych — strike that.
Different psychosurgical procedures have a different success rate depending on the condition for which is being treated?
A: Yes.
Q: So for example, cingulotomy has a higher success rate for depression patients or bipolar patients than OCD patients, correct?
A: I don't know if that's exactly entirely accurate.
Q: Okay. If we look at the statement highlighted, it says, In terms of efficacy, most recent studies show approximately 38 percent of all refractory psychiatric patients have significantly benefitted from this procedure. And then it says, OCD patients had approximately a 30 percent response rate, correct?
A: Correct, yes.
Q: And does that not suggest there is a higher success rate for major depressive patients and bipolar disorder patients than OCD patients?
A: Not necessarily. You have to look at those specific papers that have broken down those

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together. So it's very difficult to pull that out of the literature.
Q: You pulled out what you felt was the most accurate and reliable numbers based on your review of the literature, correct?
A: Conservative number, yes, sir.
Q: And you stated that the OCD patients had approximately a 30 percent response rate,

A: From the reports, yes, from the literature.
Q: Right. And again, it was from the most accurate, reliable literature you could find at the time you submitted this for publication, correct?
MR. MALONE: For cingulotomy?
Q: For cingulotomy.
A: For cingulotomy, yes.
Q: And we can look at the footnotes you reference, 37 to 39, to determine what literature you relied on, correct?
A: Yes, yes.
Q: And if we look at the literature cited in footnote 37 through 39, can you tell me the years in which that literature was published?
A: 1991, '95, '96.

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rates for OCD combining capsulotomy and cingulotomy,would you not have pointed that out in your literature?

A: I would have.

Q: Do you currently have a copy of the article you submitted to Psychline for publication?

A: Ithink so.

Q: Are you able to presently pull from your files the medical research you would have reviewed to prepare your CNS article showing success rates for psychosurgery?

A: I should have papers.

Q: Okay.

A: Yes.

Q: And how would that be segregated in your files?

A: I don't know. It's all together.

Q: Well,that's what I'm getting at. How would you know, if you went to your office right now and tried to find all the literature reviewed and relied on for your article, how would you do that?

A: They would probably be in files pertaining to psychosurgery.

Q: Okay.Would you have a separate subfiie for CNS Spectrums?

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A: I may, I'm not sure.

Q: In other words, is there any way you can reliably, at this point, show us a copy of articles or put together a list of articles that you know you would have researched and reviewed to prepare your CNS Spectrums article showing the success rate for surgery?

MR. MALONE: That's what the footnotes are. Are you asking beyond the footnotes?

MR. LINTON: Yes, thank you.

MR. MALONE: Well —

Q: Maybe I can ask it this way, dcctor. Cut to the chase.

A: Yeah.

Q: Were there —

MR. MALONE: Are you suggesting he's committed plagiarism by going back and looking at the articles to see if there's a footnote?

MR. LINTON: Not at all. Not at all.

Q: I'mjust rrying to see how you wouid reconstruct what you reviewed, and I think Mr. Malone aptly stated you'd look at the footnotes, correct?

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A: Yes.

Q: Beyond that, you couldn't say, the footnotes would include anything that you felt was reliable to use as a basis for reporting your article, correct?

A: Yes.

Q: And would there be any way to find out what additional literature you reviewed and you rejected as being unreliable?

A: I can't recall right now. That was a long time ago.

Q: Would there be any way you could reconstruct that?

A: Potentially.

Q: Okay. What would you have to do to reconstruct that?

A: Look through all my files and everything else.

Q: And that, would you have to do that just from memory, oh, I remember now looking at this, or would it be segregated in your files to show what literature you reviewed to publish this article?

A: Both. I don't know yet, I have to go through it.

Q: Okay.

A: I can't recall the details.

Q: Would you agree that psychosurgery is one of the most controversial areas in neurosurgery and psychiatry?

A: Yes, it can be.

Q: Would you agree that few other therapies have generated as much controversy?

A: Yes.

Q: Would you agree that few other therapies have at times generated more abuse?

A: Yes.

Q: Why is it controversial?

A: That's a very complex question. Again, from the old lobotomy days, so there's a lot of overzealous use of psychosurgery in rhe past, 1950s, '40s, so that has really caused a lot of problems with this type of therapy, but it's still being performed. It's therapy in select number of institutions in the world.

Q: How many institutions can you identify that are presently doing psychosurgery?

A: That's a tough question. I don't recall. I can't tell you exactly.

Q: Can you tell us what institutions in the United States are presently doing psychosurgery?

A: I wouldn't know all of them, but I know several that are.

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that you're aware of that are used outside the Cleveland Clinic for experimental surgery?
A: I'm sure there are, but I don't know of the details of it.
Q: Are you aware whether any psychosurgical procedures are paid for by Medicare or Medicaid?
A: I don't know.
Q: Are you aware of whether any psychosurgical procedures that you've been involved in have been paid for or rejected by a health insurer as being experimental?
A: Don't know the answer to that.
Q: Would you agree that a multi-disciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists and neurosurgeons should be assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric surgery, neurosurgery?
A: I think at 2001, yes.
Q: Why do you believe such a multi-disciplinary team should be assembled?
A: At this time because of the complexity of the condition.

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Q: What about the complexity of the condition requires a multi-disciplinary team to be assembled?
A: Sometimes patients may be incapacitated, they may not be able to give informed consent. This is a very controversial area, yet the patients are very disabled. So by instituting this kind of mechanism, we are trying to make sure that we are looking at all possible areas.
Q: And you would agree that one of the reasons why you should have such a multi-disciplinary team is to make sure that the patient being operated on has the surgery for — strike that. Bad question.
One of the reasons to have such a multi-disciplinary team is to prevent misuse of the procedure?
A: Rephrase that question.
Q: Sure. Is one of the reasons why a multi-disciplinary team should be assembled is to prevent misuse of the procedure?
A: Potentially, yes.
Q: Because in the past, there has been a problem about psychosurgery being performed on patients who might not have fully consented to the

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procedure?
A: I don't know if that's entirely correct. I don't know the details of the past experience, but you're talking to the older days where there was a lot of abuse and not proper consenting. So it's a very complex issue from many years ago.
Q: Let me ask it this way. Would you agree that the multi-disciplinary team puts in place a system of checks and balances to make sure that the surgery is being done only on the appropriate candidates?
A: That's our intention.
Q: And that it is done only when a patient fully understands the risks and benefits of the procedure and offers proper informed consent?
A: Yes, the patient or the surrogate.
Q: In fact, both?
A: Right.
Q: Why is a neuropsychologist to be included on the multi-disciplinary team?
A: Predominantly for assessments, preoperative and postoperative neuropsychological testing to be administered.
Q: What can the neuropsychologist do that a psychiatrist or neurosurgeon cannot?
A: Administer complex neuropsychological testing.

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Q: Why is a neurologist to be included on a multi-disciplinary team?
A: Just to cover the bases in terms of neurological status of the patient, give another opinion about the neurological condition as well as a psychological condition.
Q: Would it be fair to say that as a neurosurgeon, you typically see neurosurgical perspectives, in other words, perspectives on care or treatment from a surgical standpoint, where a neurologist presents a nonsurgical perspective?
A: That's a way of looking at it, yes.
Q: And that's what a neurologist would bring to the team that a neurosurgeon would not have?
A: Right.
Q: Why would a lawyer be included on the multi-disciplinary team?
A: Again, just to make sure that all the legality, legal issues are addressed.
Q: Such as informed consent?
A: Informed consent, et cetera. I mean, really —
Q: Competency of the patient?
A: That and many others.
Q: What others?
A: It's complex. I mean it's patient specific, so

A: There is another physician, Dr. Don Malone who's involved.
Q: He's a psychiatrist, correct?
A: Psychiatrist.
Q: No relation to Jim Malone, the attorney seated beside you?
A: No.
Q: Anybody else besides that?
MR. MALONE: You don't know that. Maybe.
A: Maybe not.
MR. MALONE: See, don't answer questions you don't know.
Q: Anybody else besides you and Dr. Malone?
A: Didn't you tell me —
MR. LINTON: Irish are all related some way.
MR. MALONE: He's not Irish.
Q: Anybody else besides you and Dr. Malone?

members? I think that's confidential, right, in terms of the study?
MR. MALONE: If you believe it's confidential, then you don't have to answer it.

Q: Here at the Cleveland Clinic are there any other people besides you and Dr. Malone responsible for implementing this new rule relating to the multi-disciplinary team?
A: Yes.
Q: Okay. What other positions?
A: At least a neurologist and others.
Q: Were you the person responsible — strike that. Were you the one recommending this rule or did somebody else recommend that it should be put in place?
A: I am recommending it.
Q: Why?
A: Why?
Q: Why?
A: Because we want to have a complex problem dealt with, and we believe current practice of surgery for psychiatric disorders should involve, in April, 2001, a multi-disciplinary team.
Q: What has changed about the psychosurgical practice in 2001 that wasn't there in 1998?
A: Well, again, it's an evolution in progress. So what's happening is many different groups are realizing that this is an important area of further growth and further work in terms of

surgery. And as a result, they have put their heads together, and over time, this has come about, and that's why we are recommending that now.
Q: When you were in Toronto was there a similar multi-disciplinary team in place?
A: I don't think so. I'm not sure of that.
Q: Do you know what type of team was in place?
A: I am not sure of that.
Q: Okay. How about when you were in Sweden, do you know what type of team was in place?
A: Not sure of that.
Q: Aside from you being here, is there anything that would have prevented a multi-disciplinary team like the one you now have in place from being in place here at the clinic in 1998?
MR. MALONE: Objection. Go ahead.
A: Rephrase that question.
Q: Sure. Would it have been feasible to put

in 1998 as you now have and require in 2001?
MR. MALONE: Objection. Go ahead.
A: I think, yeah. I mean this is just basically different individuals, so it's feasible for anybody to implement this.

Q: So in 1998 the Cleveland Clinic could have instituted a multi-disciplinary team consisting of the same specialists as outlined in your article, correct?
A: It's possible, yes.
Q: The Cleveland Clinic had employed or available to it in 1998 psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists and neurosurgeons, correct?
A: Yes.
Q: Do you also think it's advisable that the members of this team, this multi-disciplinary team have expertise in psychosurgery?

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A: Yes.
Q: They are going to be relying on the success rates that the surgeon quotes in determining whether or not to take the risk of surgery?
A: Yes.
Q: They're going to be relying on that information in making an informed decision as to whether or not to proceed with the surgery?
A: Yes.
Q: That's why it's critical to inform the patient of an accurate success rate?
A: Yes.
Q: Would you agree that a patient can only make an informed decision if the patient is given an accurate success rate by the surgeon during the informed consent process?
MR. MALONE: I'm going to show an objection. That's not the law of Ohio, counsellor.
Q: Would you agree or disagree?
MR. MALONE: It's a misstatement of the law. I'm going to let him answer the question, but he's misstating the law.
A: I think the patient has to understand what the risks are as best told by the surgeon based on

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their knowledge, and what the complications are and what the alternatives are, and then once they understand that, they can decide whether to go on with the procedure or not.
Q: And obviously to obtain informed consent, you need to quote accurate success rates to the patient, correct?
MR. MALONE: Objection. Same objection.
Q: Correct? Correct, doctor?
MR. MALONE: You can answer if you understand.
A: Yes.
Q: Because if inaccurate success rates were quoted to a patient, you had not obtained that patient's informed consent?
MR. MALONE: Objection.
Q: Correct?
MR. MALONE: Wait a minute, Bob, just calm down a second.
Q: I'm talking about from your medical perspective?
MR. MALONE: Wait a second. I made an objection. Let me just finish. Calm down. You may answer the question.
A: Can you repeat the question?

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MR. LINTON: Sure. Kathie, can you read that back, please?

(Thereupon, the requested portion of the record was read by the Notary.)

A: So if an — rephrase that question.
Q: The informed consent process requires that an accurate success rate be quoted to a patient, correct?
MR. MALONE: Objection. Go ahead.
A: To the best knowledge of the surgeon, yes.
Q: And if an inaccurate success rate is quoted to the patient, then that patient has not provided informed consent?
MR. MALONE: Same objection.
A: It depends on what — yeah, the patient has to understand the success, likelihood of success, likelihood of complications and alternatives and then come up with a decision.
Q: And if inaccurate success rates are quoted to the patient, instead of accurate success rates, then the patient has not provided informed consent?
MR. MALONE: Same objection. Go ahead.

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A: Then the patient does not fully know the percentage of benefits —
Q: And therefore —
A: — that they may obtain.
Q: And therefore cannot properly and fully consent to the procedure?
MR. MALONE: Objection.
A: Again, it depends on all three components that we discussed.
Q: I understand, and if any of those three components are not stated accurately, then the patient has not provided informed consent, correct?
MR. MALONE: Same objection.
A: Yes.
Q: And the standard of care requires that, does it not, in your profession?
A: That's the way —
MR. MALONE: Objection.
A: — I understand.
Q: And that's the way it's been done by reasonable neurosurgeons in your field for as long as you've trained or practiced as a neurosurgeon, correct?
A: I can't comment for others, but this is the way I do it.

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A: I would say approximately that, yes.
Q: Well, is it 30 to *40* or is it *40?*
A: Up to *40* percent.
Q: So if you were to state as of this date an accurate success rate for cinguiotomy radiofrequency here at the Cleveland Clinic, would it be 30 to *40* or would it be *40?*
A: I would say, I would say up to *40* percent.
Q: And likewise if you were to state today a success rate for capsulotomy here at the Cleveland Clinic, what would you quote the success rate as?
A: *40* to *50* percent.
Q: What do you base that on?
A: Based on literature as well as interaction with colleagues and academicians across the world.
Q: And there is no basis that you're aware of in the literature as you sit here — strike that.
There is no support in the literature for a success rate for combined cingulotomy and capsulotomy at the same time?
A: I don't know of any literature.
Q: And you've thoroughly researched this area, the area of psychosurgery, for the past two years to publish authoritative peer review journals on the subject, correct?

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A: Yes, but I may have missed an article. I don't claim to have read every single article.
Q: I understand, but you certainly make it your goal to thoroughly research and review the literature, correct?
A: Yes.
Q: And in your thorough review and research of the literature, you did not find a single study that combined those two procedures, capsulotomy and cingulotomy at the same time in a single procedure, correct?
A: Not to my recollection. Just a couple more questions.
Q: Couple more?
A: Yeah.
Q: The improvement, the one-third improvement in the YBOCS score, over what period of time would you follow a patient until you say that they have reached maximum medical improvement from the procedure?
A: I would say the numbers would be at least one year.
Q: Okay. The same for cinguiotomy and capsulotomy?
A: Yes.
Q: There's no difference, by the way, in terms of success rates between a Gamma Knife procedure and a radiofrequency procedure based on your review of the literature, is there?
A: There's some newer studies coming out now, that will be coming out that are showing different success rates than what's reported.
Q: As the literature now exists, does it show that they're equally efficacious or successful?
A: As of now it shows they are pretty much the same, yes.
Q: And has that been the case for as long as you've been familiar with both procedures, that they are about the same?
A: Based on reputable papers, yes.
Q: And that literature would have likewise existed as of 1998, the literature showing they're about the same success rates, Gamma Knife versus radiofrequency?
A: Most likely, yes.
Q: What does the new literature that's coming out show which is more successful?
A: I can't disclose that until it comes out.
Q: Okay. I assume the expectation is to be Gamma Knife?
A: Again, I can't, I don't know if I should disclose

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that. It's not fair to authors.
Q: Isn't it fair to say, doctor, that the Gamma Knife procedure is a safer procedure with fewer side effects than a radiofrequency procedure?
A: Well, I think that the numbers of Gamma Knives for psychosurgery is not large enough to really draw a comparison. You really need a prospective controlled study to compare Gamma Knife versus radiofrequency to come up with that kind of answer.
Q: Didn't the Brown group find that they were equally efficacious?
A: Yes, but that's a small cohort, so you're talking about you need a, really to make a definitive answer, you need a prospective study.
Q: I understand. Based on the best literature available at the time of your publication in CNS Spectrums, did you not find the Brown study to be the most reliable literature out there on the subject?
A: Yes, one of them.
Q: And can we agree that Gamma Knife is a noninvasive procedure?
A: Another complex — yes, you're not opening the skull.

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"Basal ganglia dysregulation has also been implicated in the pathoneurophysiology of affective disorders, including major depression and bipolar disorder."

Recent functional imaging studies have consistently found evidence that corroborate this model of OCD pathogenesis. Increases in activation correlating with OC symptoms have been shown to occur in the OFC, the caudate, the thalamus, and the cingulate areas: however, PET and fMRI studies[18,19,20] show that treatment with appropriate medications — including selective serotonin reuptake inhibitors — and behavioral therapies, decreases the abnormally increased metabolism in these areas. Such areas of activation and responses to treatment might prove useful in assessing future neurosurgical treatments for OCD.

Affective Disorders

Basal ganglia dysregulation has also been implicated in the pathoneurophysiology of affective disorders. including major depression and bipolar disorder (Figure 5). Much of the work implicating the basal ganglia and other structures in the pathogenesis of affective disorders comes from imaging studies[21,22,23] using PET and fMRI. Abnormalities in metabolism have been demonstrated in the OFC, the cingulate, the basal ganglia, and the amygdala.

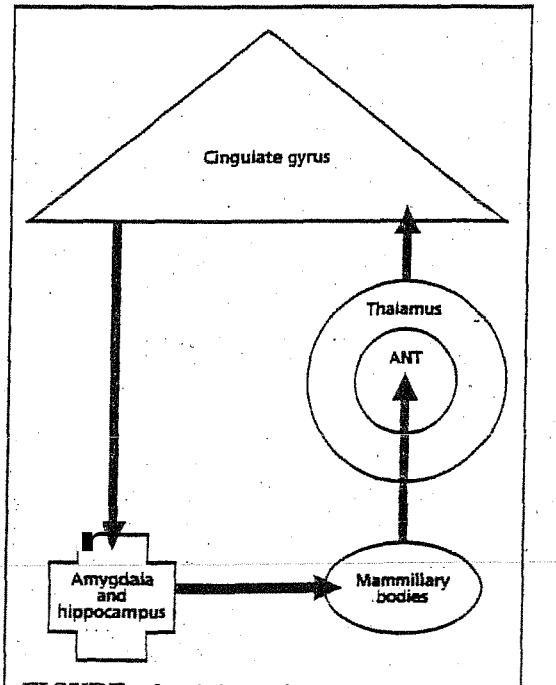

FIGURE 4. Schematic of Papez circuit. This diagram demonstrates the major anatomic structures and connections involved in the Papez circuit of emotion.

ANT=anterior thalamic nucleus.

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In order to examine affective disorde from a neurophysiological point of view, em tion can be divided into three components: (an expressive component (affect);(2) an inte nal/representitive component (mood); and (: a modulatory component.[24] The expressiv component of emotion, known as *affect*, repr sents the external manifestation of a person internal emotional state. This can be furth subdivided into two subcomponents: (1 endocrine/humoral; and (2) skeletomoto Connections between the corticomedial amyg dala and the hypothalamus via the stria term nalis regulate the release of cortisol an epinephrine in relation to emotional stimul Basolateral amygdala connections with th basal ganglia directly influence skeletomoto motivation and behaviors in response to emo tional stimuli.

The structures subserving the internal rep resentation of an emotional state, known a *mood*. remain obscure[25]; however, experimen tal experience implicates the amygdala, th frontal/cingulate cortices. the basal ganglia and the hippocampus as possible underlyin structures.[26] Certainly, the Papez circuit als contributes *to* this internal representation o emotional state. The third component repre sents a modulatory component between the expressive and internal emotional states: the medial OFC, the cingulate cortex, and the basolateral amygdala have been heavily implicated in this role.[27] These three components can be condensed into a dual circuit model. analogous to the one proposed for OCD. In the dual circuit model, a limbic-thalamic-cortical loop consisting of the basolateral amygdala, the DM nucleus, and the medial and ventrolateral frontal cortices runs parallel with a limbic-striatal-pallidal-thalamic circuit that consists of the ventra1 striatum, the ventral pallidum. and the thalamus.[28,29] It is possible that symptoms of affective disorders could be the result of an imbalance in the activity between these circuits. Given the numerous connections between these two proposed circuits and the limbic system, the Papez circuit must work in conjunction with these to fully express the symptoms of affective disorders.

It is important to remember that. unlike the model for PD, these models of psychiatric disease inherently have little basis in animal models: therefore, these proposed neural circuits are mostly based on anatomic connections and the aforementioned functional

imaging studies. While the proposed neural circuits may appear too simplified, they serve as a springboard for future functional imaging and physiological mapping studies from which neurosurgical and pharmacological therapies can be developed—similar to how such treatments were developed for PD.

THE STEREOTACTIC LESION: THE STANDARD APPROACH TO NEUROMODULATION

Surgical interventions to treat psychiatric disease date back to the earliest days of modern neurosurgery. As early as 1891, a Swiss psychiatrist named Burckhardt.'"reported the results of cortical excisions in psychiatric patients. In 1935, Nobel laureate Egas Moniz observed: "It is necessary to alter these synapse adjustments and change the paths chosen by the impulses in their constant passage so as to modify corresponding ideas and force thoughts into different channels...By upsetting the existing adjustments and setting in movement in other [connections], I [expect] to Le able to transform the psychic reactions and to relieve the patient thereby."[31]

Moniz made the critical analytic jump to link the seemingly irrational behaviors and thoughts of psychiatric patients with a disordered neural substrate that. when altered in a surgical fashion, would result in the definitive change of the seemingiy ethereal entities of thought and mind itself. All of these procedures. from the initial attempts at lobotomy to the stereotactic interventions explored below, utilize nervous system lesions as the primary means of neuromodulation—the process of altering neurological function for therapeutic benefit through neurosurgery.

Since 1935, neurosurgery has been performed for a wide variety of psychiatric disorders. from schizophrenia and anxiety disorders to sexual and eating disorders. The first procedures for psychiatric disease grew out of Fulton and Jacobsen's[32] observation that frontal lobe ablation could result in the lessening of anxiety states in chimpanzees. Indeed. the first neurosurgical procedure for psychiatric disease. the standard lobotomy, sought to interrupt white matter tracts associated with the frontal lobes. This procedure started as a rather extensive one and became more refined as the volume of brain in the surgical target became smaller. This trend towards increasingly discrete lesions culminated in applying stereotaxis to psychiatric neurosurgery. In 1947, Spiegel and Wycis[33] introduced the first subcortical stereotactic neurosurgical procedure performed on humans—the dorsomedial thalamotomy—which serves as the model on which all modern psychiatric neurosurgical procedures are based.

The four psychiatric neurosurgical procedures currently in use are cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leukotomy—all stereotactic interventions. These procedures are typically performed on severe, refractory psychiatric patients. First a patient must meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (*DSM-IV*) criteria for a particular psychiatric disease, such as OCD or affective disorder. Next, a patient must fail several rounds of treatment. with multiple psychotropic medications combined with appropriate psychotherapy before he or she is considered for surgical treatment. Therapeutic failure is determined by quantitative analysis using the most appropriate

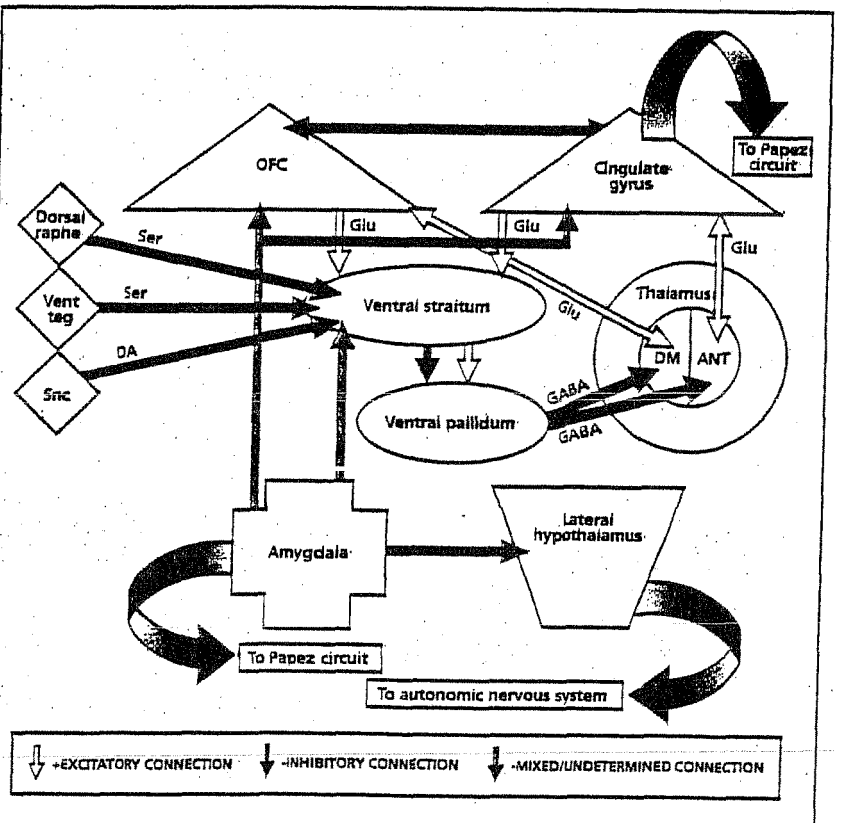


FIGURE 5. Schematic of affective disorder model. This diagram demonstrates the major anatomic structures and connections involved in the pathogenesis of major depression and bipolar disorder. As with obsessive-compulsive disorder. dysregulation through the basal ganglia could result in affective disorder symptoms.

OFC=orbitofrontal cerebral cortex: Ser=serotonin; Glu=glutamate; Vent teg=ventral tegmentum of midbrain; Snc=substantia nigra pars compacta; DA=dopamine; GABA=γ-aminobutyric acid; DM=dorsomedial thalamic nucleus; ANT=anterior thalamic nucleus.

Kopell BH, Rezai AR. *CNS Spectrums*. Vol 5, No 10, 2000.

"The four psychiatric neurosurgical procedures currently in use are cingulotomy, capsdotomy, subcaudate tractotomy, and limbic leukotomy—all stereotactic interventions. These procedures are typically performed on severe, refractory psychiatric patients."

and accurate psychiatric batteries of tests available, such as Y-BOCS for OCD and HAM-D for depression. Finally, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists, and neurosurgeons is assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric neurosurgery. While many previous studies of psychiatric neurosurgery have significant flaws, most notably the inherent bias of a nonrandomized, nondouble-blind study as well as the lack of objective functional imaging techniques, they suggest a viable means of treatment for a subset of patients who may have no other treatment option.

Cingulotomy

The Basis for surgery on the cingulate gyrus dates back to observations[34] in the 1940s that severing fibers from the cingulate gyrus led to a decrease in anxiety-type states. In 1952. Whitty and colleagues[35] reported the first cingulectomy. in which a 4x1 cm section of cingulate gyrus was bilaterally resected. In 1967, Ballantine[36] introduced the modern stereotactic procedure. in which a lesion was targetted by air ventriculography and made in the anterior cingulate bilaterally using thesmocoagulation. The lesion is typically made 2.0–2.5 cm from the tip of the frontal horns. 7 mm lateral from the midline, and 1mm above the roof of the ventricles, bilaterally. Today, the procedure has been refined using the latest stereotactic equipment and imaging techniques. Stereotactic cingulotomy is the most reported neurosurgical procedure for psychiatric disease in the US and Canada. In terms of efficacy, most recent studies[37-39] show approximately 30% to 38% of all refractory psychiatric patients have significantly benefited from this procedure. Patients with affective disorders had the greatest efficacy rates, with major depressive patients showing a 60% response rate and bipolar disorder patients showing a 40% response rate. OCD patients bad approximately a 30% response rate.[39] Some adverse side effects reported were seizures. weight or appetite changes. mania. and memory difficulties. It is difficult to quantify these adverse sequelae, since most of these studies involved a small cohort of patients. The largest risk (1% to 9%) was for seizures, which was easily controlled by Dilantin. In the largest published series of stereotactic cingulotomy, Bailantine and colleagues" reported no deaths among 696 patients and only 2 cases (0.3%) of hemiplegia from postoperative intracerebral hematomas.

Capsulotomy

Developed in Sweden by Lars Leksell and Ta airach in France. anterior capsdotomy has been used as a treatment option for patients with refractory psychiatric illnesses since 1949. There are two forms of this procedure—both are stereotactic operations. One technique involves the use of radiofrequency, and the other uses γ-radiation to make the lesion. In both, the target area is between the anterior and middle thirds of the anterior limb of the internal capsule at the approximate level of the foramen of Monro. Specifically, the ideal target lays at 17 mm from the midline, 10 mm rostral to the anterior commissure, and 8 mm above the intercommissural line. The lesion is approximately 15–18 mm in length and 4–5 mm in width.[40,41] Recent studies[42,43] have reported significant efficacy rates from 35% to 60%. Although the experience with γ-capsulotomy is somewhat less than that with thermocoagulation, data[41,42] shows the two subtypes of anterior capsdotomy to be equally efficacious. Reported side effects involve aspects of frontal lobe dysfunction, which include personality changes, increases in impulsiveness. and memory difficulties. These transient side effects were found to correlate with T2 changes on MRI. consistent with postoperative edema. While the relative incidences of these sequelae vary from study to study, they are far lower than their respective efficacy rates and are considered avoidable aspects of this procedure.[43-45]

Subcaudate Tractotomy

Another stereotactic procedure geared towards interrupting fibers from the OFC to the thalamus is subcaudate tractotomy ("innominatomy"). Developed in London by Knight[46,47] in 1965, the operation was designed to relieve depressive. anxiety, and obsessional symptoms while minimizing postoperative epilepsy as well as cognitive and personality deficits. The lesion is created by multiple 1x7 mm rods of yttrium-90, a β-emitter that releases lethal radiation to tissue within 2 mm. These rods have a half-life of 68 hours, after which they become inert. The target site, a region of white matter localized beneath the

head of the caudate, known as the *substantia innominata*, has been traditionally localized by ventriculogram. A stereotactic apparatus places the rods after bilateral burr holes are made just above the frontal sinus and 15 mm from the midline. The lesion itself lays at the anteroposterior level of the planum sphenoidale, extending from 6–18 mm from the midline and being 20 mm long in an anteroposterior direction. Initially, placing 2 rows of 4 rods each made the lesion. Later studies, having refined the technique, added an extra rod to each row. Although the major indication for this procedure has been for refractory affective disorder, it has also shown great promise in the treatment of malignant OCD.[30] Recent studies[31,32] have reported significant relief or obliteration of debilitating symptoms in 33% to 45% of patients. There are very few reported cases of catastrophic postoperative complications. In a series of 1300 cases of subcaudate tractotomy, one set of authors[31] report only two deaths directly caused by the procedure. The most common side effect was postoperative confusion (10%) and minor decreases in verbal and visual memory tasks. The authors felt this transient phenomenon was mostly due to postoperative edema and, based on neuropsychological tests, found these deficits to resolve after 6 months.

Limbic Leukotomy

While the three aforementioned procedures target a single anatomic substrate, a fourth procedure is designed to interrupt fibers at two separate areas—a frontothalamic loop and an area of the Papez circuit. Termed *limbic leukotomy,* the procedure was developed in England by Desmond Kelly and Alan Richardson[33] in the early 1970s. The operation consists of three 6 mm thermocoagulative or cryogenic lesions in the lower medial quadrant of each frontal lobe (to interrupt frontothalamic connections) and two 6 mm lesions in each cingulum. The results for OCD (termed *obsessional neurosis* by the principal investigators) were excellent. with up to 89% of patients being significantly improved at 16 months postsurgical follow-up. Another study[34] showed 83% improvement rates at 20 months postsurgical follow up. No catastrophic complications have been reported. Although the investigators postoperatively found occurrences of confusion. headache. urinary incontinence. and lack of initiative in some patients. all side effects cleared within a few weeks.[53,54] Based on postoperative neuropsychological testing, the investigators found no permanent objective deficits or changes in concentration, memory, intelligence, or personality.[53,55,56]

THE NEUROAUGMENTATION ERA

We are on the verge of, quite arguably, one of the most important developments in the modern history of neurosurgery — the era of neuroaugmentation. To date, psychiatric neurosurgery has focused on minimizing damage to the nervous system and. when a lesion was necessary, making the smallest effective lesion. Neuroaugmentation, through electrical, chemical, as well as other emerging modalities, allows the neurosurgeon to ameliorate nervous system disorders through additive. not destructive, means.

One of the most exciting advances with regard to neuroaugmentation in the last decade was the resurgence of *neurostimulation* techniques. Neurostimulation includes all neurosurgical interventions that utilize electrical stimulation as a therapeutic modality for neuromodulation. Electrical modulation of brain function as a therapeutic neurosurgical tool is not new, having first been performed by J. L. Pool[57] in 1948. Interestingly, much like stereotaxis, the first neurosurgical use of therapeutic brain stimulation was for psychiatric disease. Today's use of electrical neurostimulation consists of epidural and subdural surface electrodes and deep brain stimulation (DBS), in which an electrode is stereotactically placed in subcortical structures. A third technique of electric neurostimulation is vagus nerve stimulation (VNS). This renaissance of neurostimulation techniques is the direct result of a better understanding of neurophysiology from functional imaging studies. *intraoperative* brain mapping, and technological advances in implantable electrodes and programmable pulse generators. Combined with the latest developments in computer-guided. stereotactic brain navigation, which allows the exquisite targeting (up to 1mm precision) of neural structures. neurostimulation has become the cornerstone of recent neuroaugmentative efforts.

Neurostimulation has inherent *advantages* over previous lesioning procedures. Uniike a lesion. it is fully reversible and the stirnulation can be dynamically adjusted according to a patient's changing symptoms and disease progression. Coupled with the fact that the stimu-

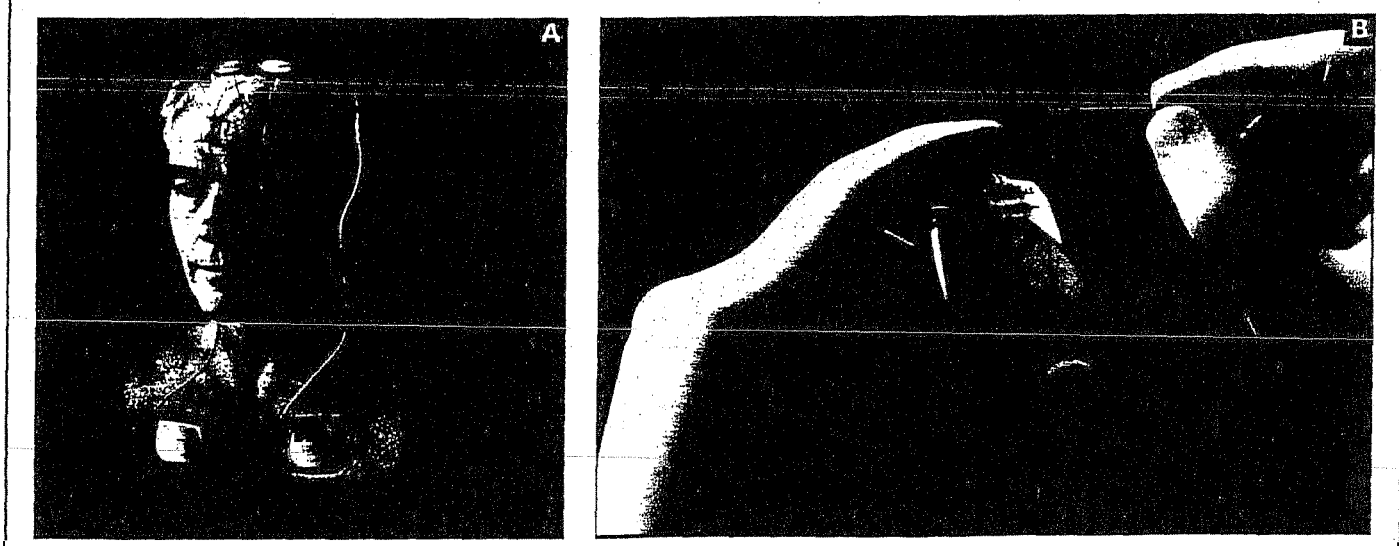
"Neuroaugmentation, through electrical, chemical, as well as other emerging modalities, allows the neurosurgeon to ameliorate nervous system disorders through additive, not destructive, means."

lation can be turned on and off without the patient's awareness. neurostimulation provides a unique opportunity for conducting double-blind studies: therefore. any given patient can serve as his or her own control group—something that could never be done with lesioning procedures due to ethical constraints on sham procedures.

Neurostimulation is now the standard of therapy for medically refractory PD. essential tremor. intention tremor. and various chronic pain syndromes. It is also being increasingly utilized for other disorders. such as intractable dystonia and epilepsy. The following question remains: Are neurostimulation techniques as safe and effective as their lesion-Lased counterparts? Based on recently published studies,[58,59] the answer is a resounding yes. In *1998.* a *New England Journal* d *Medicine* study": reported that after one year of chronic DBS. advanced. medically refractory PD patients significantly improved with regard to symptoms and activities of daily living. with a concomitant 50% reduction in medication. In a recent randomized prospective study.'" clinicians confirmed the inherent advantage of neurostimulation techniques over their lesioning counterparts. Schuurman et al[59] directly compared stereotactic thalamotomy with thalamic DBS for refractory tremor. They showed that DBS had fewer adverse side effects and was superior in overall improvement of daily functioning. The currently applied DBS system utilizes multicontact electrodes connected to a remotely programmable pulse generator (Figure 6).[60]

The exact mechanisms of neurostimulation are unknown. There are several prevailing theories explaining why electrical stimulation is effective in alleviating symptoms in various neural disorders. One theory suggests that stimulation acts like a reversible ablative lesion. inactivating nearby cells by a depolarization blockade. Such a phenomenon. occurring at high frequency (>100 Hz) stimulation, would remove afferented targets from any abnormal influences that the stimulated area might elicit. Electrical stimulation could also activate cells/axons by depolarization directly influencing activity in a neural circuit.'" A third possibility involves the tonic influence of electrical stimulation on the resting potentials of target neurons. Such neurons. according to intrinsic voltage gate properties. would begin to fire at different frequencies than when they are free of stimulation influence. This. in turn, would alter the activity of the neural circuitry involving these targets. A recent fMRI study[62] had also shown selective activation of specific cortical and subcortical structures with DBS.

Certainly. the neurocircuitry of psychiatric diseases is far less elucidated than those subserving movement disorders. The striking similarity between the abnormal neural circuitry



FIGURES 6. Schematic of deep brain stimulation system. The photograph to the left (Figure 6A) is a typically implanted bilateral deep brain stimulation system. Note the location of stimulation electrodes and pulse generators. Also shown (Figure 6E) is a close-up of the implanted quadripolar electrode and the pulse generator.

Photos courtesy of Medtronic.

Kopell BH, Rezai AR. *CNS Spectrums.* Vol 5, No 10. 2000.

of movement disorders and the proposed models of abnormal neural circuitry in psychiatric diseases, makes neuroaugmentation an attractive option for surgical intervention of refractory psychiatric conditions. Initial reports[63-65] on VNS for affective disorder and DBS for OCD are promising, and a number of further studies are in progress.

As a result of advances in our understanding of the pathophysiology of psychiatric disorders. we can explore other potential targets for pharmacological and/or surgical intervention.

With its central anatomical and physiological location, the thalamus has been a traditional target of ablative stereotactic procedures. Procedures, such as subcaudate tractotomy, limbic leukotomy, and capsulotomy, indirectly target the DM nucleus by interrupting the reciprocal connections between the frontal cortex and the thalamus. Another thalamic target For putative neuroaugmentative therapy is the anterior nucleus. With its rich connections to the cingulate gyrus. the anterior thalamic nucleus plays a vital role in the propagation of the Papez circuit. Surgical intervention in this area may serve to modulate the affect of psychiatric disease states, such as OCD and affective disorder.

The ventral striatum is implicated in the pathogenesis of many psychiatric diseases, including OCD and affective disorder. The ventral striatum serves as a vital link between the OFC and the basal ganglia. With its afferent projections from the substantia nigra, the raphe nucleus, and the centromedian thalamic nucleus, as well as its efferent projections through the GP. the caudate/putamen complex plays an important modulator role in connections from the frontal cortex to the thalamus.

Cortical targets. such as the OFC, may serve as a potential area for future intervention. The OFC is implicated in the pathogenesis of many psychiatric diseases. in which neural models are now being explored. Given the long history of well-known cognitive side effects of psychiatric neurosurgical procedures on the frontal lobe. it may seem that targeting the OFC might not be the ideal solution; however. modern imaging techniques. coupled with neuroaugmentation's inherent ability to modulate activity by dynamically controlled nondestructive input. suggests that targeting the OFC and other cortical areas may be of benefit.

Interestingly, during recent DBS interventions for PD, two separate groups[66,67] reported that subthalamic nucleus stimulation elicited depression and laughter from patients. This could prove interesting to explore For future neuroaugmentative therapies to treat affective disorder.

Since the currency of nervous system communication involves both electrical and chemical transactions. another modality for future neuroaugmentative therapy involves the use of chemicals. Already, drugs (ie, morphine and baclofen) are used in neuroaugmentative procedures for chronic pain and spastic disorders. As drug-delivery pumps and microcatheters are further improved, chemicals that mimic neurotransmitters or standard psychotropic medications could be delivered directly to brain targets in doses that would minimize systemic side effects.

CONCLUSIONS

We have reached an exciting crossroad for psychiatry and neurosurgery. The culmination of all aforementioned technologies have given new therapeutic options to explore. Stereotactic radiosurgical techniques, such as the γ-knife, have allowed neurosurgeons to refine lesioning procedures to the point of being bloodless. Neuroaugmentative techniques, combined with modern functional imaging and psychiatric batteries, offer investigators a tool to finally conduct a randomized, double-blind prospective study — something that has been lacking in researching psychiatric neurosurgery. Ultimately, electrical and chemical neuroaugmentative modalities could be merged with exquisite microprocessor controls that detect changes in neural function and can dynamically and automatically adjust neuromodulating input. These neuroaugmentative techniques could be combined with emerging molecular biological strategies, such as vector-based gene therapy, in order to replace entire neural networks ihat have become affected by psychiatric and other neurological diseases. Successful neurosurgical intervention in patients with various psychiatric diseuses will lead to new insights into human brain function that will have long-reaching impacts on medicine and all aspects of neuroscience. CNS

"Interestingly, during recent DBS interventions for PD, *two* separate groups reported that subthalamic nucleus stimulation elicited depression and laughter from patients. This could prove interesting to explore for future neuroaugmentative therapies to treat affective disorder."

"Since the currency of nervous system communication involves both electrical and chemical transactions, another modality for future neuroaugmentative therapy involves the use of chemicals."

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"Neuroaugmentative techniques, combined with modern functional imaging and psychiatric batteries, offer investigators a *tool* to finally conduct a randomized, double-blind prospective study—something that has been lacking in researching psychiatric neurosurgery"

Greetings!

By Jack M. Gorman, MD

With this, the October. 2000 volume of *CNS Spectrums.* I assume the role of editor-in-chief. This calls for an explanation, several expressions of gratitude. and a few requests.

I considered long and hard whether to accept the assignment of editor-in-chief of *CNS Spectrum.* but two things sealed my affirmation. First. I had the opportunity to discuss the idea with one of psychiatry's preeminent journal editors. Nancy Andreason. MD. PhD. editor-in-chief of the *American Journal of Psychiatry.* Nancy. a close personal friend. is perhaps the discerning intellect in our field and the gold standard by which editors of scientific journals are judged. I asked her what she thought and she replied, "Oh, I read *CNS Spectrums.* it's quite good." Few people are asked to read more things than Nancy Andreason. and her positive judgement of *CNS Spectrum* meant a great deal to me.

Second, I took advantage of the "ace up my sleeve" I rely on so often. Academic physicians lead a rarefied life: we are often called upon to render opinions about good clinical practice and what is of potential interest to practicing psychiatrists and neurologists. even though relatively little of our time is spent seeing patients. I am fortunate, however. to be married to a very busy and highly skilled practicing physician, Lauren Kantor Gorman, MD. Lauren. a psychiatrist. spends many of her waking moments seeing patients or talking to them on the telephone. and consequently must limit herself to the most informative journals. *CNS Spectrum* is one of them.

And so I had both academic and clinical approbation for *CNS Spectrums.* confirming my own longstanding opinion that this journal maintains very high academic standards while at the same time providing practical and readable information for practicing psychiatrists and neurologists. From these considerations. the decision to become the second editor-in-chief followed easily.

The expressions of gratitude go similarly easily to a number of key people. More than anyone else. however, we all must thank Eric Hollander, MD. the founding editor of *CNS Spectrum.* Eric. one of the leaders in psychiatric research and also a fine clinician. is fully responsible for the wonderful state of *CNS Spectrum.* If I can maintain the journal at the level he has set then I will consider myself a success indeed as the new editor.

I must also thank my friend, James La Rossa Jr., the CEO and publisher of MedWorks Media, a company with a group of journals that includes *CNS Spectrums. Mental Fitness, Psychopharmacology Bulletin. Primary Psychiatry, TEN—The Economics of Neuroscience,* and *ONE — OncologyEconomics.* I have known James for many years now and have found him always to be a supportive and generative leader. His vision has led to the creation of this fine family of journals and working with him on *CNS Spectrum* will be one of the pleasures of the undertaking.

I am only beginning to know the staff at MedWorks and *CNS Spectrums.* but have already found them to be a incredible group of dedicated and intelligent professionals I also want to thank my assistant at Columbia University Christopher Tulysewski who will play an important role in coordinating activities for *CNS Spectrum.*

Now far the requests. There are only two for now, because they are important. *CNS Spectrums* has focused so far on publishing review articles centered around a theme. Each article is peer reviewed and the themes are selected to represent cutting-edge topics of interest to psychiatrists and neurologists. We will continue that focus, but in addition will place greater emphasis on publishing several original, peer-reviewed. data-driven research articles each month. We request. therefore. that readers send us their finest research manuscripts on psychiatric or neurologic topics (or both) for consideration for publication. We are dedicated to rapid review and publication and will be a venue for you to get your work in press and published more quickly than most other journals. Our readership is broad: almost every psychiatrist and neurologist in the United States receives *CNS Spectrum* and therefore your article will reach a wide audience.

My second request is that you let us know what you think of *CNS Spectrums* and **how** we can be better. We want you to look forward to getting *CNS Spectrums* each month. *to* enjoy reading it, and to find it helps you both understand current trends in research and the most up-to-date treatments for psychiatric and neurologic disease. Don't hesitate to drop me a note if you have an observation or suggestion that you think might be helpful.

Now. before you proceed to actually reading this month's volume, let me make a few comments about the articles it contains. Like all journals. it is necessary to have articles for several volumes ready for publication months in advance. Hence, this volume of *CNS Spectrums* represents the work of the founding editor, Dr. Hollander. It will be several months before articles that I have specifically chosen will be included, but if I am true to my pledge to maintain Eric's high standards the change should be largely invisible to the reader.

This issue of *CNS Spectrum,* which is the first of two issues on neurosurgery guest edited by Ali R. Rezai, MD, is particularly thought provoking because it deals with treatments that were pioneered by neurology and

Dr. Gorman is professor of psychiatry and vice chair for research at Columbia University College of Physicians & Surgeons. He is also the editor of this journal.

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and accurate psychiatric batteries of tests available, such as Y-BOCS for OCD and HAM-D for depression. Finally, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists, and neurosurgeons is assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric neurosurgery. While many previous studies of psychiatric neurosurgery have significant flaws, most notably the inherent bias of a nonrandomized, nondouhle-blind study as well as the lack of objective functional imaging techniques, they suggest a viable means of treatment for a subset of patients who may have no other treatment option.

Cingulotomy

The Basis for surgery on the cingulate gyrus dates back to observations[34] in the 1940s that severing fibers from the cingulate gyrus Led to a decrease in anxiety-type states. In 1952. Whitty and colleagues[35] reported the first cingulectomy. in which a 4x1 cm section of cingulate gyrus was bilaterally resected. In 1967, Ballantine[36] introduced the modem stereotactic procedure. in which a lesion was targetted by air ventriculography and made in the anterior cingulate bilaterally using thermocoagulation. The lesion is typically made 2.0–2.5 cm from the tip of the frontal horns. 7 mm lateral from the midline, and 1 mm above the roof of the ventricles, bilaterally. Today, the procedure ha5 been refined using the latest stereotacric equipment and imaging techniques. Stereotactic cingulotomy is the most reported neurosurgical procedure far psychiatric disease in the US and Canada. In terms f efficacy, most recent studies[37-39] show pproximately 30% to 38% of all refractory sychiatric patients have significantly benefted from this procedure. Patients with affective disorders had the greatest efficacy rates, with major depressive patients showing a 60% response rate and bipolar disorder patients showing a 40% response rate. OCD patients had approximately a 30% response rate.[39] Some adverse side effects reported were seizures. weight or appetite changes. mania. and memory difficulties. It is difficultto quantify these adverse sequelae, since most of these studies involved a small cohort of patients. The largest risk (1%to 9%) was for seizures, which was easily controlled by Dilantin. In the largest published series of stereotactic cingulotomy, Ballantine and colleagues" reported no deaths among 696 patients and only 2 cases (0.3%) of hemiplegia from postoperative intracerebral hematomas.

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Subcaudate Tractotomy

Another stereotactic procedure geared towards interrupting fibers from the OFC to the thalamus is subcaudate tractotomy ("innominatomy"). Developed in London by Knight[46,47] in 1965, the operation was designed to relieve depressive. anxiety, and obsessional symptoms while minimizing postoperative epilepsy as well. as cognitive and personality deficits. The lesion is created by multiple 1x7 mm rods of yttrium-90, a β-emitter that releases lethal radiation to tissue within 2 mm. These rods have a ha?.€-life of 68 hours, after which they become inert. The target site, a region of white matter localized beneath the

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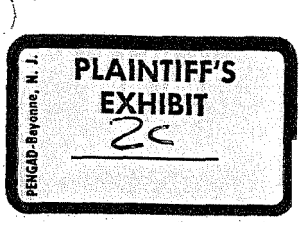

and accurate psychiatric batteries of tests available, such as Y-BOCS lar OCD and HAM-D for depression. Finally, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists, and neurosurgeons is assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric neurosurgery. While many previous studies of psychiatric neurosurgery have significant flaws, most notably the inherent bias of a nonrandomized, nondoubie-blind study as well as the lack of objective functional imaging techniques, they suggest a viable means of treatment for a subset of patients who may have no other treatment option.

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The Continuing Evolution of Psychiatric Neurosurgery

By Brian Harris Kopell, MD, and Ali R. Rezai, MD

ABSTRACT

In this article, the authors examine the growth of the discipline of psychiatric surgery from the earliest leswning procedures to the neuroaugmentative strategies used today. Special attention is paid to the neural circuitry that underlies psychiatric disorders and how surgical manipulation of these circuits might result in the amelioration of the disease state. Also examined is the effect that the technology curve has had on psychiatric surgery with regard to functional imaging and neurosurgical equipment. Finally, the authors use the current state of psychiatric surgery to speculate on some of the future directions that psychiatric neurosurgical procedures might take.

CNS Spectrums *2000;5(10):20-31*

INTRODUCTION

Few other medical treatments in history have been the focus of such controversy, debate, and misunderstanding as neurosurgery for psychiatric disorders. The term *psychosurgery*, which has traditionally been applied to these procedures, itself is a misnomer. *Psychosurgery* implies an intervention that directly targets the psyche or mind. Surgery for mental disorders intervenes on psychiatric patients' nervous systems in order to lessen their debilitating symptoms; therefore, the term *psychiatric neurosurgery* is a more accurate term and more reflective of the modem practice of these procedures.

Even as the practice of neurosurgery for psychiatric illness decreased in frequency following the introduction of Thorazine in 1954, the negative bias towards it continued to grow.' Charges of abuse and allegations of surgery for social control culminated in the establishment of a national commission in **1977** that examined psychiatric neurosurgical practices in the United States—from freehand frontal lobotomies to srereotactic lesioning procedures. Careful emphasis was taken to review the efficacy and safety of these procedures. As the chairman of the commission reported in his review, the findings were surprising: "We looked at the data and so they did not support our prejudices. I, for one, did not expect to come out in favor of psychosurgery. But we saw that some very sick people had been helped by it."[2] The commission was so impressed by the potential benefit of psychiatric neurosurgery that it recommended a review board be formed in order to study these procedures in a more scientific manner. nevertheless, this review board was never formed.

An extensive literature review by a pediatrician with a masters in public health was published by the Office of Technology Assessment in 1986 that cooied the ardor to perform psychiatric neurosurgical procedures. This review concluded that since psychiatric neurosurgery had never been studied in **a** randomized. double-blind prospective fashion. it should be considered experimental until **a** study proved otherwise. Coupled with the advent of newer, more effective psychotropic medications, psychiatric neurosurgery fell by the wayside. Today, only a few centers worldwide perform these procedures.

Nevertheless. there are several reasons to continue to evaluate the role of neurosurgery in treating psychiatric disease. Despite adherence to therapeutic guidelines and conscientious compliance, there still exists **a** population of psychiatric patients — particularly. among patients with obsessive-compulsive disorder (OCD)—who are refractory to conservative treatment with medications and psychotherapy. In the most recent review' of current treatment strategies, 15% to 30% of all OCD patients showed an unrelenting downward course despite all pharmacologic and psychotherapeutic treatments. Affective disorders, including major depression and bipolar disorder, similarly have a treatment-resistant subset of patients.[4,5] For some of these patients. surgery may still be a viable treatment alternative.

In addition to possibly being an effective treatment alternative for patients refractory to current pharmacologic and psychotherapeutic strategies, psychiatric neurosurgery may be cost-efficient. **A** study has shown that psychiatric neurosurgery map be less expensive than long-term conservative treatments with medications and psychotherapy. In addition, other reports;." show that the number and length of hospital visits were significantly decreased following psychiatric neurosurgery on severe OCD patients.

One of the challenges of treating psychiatric disease is the quantitative analysis of patients before and during the course of treatment. Modern psychiatric testing batteries, such as the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Clinical Global Impressions Scale. and the Hamilton Depression Scale (HAM-D), allow for more accurate. objective evaluations of patients undergoing psychiatric neurosurgery, Today, state-of-the-art brain imaging

Dr. Kopell is fellow in stereotactic/functional neurosursery in the Department of Neurosurgery at New York University in New York City; Dr. Rezai is associate professor of neurosurgery and head. section of stereotactic and functional neurosurgery, at the Cleveland Clinic Foundation in Ohio.

Disclosure:
Dr. Rezai received an honorarium for clinical presentation/teaching purposes from Medtronic.

"The four psychiatric neurosurgical procedures currently in use are cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leukotomy—all stereotactic interventions. These procedures are typically performed an severe, refractory psychiatric patients."

and accurate psychiatric batteries of tests available, such as Y-BOCS for OCD and HAM-D for depression. Finally, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists, and neurosurgeons is assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric neurosurgery. While many previous studies of psychiatric neurosurgery have significant flaws, most notably the inherent bias of a nonrandomized, nondouble-blind study as well as the lack of objective functional imaging techniques, they suggest a viable means of treatment for a subset of patients who may have no other treatment option.

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Lawyer's Notes

CURRICULUM VITAE

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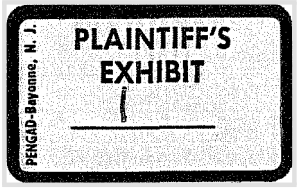

PROFESSIONAL/ACADEMIC APPOINTMENTS

January 2000- Associate Professor
Department of Neurosurgery
The Cleveland Clinic Foundation
Cleveland, Ohio

January 2000- Co-Director, Center for Functional and Restorative Neuroscience
The Cleveland Clinic Foundation
Cleveland, Ohio

January 2000- Head, Section of Stereotactic and Functional Neurosurgery
The Cleveland Clinic Foundation

July 199s-January 2000 Assistant Professor
Department of Neurosurgery
New York University School of Medicine
New York, NY

July 1998-January 2000 Director of Neurosurgery
New Yorlc University-HJD
New York, NY

July 1998- January 2000 Director, Center for Functional and Restorative Neurosurgery
New York University-HJD
New York, ***NY***

Aug 1998-January 2000 Assistant Attending, Neurosurgery
Bellevue Hospital Center
New York, NY

Sep 1998-January 2000 Attending Nemosurgeon
Manhattan Veterans Administration Hospital
New York, NY

October 199s-January 2000 Attending Neurosurgeon
NYU Downtown Hospital

New York, NY

July 1996-May 1997	Teaching Assistant in Neurosurgery Department of Neurosurgery NYU Medical Center New York, *NY*
Jan 1991-July 1991	Teaching Assistant in Surgery Department of Surgery New York University Medical Center New York, *NY*

EDUCATION

Medical	University of Southern California School Of Medicine, Los Angeles, CA MD, May 1990
Undergraduate	University of California, Los Angeles Los Angeles, CA BS in Biology, June 1986

POST-GRADUATE TRAINING

May 1997-May 1998	Clinical Fellow, Stereotactic and Functional Neurosurgery Division of Neurosurgery University of Toronto Toronto, CANADA
May 1998-July 1998	Functional Neurosurgery Department of Neurosurgery The Karolinska Institute Stockholm, Sweden
July 1996-May 1997	Chief Resident, Department of Neurosurgery New York University Medical Center New York, *NY*
May 1994- July 1995	Research Fellow, Maglietoencephalography (MEG) NYU Center for Neuromagnetism (Dr. Rodolfo Llinas) Department of Neurosciences & Physiology New York University School Of Medicine New York, *NY*
July 1991-June 1996	Resident, Department of Neurosurgery New York University Medical Center New York, *NY*
July 1990- June 1991	Intern, Department of Surgery New York University Medical Center

AWARDS AND HONORS

American Association of Neurological Surgeons William H. Sweet Investigator Award, 1998

Congress of Neurological Surgeons Clinical Fellowship Award, 1997

Bottrell Fellowship Award in Neurosurgery, 1997

Top o' Cock Award, The Dewar Society
Society 37th annual meeting, Cambridge, Ontario 1995

Alpha Omega Alpha, 1989

University of Southern California Merit Scholarship award, 1989-90

Dean's Scholar, third and fourth year clinical rotations, 1988-90

University of Southern California Hendricks academic/honors scholarship, 1988-89

Deans Honors, first and second year basic science 1986-1988

Homan's Scholarship for Academic Achievement, 1988

UCLA Dean's Honors: 1984-1985

President's Undergraduate Fellowship Research Award 1985-86

LICENSE

Ohio (2000-)

New York (1991-)

American Board of Neurological Surgery
Written examination (1993)

Certificate of Registration, The Ontario College of Physicians and Surgeons, Toronto, Ontario, CANADA 1997

EDITORIAL POSITIONS

Editor, *Neurological Research* Journal: Special Focus Issue "Future Directions in Neurostimulation", 2000

Editor, *CNS Spectrums*, Special issue on Surgery for Psychiatric disorders, 2000

Editor, *Neurosurgey Clinics of North America:* "Neurosurgery for Psychiatric Disorders", 2001

Editoiial Board, World Federation of Neurosurgical Societies, 2000-

Editorial Board, Neurological Research

Editorial Board, Psychline journal, 2000

Editor, Young Neurosurgeons Newsletter, American Association of Neurological Surgeons, 1999-2001

Editor, Web page, World society for Stereotactic and Functional Neurosurgery

Editor, Web page, American Society of Stereotactic and Functional Neurosurgery

Ad Hoc reviewer, Neurosurgery Journal

As Hoc reviewer, Surgical Neurology

Ad Hoc reviewer, NDSB review committee, NINDS, NIH

Ad Hoc reviewer, VA national Merit review section

PROFESSIONAL COMMITTEES/BOARDS

International Board, World Federation of Neurosurgical Societies 2000-

Executive Board, Joint Section of Stereotactic and Functional Neurosurgery, 2000-

Public Relations committee, Congress of Neurological Surgeons: 2001-

CME Liaison, Joint section on pain, 2001

AANS/CNS Committee on resident research, 2001

Public Relations Committee, Congress of Neurological Surgeons 1999

Scientific Committee, Congress of Neurological Surgeons, 1999

Special Course Committee, Congress of Neurological Surgeons, 1999

Young Neurosurgeons Committee of the American Association of Neurological Surgeons (1997-2001)

Young Neurosurgeons Committee Liaison to the AANS/CNS Joint Section-Stereotactic and Functional (1997-)

Sergeant at arms Committee, CNS Meeting: New Orleans, LA (1997)

AANS Marshal's Subcommittee, AANS meeting: Minneapolis, Minnesota (1996)

Bellevue Hospital Center Medical Board (elected 1995-96)

Sergeant at arms Committee, CNS meeting: San Francisco, CA (1995)

House Staff Affairs Committee, New York University Medical Center and Bellevue Hospital Center (1995-96)

PROFESSIONAL MEMBERSHIPS

American Association of Neurological Surgeons

Congress of Neurological Surgeons

American Association of Neurological Surgeons and Congress of Neurological Surgeons Section on Stereotactic and Functional Neurosurgery

American Association of Neurological Surgeons and Congress of Neurological Surgeons Section on Pain

World Federation of Neurosurgical Societies

International Neuromodulation Society

Movement Disorder Society

American Society for Stereotactic and Functional Neurosurgery

World Society for Stereotactic and Functional Neurosurgery

American Academy of Pain Medicine

American Neuromodulation Society

American Pain Society

Society for Neuroscience

National Spine Network

American Association for Advancement of Sciences

American Medical Association

RESEARCH EXPERIENCE

1997-1998	Functional Brain Imaging (Functional Magnetic Resonance Imaging) University of Toronto Dr. David Mikulis Toronto, Ontario, Canada
1994-96	Research Fellow, Functional Brain Imaging Magnetoencephalography (MEG) laboratories Center for Neuromagnetism Dr. Rodolfo Lliias Department of Physiology and Neurosciences New York University School Of Medicine New York, NY
1988-90	Research Assistant, Neurosurgery laboratories Dr.'s Martin H. Weiss, Michael L.J. Apuzzo, and Berislav Zlokovic Department of Neurosurgery USC School of Medicine, Los Angeles, CA
1987	Research Associate, Molecular Immunology laboratories Dr.'s John L. Faliey and Otoniel Martinez Maza Center For Interdisciplinary Research in Immunology & Disease UCLA School of Medicine, Los Angeles, CA
1983-86	Research Assistant, Medical Immunology Laboratories Dr.'s Vali Kermani and John L. Fahey Departments of Microbiology & Immunology and Pathology UCLA School of Medicine, Los Angeles, CA

Course/Symposium Director

1. "Spinal Pain: Contemporary Management Strategies and Advanced Techniques", New York University Medical Center & Hospital for Joint Diseases, October 16, 17, 1998.

2. "Neurostimulation: Deep brain and spinal cord", American Association of Neurological Surgeons Annual Meeting Practical Clinic, April 26, 1999.

3. "Stereotactic: Functional and Restorative Neurosurgery: Advances and Prospects for the new Millennium". New York, NY, June 11-13, 1999.

4. "Deep brain stimulation" Special Course, Scientific Session, Congress of Neurological Surgeons Annual Meeting, Boston, October 1999.

5. "Contemporary management of movement disorders" ,American Association of

Neurological Surgeons Annual Meeting Practical Clinic, San Francisco, CA April 2000.

6. "Special Symposium: Neurosurgical management of movement disorders", American Association of Neurological Surgeons Annual Meeting, San Francisco, CA, April 2000.

7. "Deep Brain Stirnulation for Parkinson's Disease: Skills for Preoperative patient selection and post-operative management" The Lerner Research Institute, Cleveland Clinic Foundation,
Cleveland, OH, June 2000.

8. "Subtlialamic Nucleus Stimulation Surgery and Programming",
Cleveland Clinic Foundation, Cleveland, Ohio, Nov 2000.

9. "Deep Brain Stimulation for Parkinson's disease" Interactive Online CME course, Nov 2000

10. "Neuromodulation: Defining the Future" Cleveland, Ohio, June 2001.

Course/Symposium Faculty

1. AANS Practical Clinic: Frameless Stereotactic Devices. Interactive Image-Guided Neurosurgery, American Association of Neurological Surgeons, Orlando, FL (April 1995).

2. AANS Practical Clinic: Interactive Image-Guided Neurosurgery. American Association of Neurological Surgeons, Minneapolis, MN (May 1996).

3. AANS Practical Clinic: Stereotactic Surgery; Principles, Techniques, and Instrumentation. American Association of Neurological Surgeons, Minneapolis, MN (May 1996).

4. AANS Practical Clinic: Stereotactic Surgery; Principles, Techniques, and Instrumentation. American Association of Neurological Surgeons. Denver, Colorado (April 1997).

5. AANS Practical Clinic: Interactive Image-Guided Neurosurgery. American Association of Neurological Surgeons, Philadelphia, PA (April 1998).

6. AANS Practical Clinic: Stereotactic Surgery; Principles, Techniques, and Instrumentation. American Association of Neurological Surgeons, Philadelphia, PA (April 1998).

7. Surgery for Movement Disorders: Department of Neurology and Neurosurgery, University of Toronto School of Medicine, Toronto, Ontario, Canada (May 1998).

8. Spinal Pain: Contemporary Management Strategies and Advanced Techniques, New York University Medical Center & Hospital for Joint Diseases, New York, NY (Oct 1998).

9. AANS Practical Clinic: Neurostimulation, New Orleans (April 1999).

10. AANS Practical Clinic: Interactive Image-Guided Neurosurgery. American Association of Neurological Surgeons, New Orleans (April 1999).

11. Surgery for Movement Disorders: An Advanced Workshop, University of Toronto School of Medicine, Toronto, Ontario, Canada (May 1999).

12. Stereotactic, Functional and Restorative Neurosurgery: Advances and Prospects For the New Millennium. New York, NY (June 1999).

13. Interventional Therapies Workshop: Pain Management, Memphis, TN (August 1999).

14. CNS Practical Course: Image-Guided Cranial Navigation, Boston, MA (October 1999).

15. AANS Practical Clinic:Contemporary management of movement disorders, American Association of Neurological Surgeons Annual Meeting (April 2000)

16. AANS Special Course: Neurosurgical management of movement disorders" American Association of Neurological Surgeons Annual Meeting (April 2000).

17. Deep Brain Stimulation for Parkinson's Disease: Skills for Pre-operative patient selection and post-operative management , Cleveland, OH, (June 2000).

18. Applications of Stereotactic Navigation to Epilepsy Surgery Symposium, Cleveland, OH (June 2000).

19. CNS Practical Course: Movement Disorder Surgery, Congress of Neurological Surgeons San Antonio, TX (Sep 2000)

20. Interventional Therapies Workshop: Pain Management, Memphis, TN (November 2000).

21. Deep Brain Stimulation: Electrophysiological Techniques and Emerging Treatments in Movement Disorders and Epilepsy, Cleveland, Ohio (March 2001).

Scientific Oral Presentations/Invited Lectures

1. "Histamine blocks Interleukin-2 (IL-2) gene expression and regulates IL-2 receptor gene expression". UCLA Department of Microbiology and Immunology, Los Angeles, CA (May 1986).

2. "Role of Epstein Barr Virus in polyclonal activation of B cells in HIV infection". Center For Interdisciplinary Research in Immunology and Disease, UCLA School of Medicine, Los Angeles, CA (September 1987).

3. "Spinal Tuberculosis (Pott's disease)." New York Neurosurgical Society , New York, NY (March 1994).

   Modern Management of Spinal Tuberculosis." Congress of Neurological Surgeons, Chicago, IL (October 1994).

4. "Clinical Application of Magnetoencephalography in Neurosurgery" New York Neurosurgical Society , New York, NY (March 1995).

5. "Introduction of Magnetoencephalography (MEG) to the Stereotactic Technique." Society For Stereotactic and Functional Neurosurgery. Marina Del Rey, CA (March 1995).

6. "Criteria Associated with Dissemination in Ependymomas of the Central Nervous System. Congress of Neurological Surgeons, San Francisco, CA (October 1995).

7. "Functional Brain Imaging in Neurosurgical Patients", New York Neuroscience Symposium, New Yorlc, NY (November 1995).

8. "Magnetoencephalography (MEG): Applications in Image-Guided Stereotactic Neurosurgery." Congress of Neurological Surgeons San Francisco, CA (October 1995).

9. "Spinal Tuberculosis-Pott's Disease", New York University Department of Neurology Grand Rounds (November 1995).

10. "Utility of Non-Invasive Functional Brain Imaging in Neurosurgery", New York University Department of Neurosurgery Grand Rounds (November 1995).

11. "Magnetoencephalography Brain Mapping", Neurosurgery: 19th Annual Post-graduate Course, New York, NY (December 1995).

12. "Clinical Applications of Magnetoencephalography (MEG) Brain Imaging", Cornel1 Medical College/New York Hospital Department of Neurology Grand Rounds, New York, NY (March 1996).

13. "Surgical Management of Spinal Osteomyelitis." American Association of Neurological Surgeons, Minneapolis, MN (April 1996).

14. "The Interactive Use of Magnetoencephalography (MEG) Functional Imaging in Stereotactic Neurosurgery." European Society for Stereotactic and Functional Neurosurgery, Milan, Italy (June 1996).

15. "Clinical Application of Functional Brain Imaging in 75 Patients Harboring Lesions Associated with the Eloquent Cortex. Congress of Neurological Surgeons, Montreal, Canada (September 1996).

16. "Functional Neuroimaging", Clinical Neurosciences in the year 2000 Symposium, New York, New York (October 1996).

17. "Central Nervous System Trauma", New York University School of Medicine Surgical Core Lecture (1997).

18. "Magnetoencephalography (MEG) Functional Brain Imaging", Neurology/Neurosurgery Grand Rounds, Georgetown University Medical Center, Washington DC (January 1997).

19. ""Deep Brain Stimulation: Current application and future prospects", Neurology/Neurosurgery Grand Rounds, Medical College of Georgia, Augusta, GA (October 1997).

14. "Contemporary Management of Spinal Osteomyelitis." North American Spine Society, New York, NY (Oct 1997).

21. "Neurosurgical Emergencies", University of Toronto School of Medicine Surgery/Medicine Core Lecture, Toronto, Ontario, Canada (November 1997)

22. "Deep brain stimulation for the treatment of movement disorders and chronic pain", Neurosurgery Grand Rounds, Medical University of South Carolina, Charleston, SC (November 1997).

23. "Evaluation and management of the comatose patient", University of Toronto School of Medicine Surgery/Medicine Core lecture, Toronto, Ontario, Canada (November 1997).

24. "Deep Brain Stimulation (DBS): Past, Present, and the Future", New York University Department of Neurosurgery Grand Rounds. New York, ***NY*** (November 1997).

25. "Chronic deep brain stimulation for the management of intractable pain and movement disorders", Neurology/Neurosurgery Grand rounds, Georgetown University Medical Center, Washington, DC (December 1997).

26. "Chronic brain stimulation: Current and future clinical application", Neuroscience Grand Rounds, Allegheny Neuroscience Institute, Pittsburgh, Pennsylvania (March 1998).

27. "Chronic Thalamic Stimulation for Tremor" Neuroscience, Neurology group, New York, ***NY*** (April 1998).

28. "Deep Brain Stimulation for Intractable Neuropathic Pain: Contemporary Management and outcome in 80 patients." American Association of Neurological Surgeons, Philadelphia, Pennsylvania (April 1998).

29. "Magnetoencephalography (MEG): Basic science and Clinical Application", Neurosciences Grand Rounds, University of Toronto, Toronto, Canada (May 1998).

30. "Functional MRI and deep brain stimulation (DBS): A novel approach for the study of brain function". Neurosurgery/Neuroscience Conference, The Karolinska Institute, Stockholm, Sweden (June 1998).

31. "Deep Brain Stimulation for Intractable Neuropathic Pain: Contemporary Management and outcome in 90 patients". Department of Neurosurgery Grand Rounds, The Karolinska Institute, Stockholm, Sweden (June 1998).

32. "Functional MRI localization of cortical and sub-cortical activation during deep brain stimulation", Neuroradiology/Neuroscience Conference, University of Toronto, Toronto, Canada (July 1998).

33. "Neurosurgical Management of Movement Disorders", Neurology Grand Rounds, New Yorlc University School of Medicine, New York, ***NY*** (October 1998).

34, "Surgical Approaches to Parkinson's Disease", Fifth Annual Long Island APDA Symposium, Melville, ***NY*** (October 1998).

35. "Magnetoencephalography (MEG) Functional Imaging" Congress of Neurological Surgeons,
Seattle, Washington (October 1998).

36. "Long-term outcome of deep brain stimulation for Parkinsonian, Essential, and Cerebellar tremors." Congress of Neurological Surgeons, Seattle, Washington (October 1998).

37. "Deep Brain Stimulation For The Management Of Chronic Pain", Pain Medicine & Palliative Care Case Conference, Beth Israel University Hospital, New York, NY (October 1998).

38. "Neurosurgical Management of Movement Disorders" Athena Neuroscience and Medtronic Neurological. New York, ***NY*** (November 1998).

39. "Neurosurgical Management of Chronic Pain" New York University Medical Center Pain rounds, New York, NY (November 1998).

40. "Deep Brain Stiniulation – New Treatment For Tremors", American Parkinsons's Disease Association Lecture, St. Joseph Hospital, Flushing, ***NY*** (November 1998).

41. "Deep Brain Stimulation For Chronic Pain", Pain Medicine Grand Rounds, Hospital For Joint Diseases & Tisch Hospital, New York, ***NY*** (December 1998).

42. "Spinal Cord Stimulation for Chronic Pain", Orthopedic surgery grand rounds, NYU Medical Center, New York, NY (December 1998).

43. "Deep Brain Stimulation for the treatment of Parkinson's disease", Neurology Grand rounds, State University of New York, Down State, Brooklyn, ***NY*** (December 1998).

44. "Alternative Surgical Management Strategies for Refractory Chronic Spinal Pain", Degenerative Diseases of the Spine: Diagnosis and Management. New York, NY (December 1998).

45. "Neurosurgical Management of Movement Disorders", Neurosurgery grand rounds, Cornell University/New York Hospital. New York, ***NY*** (December 1998).

46. Neurostiniulation and Functional Brain Imaging" Medtronic Scientific Forum, Minneapolis, Minnesota (January 1998).

47. "Deep Brain Stimulation for the Management of Movement Disorders", North Shore University Hospital, Neurology Grand Rounds, Long Island, NY (January 1999).

48. "Functional and Stereotactic Neurosurgical Advances": Parkinson's Disease: Clinical Update Symposium. New York, ***NY*** (February 1999).

49. "'Deep Brain Stimulation in the Management of Movement Disorders'' NYU Medical Alumni Weekend. New York, NY (April 1999).

50. "Thalamic Stimulation for Chronic Pain", American Association of Neurological Surgeons, New Orleans, LA (April 1999).

51. "Functional Brain Imaging and Neurostimulation", American Association of Neurological Surgeons, New Orleans, LA (April 1999)

52. "Movement Disorders: Principles of Surgery-Imaging, Equipment and Technique" Surgery for Movement Disorders: An Advanced Workshop. Toronto, Canada (May 1999).

53. "Thalamic Stimulation for Chronic Pain". stereotactic, Functional and Restorative Neurosurgery: Advances and Prospects for the new Millennium, New York, NY (June 1999).

54. "Functional Brain Imaging and Neurosurgery" The Third Congress of the Asian Society for Stereotactic, Functional, and Computer-Assisted Neurosurgery, Seoul, Korea (June 1999).

55. "Functional Brain Imaging and Neurostimulation". Stereotactic, Functional and Restorative Neurosurgery: Advances and Prospects for the new Millennium, New York, NY (June 1999).

56 "Deep Brain Stimulation: Equipment and Technique", Stereotactic, Functional and Restorative Neurosurgery: Advances and Prospects for the new Millennium, New York, ***NY*** (June 1999).

57. "Chronic Subthalamic Nucleus Stimulation for Parkinson's Disease" The Third Congress of the Asian Society for Stereotactic, Functional, and Computer-Assisted Neurosurgery, Seoul, Korea (June 1999).

58. "Surgical Management of Parkinson's Disease" The Third Congress of the Asian Society for Stereotactic, Functional, and Computer- Assisted Neurosurgery, Seoul, Korea (June 1999).

59. "Brain Stimulation: Current Clinical Application and Future Prospects'' Neuroscience Grand Rounds, Cleveland Clinic Foundation, Cleveland Ohio (June 1999).

60. "Mechanisms of Spinal Cord Stimulation", Interventional Therapies Worlcshop. Memphis, TN (August 1999)

61. "Complications of Neuromodulation Surgery" Interventional Therapies Worlcshop. Memphis, TN (August 1999).

62. "Neurostimulation: Surgical Techniques" Interventional Therapies Worlcshop. Memphis, TN (August 1999).

63. "Neurosurgical management of movement Disorders", Allied Educational Foundation Annual National Symposium, Monticello, NY (September 1999).

64. "Motor cortex stimulation for chronic atypical facial pain", Trigeminal Neuralgia Association (October 1999)

65. "Neurosurgical management of chronic pain", New Yorlc University Department of rehabilitation medicine grand rounds, New York, NY (October 1999).

66. "Spinal Infections" New York University/Hospital for Joint Disease Department of Orthopedics grand rounds, New York, *N Y* (October 1999).

67. "Brain Stimulation: Current clinical application and future prospects" University of Medicine and Dentistry of New Jersey, Department of Neurosurgery grand rounds, Newark, New Jersey (November 1999).

68. "Alternative surgical management strategies for refractory chronic pain", New York University Degenerative disease of the spine Symposium, New York, ***NY*** (December 1999)

69. "Surgical management refractory chronic pain" New York University/Hospital for Joint Disease pain management symposium, New York, ***NY*** (December 1999).

70. "Neurosurgical Management of Chronic Pain" Long-Island Pain Symposium, New York, NY (January 2000).

71. "Functional Brain Imaging and Neurostimulation" State University of New York, Syrracuse Research symposium, Syracuse, NY (February 2000).

72. "Neurostimulation" Cleveland Clinic Foundation, Departments of Neurosurgery Grand rounds, Cleveland, OH (March 2000)

73. "Neuromodulation: Current therapies and future application" Neurosurgery Core Curriculum lecture, Cleveland, OH (May 2000).

74. "Brain stimulation: surgical principles" American Association of Neurological Surgeons San Francisco, CA (April 2000).

75. "Deep brain stimulation: Surgical technique, pitfalls and complications" American Association
of Neurological Surgeons, San Francisco, CA (April 2000).

76. "Parkinson's Disease: What else is new. Special Seminar, Cleveland Ohio (May 2000).

77. "Surgical methodology and risk assessment for Parkinson's disease" Deep Brain stimulation for Pakinson's disease, skills for pre-operative patient selection and post-operative management Symposium, Cleveland, OH (June 2000).

78. "Regional anatomy of the Subthalamic nucleus and globus pallidus as it relates to efficacy and side effects", Deep Brain stimulation for Pakinson's disease, skills for pre-operative patient selection and post-operative management Symposium, Cleveland, OH (June 2000).

79. "Deep brain stimulation techniques and animal results for Epilepsy", Cortical Dyspiasias and Epilepsy: pathophyisology, diagnosis and management. 11th International Cleveland Clinic-Bethel Epilepsy Symposium, Cleveland, OH (June 2000).

80. "Deep brain stimulation surgery for epilepsy" Cortical Dysplasias and Epilepsy: pathophyisology, diagnosis and management. 11th International Cleveland Clinic-Bethel Epilepsy Symposium, Cleveland, OH (June 2000).

80. "Clironic Subthalamic Nucleus Stimulation for Parkinson's disease'' Congress of Neurological Surgeons, San Antonio, TX (Sep 2000).

81. "Subthalamic Nucleus Stimulation Surgery" Congress of Neurological Surgeons,

San Antonio, TX (Sep 2000)

82. "Brain stirnulation": Current clinical application and future prospects" Applied Neural Control Research, Cleveland, OH (Sep 2000).

83. "Magnetoencephalography (MEG) mapping of the sensorimotor cortex in patients with tumors, Congress of Neurological Surgeons, San Antonio, TX (Sep 2000).

84. "Neurosurgical Management of Chronic Pain" Pain Management Grand Rounds: The Cleveland Clinic Foundation, Cleveland, OH (Oct 2000).

85. "Motor cortex stimulation for Chronic Pain" University of Toronto Bottrell research symposium, Toronto, CA (Nov 2000)

86. "Implant Techniques for Neurostimulation and Intrathecal Systems" Interventional Therapies Workshop, Memphis, TN (Nov 2000).

87. "Outcomes and Complications for neurostimulation and intrathecal drug therapies" Interventional Therapies Workshop, Memphis, TN (Nov 2000).

88. "Functional Brain Imaging and Chronic Pain" Pain management grand rounds, The Cleveland
Clinic Foundation, Cleveland, OH (Nov 2000).

89. "Deep brain stimulation: Current clinical application and future prospect for morbid Obesity. Endocrine Grand Rounds, The Cleveland Clinic Foundation, Cleveland, OH (Nov 2000)

90. "Brain Stimulation: Current Clinical application and fiiture prospects", *NY* Neurosurgery society section, Uniondale, *NY* (Dec 2000).

91. "Brain Stimulation for the treatment of chronic neurological disorders" Medicine Grand rounds, The Cleveland Clinic Foundation, Cleveland, OH (Jan 2001).

92. "Neurostimulation for chronic pain" Pain therapies roundtable, San Antonio, TX (March 2001).

93. "Brain Stimulation for neurological disorders" Neurology Grand Rounds, University of Texas, San Antonio, TX (March 2001).

94. "The expanding role of DBS for neurological disease: An overview" Deep brain stimulation: electrophysiological techniques and emerging treatments in movement disorders and epilepsy Satellite course, Cleveland, OH (March 2001).

95. "Electrophysiological targeting of the STN' Deep brain stimulation: electrophysiological techniques and emerging treatments in movement disorders and epilepsy Satellite course, Cleveland, OH (March 2001).

Publications

Papers

1. Kermani V, Saleh S, Donovich P, Hirji K, **Rezai AR:** Mediation of the anti-proliferative effect of cyclosporin on human lymphocytes by blockade of Interleukin-2 biosynthesis. **Transplantation** 39: 439-442, 1985.

2. Martinez-Maza **O,** Moody DJ, **Rezai AR,** Ellison GW, Myers LW, Tourtellote WW, Fahey JL: Increased spontaneous immunoglobulin secretion associated with cyclophosphamide induced immune suppression. **Journal of Clinical Immunology** 7: 107-113, 1987.

3. Kedar E, **Rezai AR ,** Giorgi RP, Gale RE, Champlin RT, Mitsuyasu RT, Fahey JL: Irnrnunomodulating effects *In Vitro* of Interleukin-2 and interferon gamma on human blood and bone marrow mononuclear cells. **Natural Immunity & Cell Growth Regulation** 7:13-30, 1988.

4. **Rezai AR,** Salazar JF, Martinez-Maza **O,** Bramhall J, Afrasiabi R, Kermani V: Histamine blocks Interleultin-2 gene expression and regulates IL-2 receptor gene expression. **Immunopharmacology and Immunotoxicolcogy** 12: 345-362, 1990.

5. Zloltovic BV, Hyman S, McComb JG, Tang G, **Rezai AR,** Weiss MH: Vasopressin uptake by hypothalamopituitary axis and pineal gland in guinea-pigs. **American Journal of Physiology** 260: 633-640, 1991.

6. Weiner HL, **Rezai AR,** Cooper PR: Sigmoid diverticular perforation in neurosurgical patients receiving high-dose corticosteroids. **Neurosurgery** 33: 40-43, 1993.

7. Levy ML, **Rezai AR,** Masri LS, Litofsky SN, Giannotta SL, Apuzzo ML, Weiss MH: The significance of subarachnoid hemorrhage after penetrating cranio-cerebral injury: Correlation with angiography and outcome in a civilian population. **Neurosurgery** 32: 532-540, 1993.

8. **Rezai AR,** Mailly K, Rosenblum JA: Sarcoid-induced acute paraplegia. **Journal Neurol Orthop Surg** 15: 87-89, 1994.

9. Jafar JJ, **Rezai AR:** Acute Surgical Management of Arteriovenous Malformations, **Neurosurgery** 34: 8-13, 1994.

10. **Rezai AR,** Lee M, Kite C, Smyth D, Jafar JJ: Traumatic posterior cerebral artery aneurysm secondary to an intracranial nail. **Surgical Neurology** 42: 312-315, 1994.

11. Lee M, **Rezai AR,** Cho J: Depressed skull fracture in children secondary to skull clamp fixation devices. **Pediatric Neurosurgery** 21: 174-178, 1994.

12. **Rezai AR,** Martinez-Maza O, Vander-niyden M, Weiss MH: Interleukin-6 and Interleukin-6 receptor gene expression in pituitary tumors. **Journal of Neuro-Oncology** 19: 131-135, 1994.

13. Lee M, **Rezai AR,** Wisoff JH: Acquired Chiari-I malformation and hydromyelia secondary to a giant craniopharyngioma. **Pediatric Neurosurgery** 22: 251-254, 1995.

14. Rezai AR, Lee M, Cooper P, Errico TJ, Koslow M: Modem Management of Spinal Tuberculosis. **Neurosurgery** 36: 87-98, 1995.

15. Lee M, **Rezai AR,** Epstein FJ: Intramedullary lipomas of the spinal cord. **Journal of Neurosurgery** 82: 394-400,1995.

16. **Rezai AR,** Hund M, Kronberg E, Deletis V, Zonenshyan M, Mogilner A, Ribary U, Llinas R, Kelly PJ: Introduction of Magnetoencephalography to the stereotactic technique. **Stereotactic and Functional Neurosurgery** 65: 37-41, 1995

17. Lee M, **Rezai AR,** Freed D, Epstein FJ: Intramedullary spinal cord tumors in neurofibromatosis. **Neurosurgery** 38: 32-37, 1996.

18. Rezai AR, Hund M, Kronberg E, Zonenshyan M, Cappell J, Ribary U, Llinas R, Kelly PJ: The interactive use of magnetoencephalography in stereotactic image-guided neurosurgery. **Neurosurgery** 39: 92-102, 1996.

19. Woo H, **Rezai** AR, Knopp E, Weiner H, Miller D, Kelly PJ: Contrast enhancing progressive multifocal leukoencephalopathy. **Neurosurgery** 39: 1031-1035, 1996.

20. **Rezai AR,** Woo H, Lee M, Cohen H, Zagzag D, Epstein FJ: Disseminated ependymomas of the central nervous system. **Journal Of Neurosurgery** 85: 618-624, 1996.

21. Hund M, **Rezai AR,** Kronberg E, Zonenshayn M, Ribary U, Jafar JJ, Kelly PJ, Llinás R: Magnetoencephalography (MEG) mapping: Basis of a new functional risk profile (FRP) in the selection of patients with cortical brain lesions. **Neurosurgery** 40: 936-943, 1997.

22 Jafar JJ, **Rezai AR,** Crowell RM: The effect of internal carotid artery occlusion on cerebral blood flow for the treatment of giant aneurysms. **Journal of Neurovascular Disease** 2: 68-73, 1997.

23 Weiner H, Freed D, Woo H, **Rezai AR,** Kim R, Epstein FJ: Intra-axial Tumors of the cervico-medullary junction: Surgical results and long term outcome **Pediatric Neurosurgery** 27:12-8, 1997.

24. Lee M, Zagzag D, **Rezai AR,** Epstein FJ: Non-neoplastic intramedullary spinal cord lesions mimicking tumors. **Neurosurgery** 43: 950-54, 1998.

25. **Rezai AR,** Woo H, ,Errico T, Cooper P: Contemporary management of spinal osteomyelitis. **Neurosurgery** 44:1018-1026, 1999.

26. **Rezai AR,** Lozano AM, Crawley AD, Chun C, Davis K, Tasker R, Dostrovsky J, Miltulis D:Thalamic stimulation and functional MRI: Localization of cortical and sub-cortical activation with implanted electrodes. **Journal of Neurosurgery** 90:583-590, 1999.

27 **Rezai AR**, Lozano AM, Crawley AD, Chun C, Davis K, Tasker R, Dostrovsky J, Mikulis D: Deep Bain Stimulation and functional MRI: Localization of cortical and sub-cortical activation with implanted electrodes. **Neurosurgical Focus** 6:3, 1999.

28. Pahapill P, Levy R, Dostrovsky JO, Davis KD, **Rezai AR,** Tasker RR, Lozano AM: Tremor arrest with thalamic microinjection of muscimol in patients with essential tremor **Annals of Neurology** 46:249-252, 1999.

29. Zonenshayan M, Mogilner AM, **Rezai AR:** Neurostimulation and functional brain imaging. **Neurological Research** 22:318-325, 2000.

30. Schiff N, **Rezai AM,** Plum F: A Neuromodulation strategy for rational therapy of complex brain injury states. **Neurological Research** 22: 267-272, 2000.

31. **Rezai AR:** Neurostimulation. **Neurological Research** 22:236, 2000.

32. Zonenshayan M, **Rezai AR,** Mogilner AM, Beric A, Sterio D, Kelly PJ: Comparison of Anatomical and neurophysiological methods for subthalamic nucleus (STN) targeting, **Neurosurgery** 47: 282-294,2000.

33. **Rezai AR:** The Imperative of Psychiatric Neurosurgery. **CNS Spectrums,** 5:17, 2000.

34. Kopell BH, **Rezai AR:** The continuing evolution of psychiatric neurosurgery **CNS Spectrums,** 5:20-31, 2000.

35. **Rezai AR:** Surgery for Psychiatric disorders. **CNS Spectrums,** 5(11)20, 2000.

36. **Rezai AR,** Francisco A, Lozano AM, Tasker R: Deep brain stimulation for intractable neuropathic pain: Contemporary management and outcome in 90 patients. (submitted).

37. Sterio D, Zonenshayn M, Mogilner A, Rezai ***AR,*** Kiprovski K, Kelly PJ, Beric A: Neurophysiological refinement of subthalamic nucleus targeting (Submitted).

38. Francisco A, **Rezai AR,** Lozano AM, Lang A, Tasker R: Long-term outcome of deep brain stimulation for Parkinsonian, Essential, and Cerebellar tremor (submitted).

39. Mogilner AY, Sterio D, **Rezai AR,** Zonensliayn M, Kelly PJ, Beric A: The Subthalamic Nucleus after Pallidotomy in Parkinson's Disease (submitted).

40. Montgomery EB, Baker KB, **Rezai *AR:*** Effects of subthalamic nucleus stimulation patterns Motor performance in Parkinson's disease (Submitted).

41. Baker KB, Montgomery EB, **Rezai AR,** Burgess R, Luders HO: Subthalamic nucleus DBS Evoked potentials: physiological and therapeutic implications (Submitted).

42. **Rezai AR,** Mogilner AM, Lozano AM, Benabid AL: Brain Stimulation: Past, Present and The Future (In preparation).

BOOK CHAPTERS

1. **Rezai AR,** Lee M, Cooper PR: Spinal Tuberculosis (Pott'sDisease). In Rom WM, Garay S (ed): Tuberculosis, Little Brown & Company, New York, NY. pp 623-635, (1996).

2. **Rezai AR,** Mogilner A, Cappell J, Llinás R, Kelly PJ: The Use of Magnetoencephalography (MEG) functional imaging in stereotactic neurosurgery. In Broggi G (ed): Advances in Stereotactic and Functional Neurosurgery-12. Springer Verlag, New York, NY (1997).

3. **Rezai AR,** Lee M, Abbott R: Benign spinal tumors, In Engler G (ed), Cole J, Merton WL, Spinal Cord Diseases: Diagnosis and Treatment. Marcel Dekker, New York, ***NY.*** pp287-313, (1998).

4. **Wezai AR,** Hutchison W, Lozano AM: Subthalamic nucleus stimulators. In Rengachary SS, Wilkins RH (ed): Neurosurgical Operative Atlas, AANS Publication, Chicago, Illinois, Volume 8: 195-207 (1999).

5. **Rezai AR,** Tasker R, Lozano AM: Ablative neurosurgery for pain control. In Rengachary SS, Wilkins RH (ed): Neurosurgical Operative Atlas, AANS Publication, Chicago, Illinois, Vol 9: 165-179 (2000).

6. **Rezai AR,** Lozano AM: Deep brain stimulation (DBS) for pain. In Burchiel KJ (ed): Pain Surgery, Thieme, New York (In Press)

7. Zonenshayn M, **Rezai AR:** Pain and trigeminal neuralgia, In Kitchen, Manji, McKhann (ed): self-assessment colour review Of clinical Neurololgy, Manson Publishing, London, England, (In press)

8. **Rezai AR,** Tasker R: Deep Brain Stimulation for Chronic Pain": In Youmans: Neurosurgery, WB Saunders, Philadelphia (In press).

9. **Rezai AR,** Zonensliyan M: "Principles of frame based stereotactic surgery" In Rengachary SS, Maciunas RJ, Wilkins RH: Neurosurgery, McGraw-Hill (In preparation)

10. Montgomery EB, Baker K, **Rezai AR:** Deep brain stimulation. In Neuroprosthetics: Theory And Practice, (In preparation).

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PUBLISHED ABSTRACTS

1. Kermani V, Weaver MS, Afrasiabi R, **Rezai AR,** Soofer B, Fahey JL: Histamine reveals intact expression of IL-2 receptors in mitogen stimulated lymphocytes from AIDS patients. **Federation Proceedings** 43:2947, 1984.

2. Martinez-Maza **O,** Moody D, **Rezai AR,** Elision LW, Tourtellote WW, Fahey JL: Increased spontaneous immunoglobulin secretion in multiple sclerosis patients following *in vivo* treatment with cyclophosphamide. **Federation Proceedings** 44:5193, 1985.

3. Montestruque S, **Rezai *AR,*** Kermani V, Bramhall J: Histamine increases intracellular calcium activity in human peripheral blood mononuclear cells, **Federation Proceedings** 44:6598, 1985.

4. Kermani V, Fazeli **A, Rezai AR,** Gatti RA, Naeim F: The effect of 1,25-dihydroxy Vitamin D3 on human lymphoid cell growth is associated with blockade of Interleukin-2 and *c-myc* gene expression. **Federation Proceedings** 45:4912, 1986.

5. Salazar JF, **Rezai AR,** Kermani V: N-methylnicotinamide blocks activation of normal and leukemic T cell lines at an early stage of the cell cycle; role of ADP-ribosylation in the transcription of IL-2. **Federation Proceedings** 45:1376, 1986.

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The Continuing Evolution of Psychiatric Neurosurgery

By Brian Harris Kopell, MD, and Ali R. Rezai, MD

ABSTRACT

In this article, the authors examine the growth of the discipline of psychiatric surgery from the earliest Leswning procedures to the neuroaugmentative strategies used today. Special attention is paid to the neural circuitry that underlies psychiatric disorders and how surgical manipulation of these circuits might result in the amelioration of the disease state. Also examined is the effect that the technology curve has had on psychiatric surgery with regard tofunctional imaging and neurosurgical equipment. Finally, the authors use the current state of psychiatric surgery to speculate on some of the future directions that psychiatric neurosurgical procedures might take.

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INTRODUCTION

Few other medical treatments in history have been the focus of such controversy, debate, and misunderstanding as neurosurgery for psychiatric disorders. The term *psychosurgery,* which has traditionally been applied to these procedures, itself is a misnomer. *Psychosurgery* implies an intervention that directly targets the psyche or mind. Surgery for mental disorders intervenes on psychiatric patients' nervous systems in order to lessen their debilitating symptoms; therefore, the term *psychiatric neurosurgery* is a more accurate term and more reflective of the modern practice of these procedures.

Even as the practice of neurosurgery for psychiatric illness decreased in frequency following the introduction of Thorazine in 1954. the negative bias towards it continued to grow.' Charges of abuse and allegations of surgery for social control culminated in the establishment of a national commission in **1977** that examined psychiatric neurosurgical practices in the United States—from freehand frontal lobotomies to stereotactic lesioning procedures. Careful emphasis was taken to review the efficacy and safety of these procedures. As the chairman of the commission reported in his review, the findings were surprising: "We looked at the data and so they did not support our prejudices. I, for one, did not expect to come out in favor of psychosurgery. But we saw that some very sick people had been helped by it."[2] The commission was so impressed by the potential benefit of psychiatric neurosurgery that it recommended a review board be formed in order to study these procedures in a more scientific manner: nevertheless. this review board was never formed.

An extensive literature review by a pediatrician with a masters in public health was published by the Office of Technology Assessment in 1986 that cooled the ardor to perform psychiatric neurosurgical procedures. This review concluded that since psychiatric neurosurgery had never been studied in a randomized. double-blind prospective fashion, it should be considered experimental until a study proved otherwise. Coupled with the advent of newer, more effective psychotropic medications, psychiatric neurosurgery fell by the wayside. Today, only a few centers worldwide perform these procedures.

Nevertheless. there are several reasons to continue to evaluate the role of neurosurgery in treating psychiatric disease. Despite adherence to therapeutic guidelines and conscientious compliance, there still exists a population of psychiatric patients — particularly. among patients with obsessive-compulsive disorder (OCD)—who are refractory to conservative treatment with medications and psychotherapy In the most recent review' of current treatment strategies, **15%** to 30% of all OCD patients showed an unrelenting downward course despite all pharmacologic and psychotherapeutic treatments. Affective disorders, including major depression and bipolar disorder, similarly have a treatment-resistant subset of patients.[4,5] For some of these patients. surgery may still be a viable treatment alternative.

In addition to possibly being an effective treatment alternative for patients refractory to current pharmacologic and psychotherapeutic strategies, psychiatric neurosurgery may be cost-efficient. A study" has shown that psychiatric neurosurgery may be less expensive than long-term conservative treatments with medications and psychotherapy. In addition, other reports:" show that the number and length of hospital visits were significantly decreased following psychiatric neurosurgery on severe OCD patients.

One of the challenges of treating psychiatric disease is the quantitative analysis of patients before and during the course of treatment. Modern psychiatric testing batteries, such as the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Clinical Global Impressions Scale, and the Hamilton Depression Scale (HAM-D), allow for more accurate. objective evaluations of patients undergoing psychiatric neurosurgery. Today, state-of-the-art brain imaging

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techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography, allow the clinical investigator a noninvasive method to directly and precisely localize brain function and anatomy. Together, these tools can help eliminate some shortcomings of past studies of psychiatric neurosurgery.

THE NEUROCIRCUITRY OF PSYCHIATRIC DISEASE

To perform psychiatric neurosurgery, appropriate surgical targets must be chosen; therefore, the pathophysiology of psychiatric disease must be elucidated. Our understanding of the neurocircuitry of psychiatric disorders is rapidly evolving. Cortico-basal ganglio-thalamic interaction is fundamental in the pathogenesis of various psychiatric diseases in humans (Figure 1). In the mid-1980s, DeLong et al[9] first suggested that there were two coordinated loops passing through the basal ganglia to the thalamus: (1) a "motor" loop that centers on the sensorimotor, caudate/putamen, globus pallidus (GP), thalamus, and premotor areas; and (2) an "associative" loop that involves cortical association areas, caudatelputamen, GP, subthalamic nucleus, and substantia nigra. The modern neurosurgical intervention in Parkinson's disease (PD) is based on this framework (Figure 2).

This article will focus on two of the most elucidated psychiatric diseases—OCD and affective disorders (both of which have been the targets of neurosurgical interventions).

Obsessive-Compulsive Disorder

While movement disorders, chronic pain, and psychiatric disease might seem dissimilar entities on the surface. they share common neural substrates. From the earliest observations of OCD. it was speculated that neuronal areas subserving motor function had a central role in its pathogenesis. Indeed, Freud[10] proposed that the neurologic substrate for the OCD patient's ego lies "at the motor end of the psychical system."? Tourette disorder, a disease characterized by motor tics as well as OCD-like symptoms. demonstrates the phenomenon of a neural substrate capable of producing motor as well as psychiatric disease states. Studies[11,12] demonstrating the strong clinical and genetic association between Gilles de la Tourette syndrome and OCD suggest that the basal ganglia plays a central role in the pathogenesis of OCD symptoms. A basal ganglia circuit, similar to the one implicated in PD, has been proposed to explain the

"Cortico-basal ganglio-thalamic interaction is fundamental in the pathogenesis of various psychiatric diseases in humans."

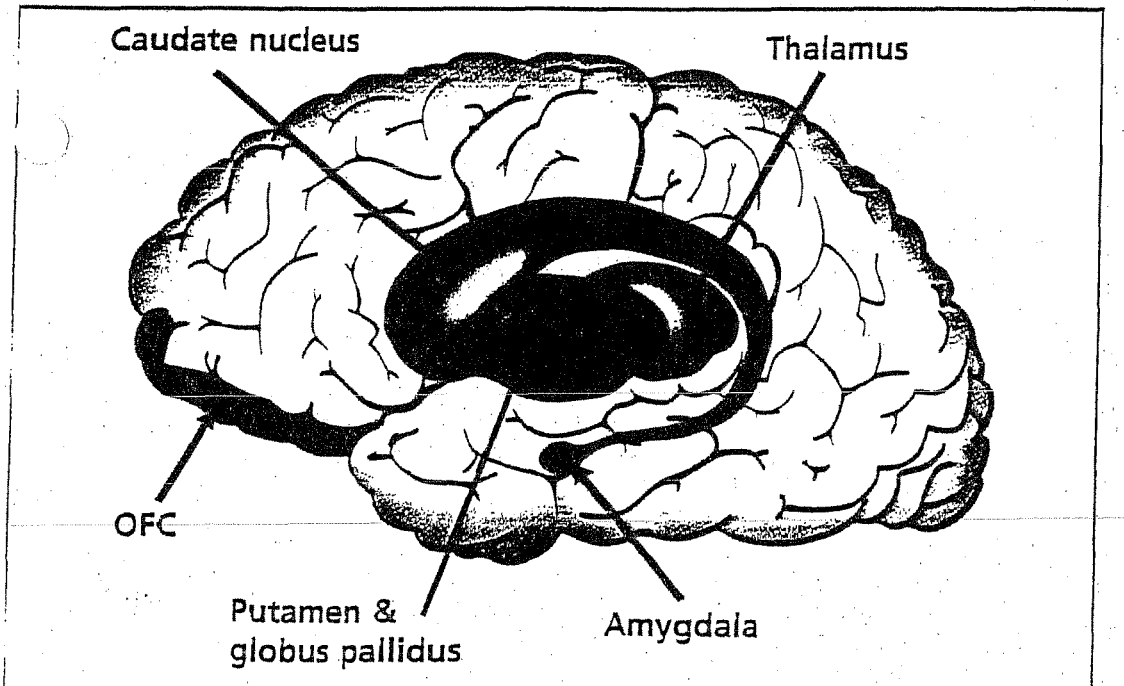

FIGURE 1. Basal ganglia and associated structures involved in psychiatric disorders. Note that medial structures. such as cingulate gyrus, fornix. mammillary bodies. hypothalamus. and midbrain nuclei, are not depicted.

OFC=orbitofrontal cerebral cortex.

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production of both motor and obsessional symptoms in Tourette disorder.':' Further analysis of the clinical spectrum of PD ha5 revealed many striking similarities between PD (a "motor" disease) and various psychiatric diseases, such as OCD and affective disorder.[14,15]

Based on these observations and the serotonergic hypothesis of OCD pathogenesis, Modell and colleagues[16] proposed a neuronal architecture for the basis of OCD. This model hypothesizes that the primary pathogenic mechanism lies in a dysregulation of the basal ganglia/limbic striatal circuits that modulate neuronal activity in and between posterior portions of the orbitofrontal cortex (OFC) and the medial, especially dorsomedial, thalamic nuclei (Figure ***3).***

These are three components to this neuronal model of OCD. The first involves a reciprocal positive-feedback loop involving the OFC and the dorsomedial thalamic (DM) nucleus by way of the anterior limb of the internal capsule. The corticothalamic projection is excitatory and mediated primarily hy glutamate and aspartate. Although the reciprocal thalamocortical projection's neurotransmitter remains to Le identified, multiple studies[14,16] suggest that it is also excitatory.

The second component of Modell's OCD model involves the OFC, the ventral striatum, the ventral pallidum. and the DM nucleus. While the transmissions of the ventral striatum to the ventral pallidurn involve multiple neurotransmitters, including γ-aminobutyric acid (GABA) and substance P, the output of this pathway by way of the ventral pallidum to the thalamus is almost exclusively inhibitory, mediated by GABA. This component is thought to serve as a modulator for the excitatory positive-feedback orbitofrontal thalamic loop described earlier. Another vital aspect of this second component of the OCD model involves serotonergic projections **from** the dorsal raphe nuclei of the midbrain to the ventral striatum. These are speculated to be

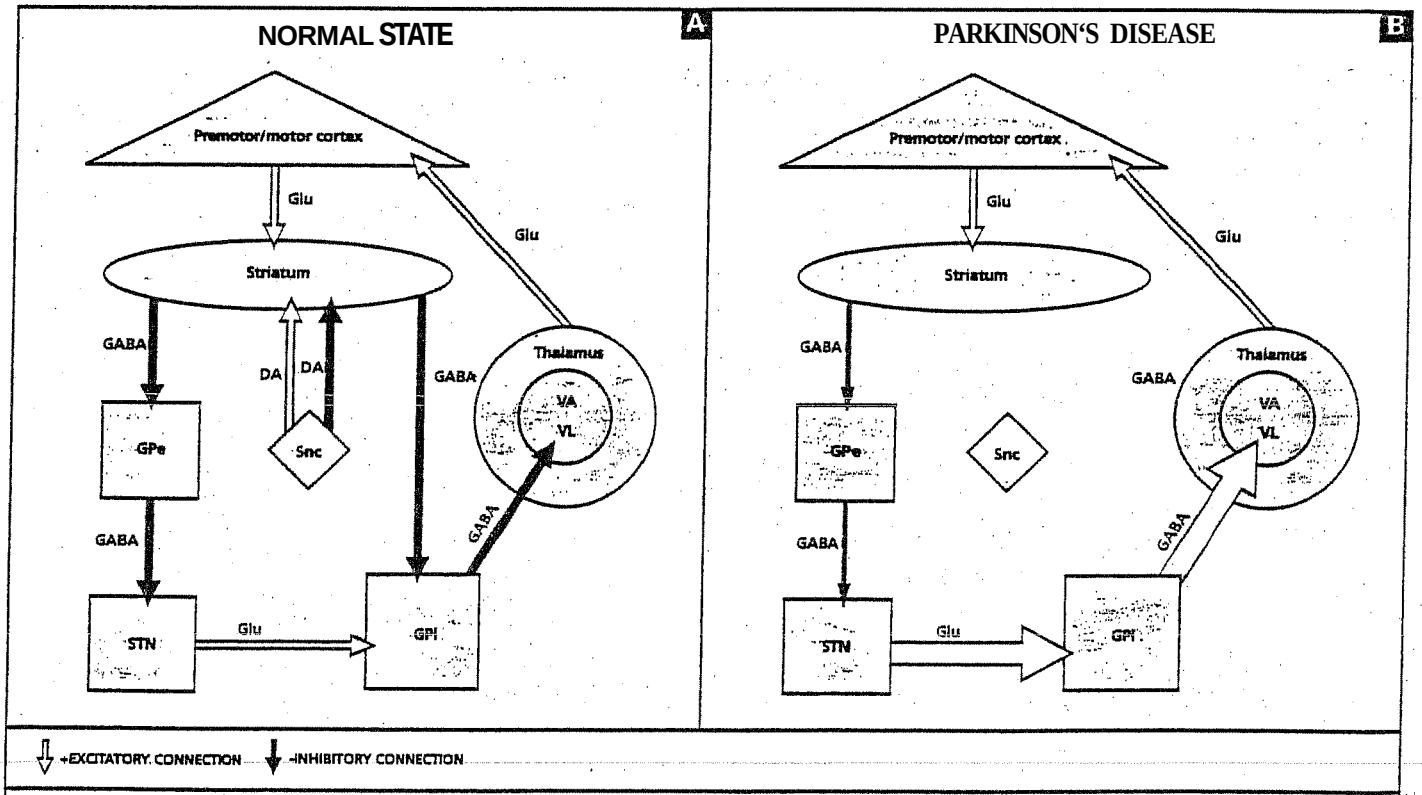

FIGURE 2. Schematic of basal ganglia function. **Loss** of dopaminergic input to the striatum due to substantia nigral degeneration results in dysregulation in basal ganglia function. The net effect is excessive inhibitory influence of the globus pallidus interna on the ventralis lateralis and ventralis anterior thalamic nuclei. Such abnormal inhibitory influence gives rise to the symptoms of **Parkinson's** disease. Black arrows represent inhibitory connections. White **arrows** represent excitatory connections.

Glu=glutamate; GABA=γ-aminobutyric acid: DA=dopamine; GPe=globus pallidus externa; Snc=substantia nigra pars compacta; VA=ventralis anterior thalamic nucleus; VL=ventralis lateralis thalamic nucleus; STN=subthalamic nucleus; GPi=globus pallidus **interna.**

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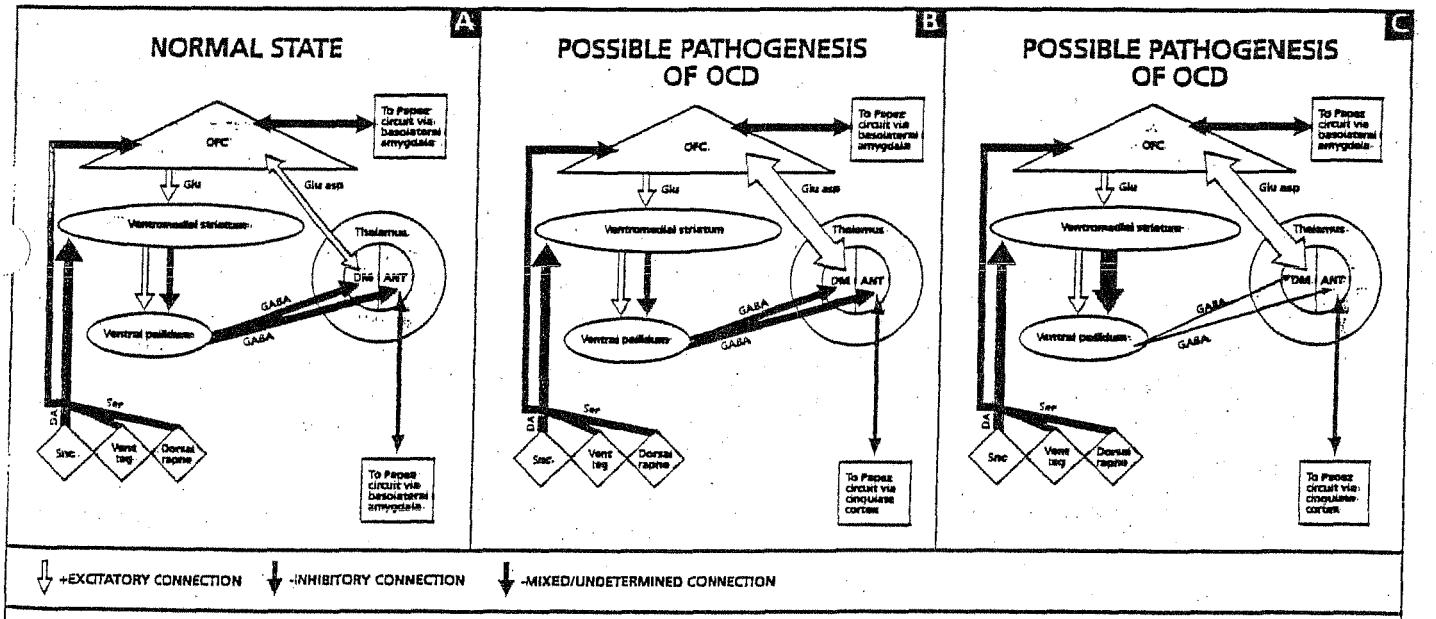
inhibitory in nature.

The third constituent of this model involves the limbic system and the Papez circuit (Figure 4). At its core, **OCD** is'an anxiety disorder; and the impact of the patient's various obsessions and compulsions on his or her emotional state is the hallmark of the disease. In **1937,** Papez" concluded that participation from the cerebral cortex is essential for the subjective emotional experience and that emotional expression is dependent on the integrative action of the hypothalamus. Papez devised a circuit based on his observations on neuroanatomic connections to integrate these two structures. The pathway begins from the hippocampal formation to the mamillary body via the fornix. The projection, via the mamillothalamic tract, continues to the anterior thalamic nuclei. From here. there are widespread connections *to* the cingulate gyrus. In the aforementioned OCD model. there are numerous connections to the Papez circuit via the DM nucleus and the OFC. These connections could subserve the anxiety/emotional component of OCD.

By synthesizing these three components, obsessive-compulsive (OC) symptoms could occur when an aberrant positive-feedback loop develops in the reciprocally excitatory frontothalamic neuronal pathway that is inadequately inhibited/modulated by striatopallidothalamic activity; **thus,** OC symptoms would be expected to appear when striatopallidothalamic activity is abnormally **decreased** or when orbitofrontothalamic activity is abnormally increased. Conversely, either increasing the modulating loop or decreasing the excitatory loop would be expected to result in a concomitant decrease in OCD symptom expression.[16] Additionally, modulation of the Papez circuit may in turn eliminate some of the disturbing affects that obsessions and compulsions have on a patient's emotional state. This mechanism is analogous to the model of PD in which dysregulation in the corpus striatum. second? to loss of dopaminergic transmission from the substantia nigra pars compacta. results in the increase in tonic inhibition of the ventralis lateralis and ventralis anterior thalamic nuclei by the internal segment of the GP interna



FIGURES 3. Schematic of OCD model. This diagram demonstrates the basal ganglia structures involved in the pathogenesis of OCD. The specific anatomic structures of the direct and indirect pathways (GPe. STN. GPi) shown in Figure 1 have been condensed into net excitatory/inhibitory influences for the **purposes** of clarity. The excitatory connections from the OFC to the ventromedial striatum and thalamus run through the anterior internal capsule and the substantia innominata. Abnormalities of dopaminergic and. especially, serotonergic influences on thr orbitalfrontal cortex (OFC) and the ventromedial striatum could give rise to one of two different scenarios: An abnormal excess of reciprocally excitatory activitv between the dorsomedial thaiamus and the OFC (Figure 3B) or excessive activity through the direct basal ganglia pathway resulting in abnormally decreased inhibitory influence of the GPi on the DM thalamus (Figure 3C). Obsessive-compulsive symptoms would thus be expected to appear when striatopallidothalamic activity is abnormally decreased or when orbitofrontothalamic activity is abnormally increased.

OFC=orbitofrontal cerebral cortex: Glu=glutamate; Asp=aspartate; GABA=γ-aminobutyric acid: DM=dorsomedial thalamic nucleus; ANT=anterior thalamic nucleus: DA=dopamine; Ser=serotonin; Snc=substantia nigra pars compacta; vent teg=ventral tegmentum of midbrain.

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