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Obsessive-Compulsive Disorder: Symptoms, Treatments, Genetics, Brain Circuits & Neurosurgery

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Obsessive-Compulsive Disorder (OCD): Summary

Core Symptoms:

- Obsessions
  - recurrent, unwanted and unpleasant thoughts or images causing marked anxiety or distress
- Compulsions
  - repetitive, ritualistic behaviors that a person feels driven to perform
- Obsession & compulsion subtypes fall along specific dimensions
- Mood &/or Anxiety disorder comorbidity in the majority of cases
- Familial, usually early-onset (often childhood, most by age 18)
- Cause (s) remain unknown
- Consistently associated with functional neuroimaging abnormalities
- Occasionally associated with focal brain injury
- Behavior therapy & medications are effective
- Highly refractory ("intractable") cases can improve with neurosurgery

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Recognizing OCD (it's not always this easy)

Contamination/Cleaning - "As Good as it Gets"

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OCD is Relatively Common around the World

That, plus early onset, made OCD the 10th Leading Cause of Disability in Developed Countries (WHO, 1997)

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OCD can be Disabling

QuickTime™ and a H.264 decompressor are needed to see this picture.

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Other Common OCD Symptoms

- Harm-related thoughts or images
  - Lead to avoidance, washing, checking, reassurance-seeking
- Disturbing aggressive, sexual or religious thoughts or images ("Taboo Thoughts")
- Symmetry/Exactness – Leads to ordering/arranging
- Compulsive Hoarding
- Incompleteness
  - Not based in fear of "something bad happening."
  - Things don't feel done; rituals continue until patient "feels right".

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A man will not go to public places because he fears he will have intolerable sexual thoughts or falsely accuse someone of committing a crime.

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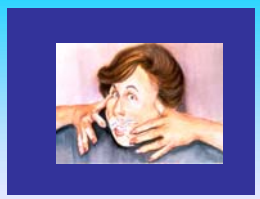

A woman's persistent urge to shout out an obscenity or blasphemy in church can be suppressed only by counting slowly backward from 100 to one.

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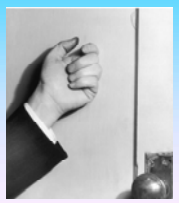
A man feels a drop in his eye as he looks up while passing a building and cannot dismiss the thought that someone with AIDS has spit out of a window.



To reassure himself, he proceeds to knock on the door of every office in the 10-story building.

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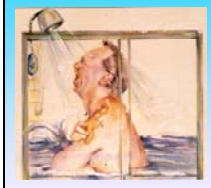
For eight years a man spends an hour a day washing his hands, showering, and dressing. He has stopped grooming and changing his clothes because the rituals required take too long.



He stays in his room, eating only a few carefully selected foods and constantly checking to see that furniture is in exactly the "right" place.

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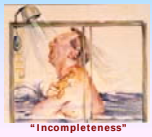
OCD Symptoms (& Pts) are Heterogeneous

Contamination
& Excessive Cleaning

"What if?":
Doubt & Checking

Symmetry, Order, Arranging



"Incompleteness"
Must be "just right"

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Co-occuring Disorders

- 90% - 1 or more Axis I dx (lifetime)
- 75% - Mood disorder
- 53% - Other anxiety disorder
- 26% - Substance use disorder
- 15% - Impulse Control disorder
- 10% - Eating disorder
- 38% - 1 or more Personality Disorders

Pinto et al., 2006

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Exposure & Ritual Prevention

- Patients actively confront feared things & situations.
- Person is encouraged not to carry out compulsive rituals after being exposed.
- Repeated exposures without the feared consequence happening result in extinction of the anxiety response, i.e., compulsive rituals. Extinction is a kind of learning.
- Very effective in people who agree to do it
  - may be as little as half the patients in some studies.
- Availability is limited by time needed; availability of expert therapists; insurance restrictions.

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CBT in the "Real World"

- 55% attended at least one session with a CBT therapist (M=37 sessions, SD=45)
- 38% received at least 13 sessions of CBT lifetime
- 24% received a continuous course of at least 13 sessions of CBT
- 6% received intensive (3x or more per week)
- All but 4 participants were also taking medications

Mancebo et al. 2006

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Medications for OCD

- Serotonin Reuptake Inhibitors (SRIs)

  -Clomipramine (Anafranil)
  -Fluvoxamine (Luvox)
  -Paroxetine (Paxil)
  -Venlafaxine (Effexor)
  -Escitalopram (Lexapro)
  -Fluoxetine (Prozac)
  -Sertraline (Zoloft)
  -Citalopram (Celexa)

- SSRIs are used before clomipramine due to less side effects and better safety profile; but some data suggest clomipramine is more effective.
- Medication combinations:
  - SRI + Antipsychotics (1st or 2nd generation)
  - SRI + Benzodiazepine anxiolytics

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Long-Term Treatment Options

- Combined Therapy (meds plus CBT) is recommended for many, especially if getting off medication is a goal.
- OCD is usually chronic
- Relapse Rates for treatments when used alone:
  - 24% of E/RP alone
  - 70-90% of SSRI alone
- Significant numbers of patients do not benefit meaningfully from existing treatments (20-35% of the total). Some of them are disabled by OCD, others can manage, but with a degraded quality of life.

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Genetics

(natural history and family patterns of illness)

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OCD Runs in Families:

Compared to relatives of healthy controls, relatives of people with OCD were 3 - 5 times more likely to have OC symptoms or OCD

Obsessions were more familial than compulsions

Tics or OC personality did not increase "familiality" of OCD

Disorders co-occur with OCD, esp. mood (Anx. Dos vary by study)

The earlier someone developed OCD, the more likely relatives were to have OCD too (Only OCD with age of onset < 18 was familial)

And people with OCD were less likely to marry
And even less likely to have children
(makes genetic studies hard)

(Nestadt et al., 2000)

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OCD Inheritance Within Families

- "Segregation analysis" looks for patterns that hint at how OCD may be inherited:
- *Is there a single gene?* (No)
- *Multiple genes?* (Probably)
- *Could there be a gene with a "major effect"* - which increases risk for illness substantially? (studies suggest this)

- Genetic Risk Prob. Differs by Symptom Subtypes

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"Candidate Genes"

- Genes coding for proteins possibly involved in OCD have variants (alleles) with different effects on brain function. So, people with some of these forms might be at greater risk.
  e.g., Serotonin (synthesis, transport, receptors, metabolism)
- Some evidence that gene variants are associated with OCD.
- Promising, but results generally not well-replicated.
- Better "phenotypes" (symptom dimensions) & whole genome association might lead to better understanding of OCD genetics.
- Current whole genome association study underway at Butler/Brown

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Towards "Natural Kinds" of OCD

Better phenotypes should get us better genetic data

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What goes on in the Brain in OCD?

High metabolism in fronto-basal regions

(before treatment)

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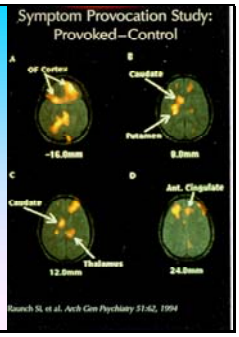
Blood flow increases during OC symptoms --
in cortico-basal-thalamic circuits



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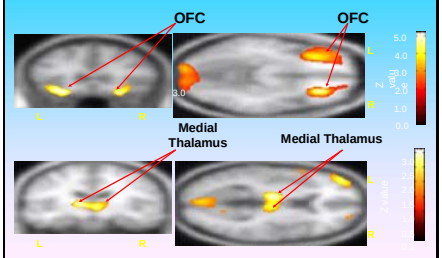
Metabolic Decreases in OCD Patients after Paroxetine (Paxil) Treatment



Saxena et al, 2001

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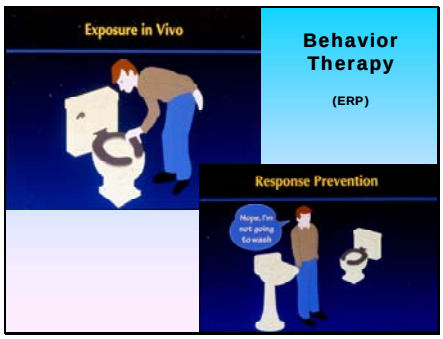

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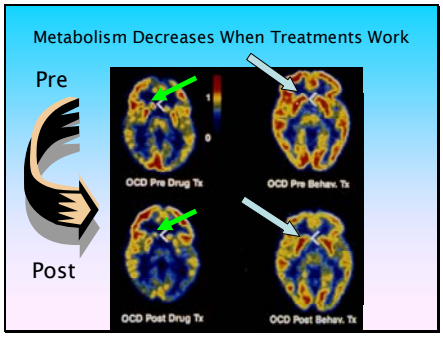

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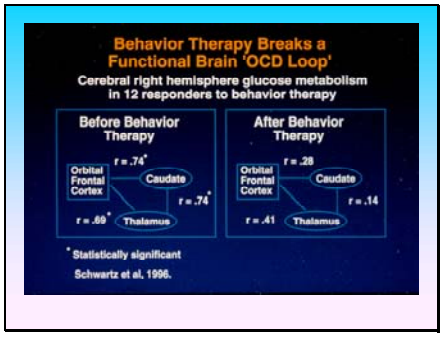

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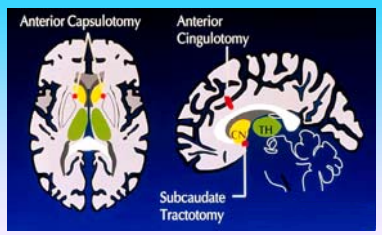
Stereotactic Lesion Procedures for OCD and MDD



Effectiveness in Open Studies: 30 - 70% (Greenberg et al., 2003)

TH=thalamus; CN=caudate nucleus.

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Neurosurgery for OCD: Collaborators & Disclosures

Butler/RI Hosp/Brown
Linda Carpenter
Gerhard Friehs
Paul Malloy
Richard Marsland
Georg Noren
Lawrence Price
Steven Rasmussen
Stephen Salloway
Audrey Tyrka

Belgium
Paul Cosyns
Loes Gabriels
Bart Nuttin

MGH
Darin Dougherty
Scott Rauch

Cleveland Clinic
Kenneth Baker
Cynthia Kubu
Donald Malone
Ali Rezai

Rochester
Suzanne Haber
(Anatomy)

Pittsburgh
Anthony Grace
(Physiology)

Univ. of Florida
Wayne Goodman
Kelly Foote
Michael Okun
N. A. Shapira

Cornell
Joseph Fins
(Ethics)

Medtronic
Keith Mullett
Mark Rise
Paul Stypulkowski
Roy Testerman

Funding (US sites):
NARSAD; Medtronic, Inc.; NIMH

DBS: Off Label for OCD	FDA Humanitarian Device Application Submitted

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What are the risks,
and how do we minimize them?

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Patient Selection: Principles

- Accurate diagnosis
  (longitudinal perspective, multiple informants)
- Sufficient severity and chronicity
- Nonresponse to adequate conventional treatments, documented
- Capacity to consent (monitored)
- Capacity for close, long-term followup
- *The treatment team is fully committed to provide that follow-up.*

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Leksell Gamma Knife

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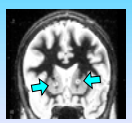
Gamma Capsulotomy in OCD:
Addition of Ventral "Shot" Associated with Improvement



Single lesions,
mid-capsule:
Ineffective

Ventral lesions added:
about 60% respond

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QuickTime™ and a
decompressor
are needed to see this picture.

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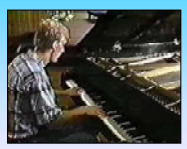
Before



After
Gamma Capsulotomy
(1 year post-shots 3 and 4)

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Behavior therapy can become possible after neurosurgery

QuickTime™ and a
decompressor
are needed to see this picture.

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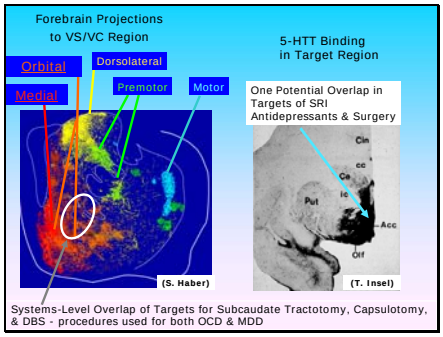

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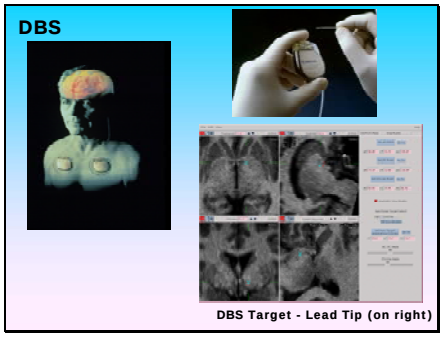

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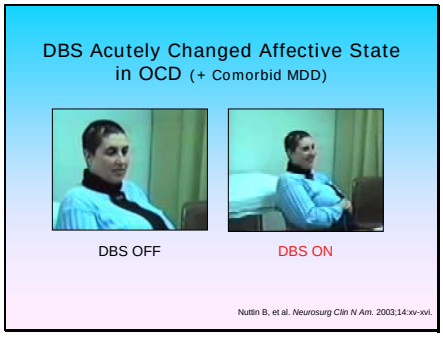

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Before & After VC/VS DBS for OCD

← Before

QuickTime™ and a
H.263 decompressor
are needed to see this picture.

QuickTime™ and a
H.263 decompressor
are needed to see this picture.

After DBS x 2 years →

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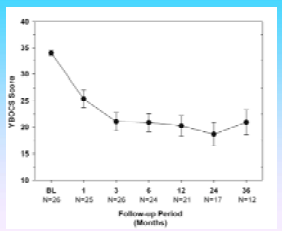
OCD Severity During Chronic DBS



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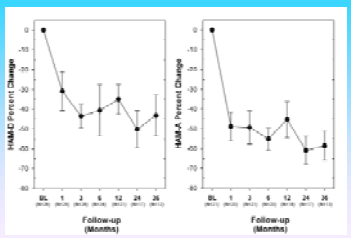

Depressive & Anxiety Symptoms

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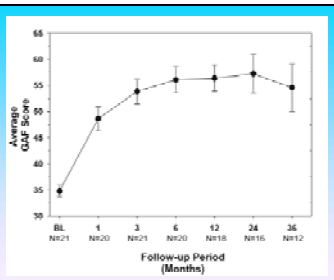

Global Assessment of Functioning During DBS

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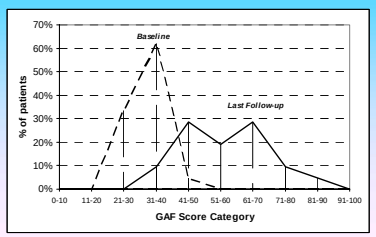
Global Assessment of Functioning:
Distribution Pre & Post DBS for OCD



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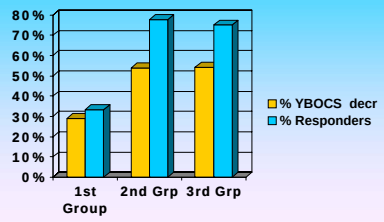
"Learning Curve": Outcomes in Early, Middle, and Most Recent Patient Groups



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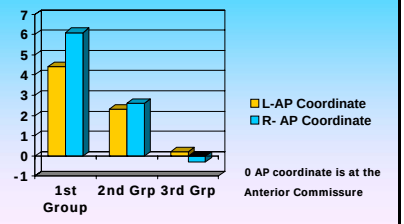
Anterior-Posterior Lead Site in Early, Middle, and Most Recent Patient Groups



0 AP coordinate is at the Anterior Commissure

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DBS for OCD: Adverse Effects

- Surgical
  - Small hemorrhage without symptoms or sequelae (1/10)
  - Superficial infection (1/10)
  - Single intraoperative seizure (1/10)
- Stimulation
  - Mood Elevation/Hypomania (Mins - Hrs in 3 pts; lasted 1/10)
  - Sensorimotor (eg, facial "hemi-smile," paresthesias)
  - Insomnia
  - Autonomic
  - Memory flashbacks
  - Anxiety and/or Panic (2/10)
- OFF effects
  - Symptom return (worsening in mood > OCD Sx)
- No AEs were persistent

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DBS for OCD: Neuropsychological Performance

Multiple cognitive domains tested before & after DBS x ≈10 mo., using practice corrected change scores.

- No pattern of pervasive worsening in any patient.
- Improvements in immediate [$t(9)=4.39$, $p<.01$, $d = 1.4$] and delayed [$t(9)=2.55$, $p<.05$, $d = 0.8$] prose passage recall
- No other significant changes.
- Effect size ($d = 0.5$) suggests visuospatial skills ($t(9)=1.66$, $p>.05$), might have shown improvement in a larger sample.

C. Kubu et al., under review

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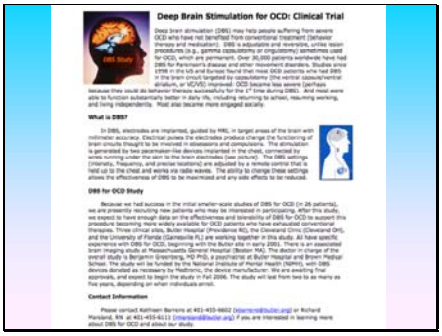

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OCD Resources

- OC Foundation (www.ocfoundation.org)
- Treatment manuals for professionals
  - Kozak & Foa (1997) – *Mastery of OCD*
  - Stekettee & Frost (2007) –*Compulsive Hoarding and Acquiring*
  - Wilhelm & Steketee (2006) -*Cognitive Therapy for OCD*
- Self-Help manuals
  - *Brain Lock*
  - *OCD Workbook*
  - *Stop Obsessing!*
  - *Compulsive Hoarding and Acquiring*
  - *Buried Treasures*