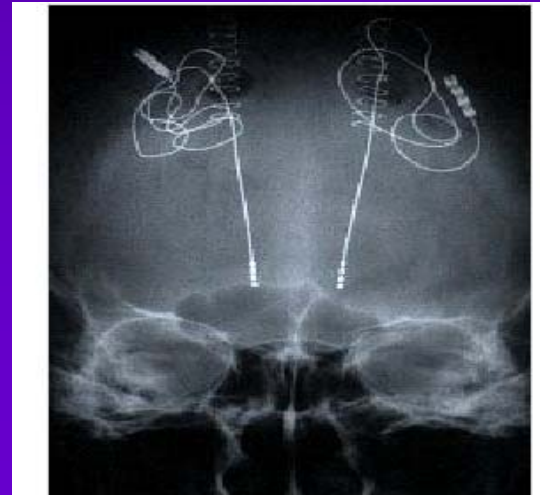


# Deep Brain Stimulation

A (Cautious) Radical Approach  
to Treatment Resistant  
Depression

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# Deep Brain Stimulation

- **Environmental Background**
  - Prevalence/Treatment Gap
  - History of Psychosurgery/Neurostimulation
- **Enabling Conditions**
  - Depression Neurocircuitry
  - Neurosurgical Techniques
- **Preliminary Results in TRD**
  - Subcallosal Cingulate Gyrus –Toronto Trials
  - Alternative Targets
- **Cautions and Future Directions**
  - Ethics
  - Evidence-based outcomes

# Rationale for Neurostimulation Therapies

- More than 30% of patients fail to achieve remission with current psychotherapies and pharmacotherapies
- Growing recognition of recurrent-chronic-degenerative nature of major depressive disorder
- Limited acceptance of ECT
- Emerging models of depression neural circuitry
- Advances in microsurgical techniques permit image guided interventions

# Deep Brain Stimulation

Disorder	Patients Treated	Deep Brain Targets
Parkinson's Disease	30,000-40,000	Globus pallidus internus, Subthalamic nucleus
Chronic Pain	1500-2000	Ventral posterior medial and lateral thalamic nuclei, periventricular and periaqueductal gray matter
Tremor	500-1000	Ventralis intermedialis thalamic nucleus, zona incerta
Dystonia	300-500	Globus pallidus internus
Cluster Headache	30-50	Posterior hypothalamus
Epilepsy	20-50	Anterior thalamic nucleus
OCD	20-50	Anterior limb of internal capsule
<b><i>Depression</i></b>	<b><i>~ 100</i></b>	<b><i>SubCallosal Cingulate, Internal Capsule, Nucleus Accumbens</i></b>
Tourette's Syndrome	10-50	Ventromedial thalamic nuclei, anterior limb of internal capsule, globus pallidus internus

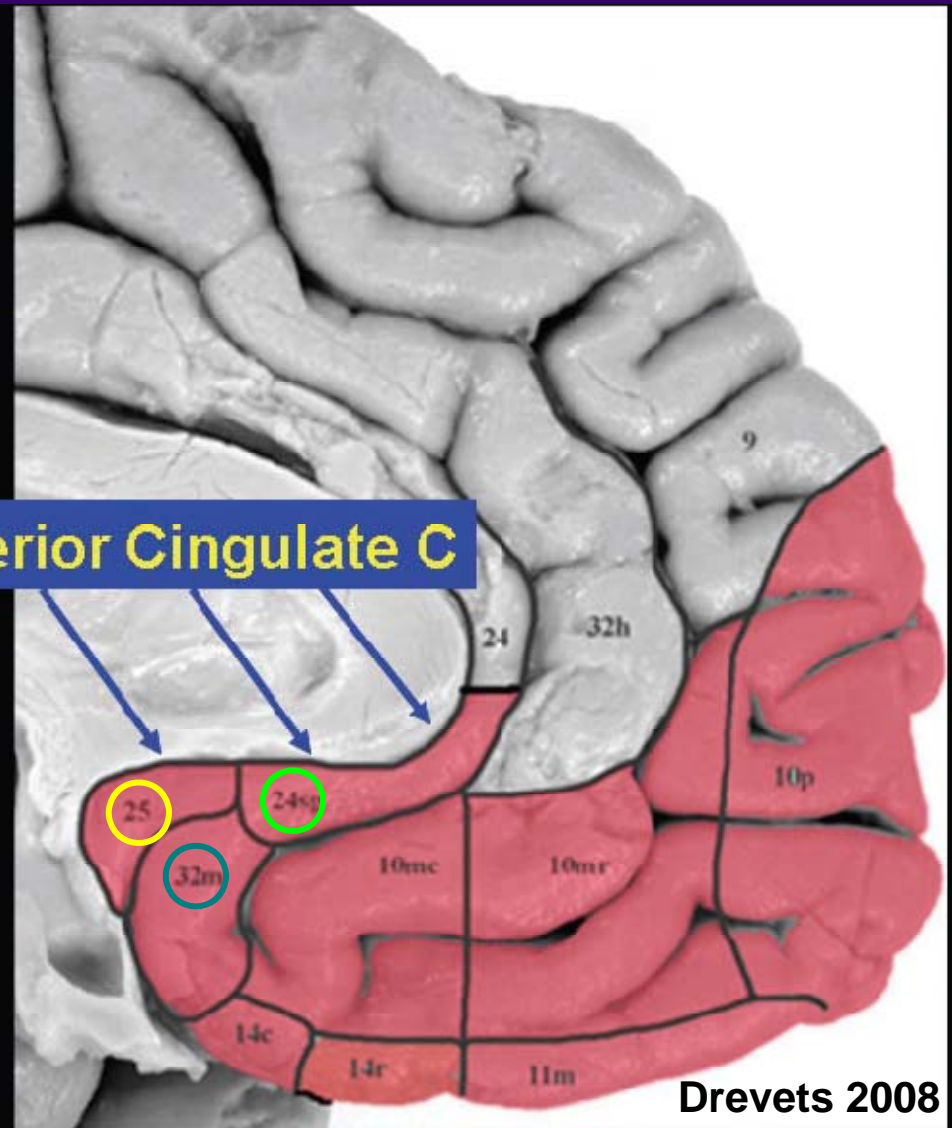
Modified from Pereira et al, 2007

# Subcallosal Cingulate Gyrus Volume

- Reduced subcallosal cingulate (BA25) volume in MDD vs. Controls
  - Accounted for by patients with more than 3 untreated episodes
- No differences in subgenual prefrontal cortex (BA24).
- No differences for BA32

Yucel et al, 2008

Anterior Cingulate C

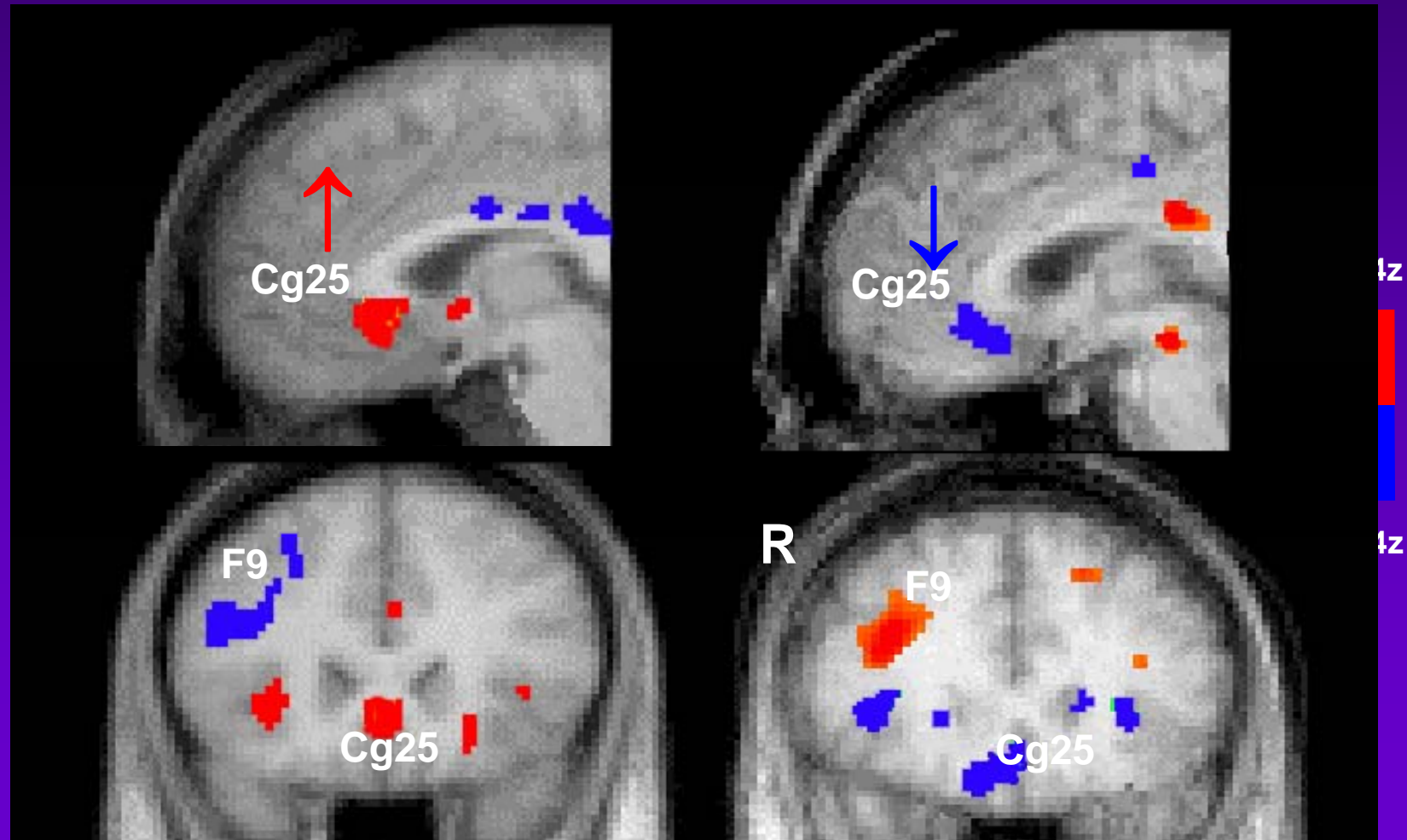


Drevets 2008

# Subcallosal Cingulate (BA 25) in Depression

Acute activation BA25  
in Transient Sadness

Reduction in BA25  
Depression Recovery



Mayberg H, et al. Am J Psych 1999



# Deep Brain Stimulation for Treatment-Resistant Depression

## Clinical Study

Helen S. Mayberg,<sup>1,2,\*</sup> Andres M. Lozano,<sup>3,\*</sup>  
Valerie Voon,<sup>4</sup> Heather E. McNeely,<sup>5</sup>  
David Seminowicz,<sup>6</sup> Clement Hamani,<sup>3</sup>  
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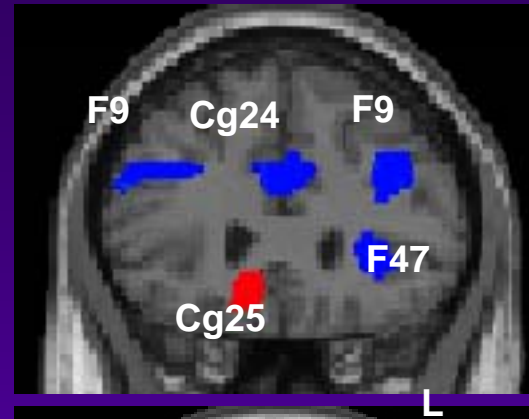
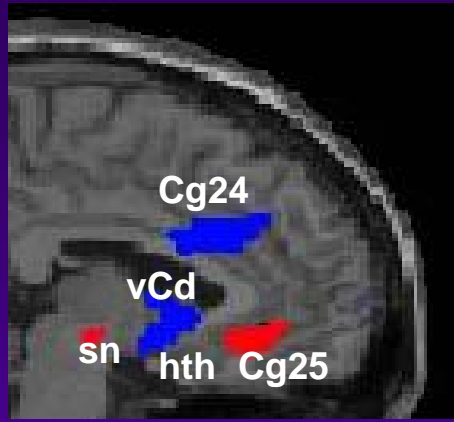
<sup>4</sup>Department of Psychiatry  
University Health Network  
University of Toronto  
Toronto, Ontario, M5P 2P2  
Canada

### Summary

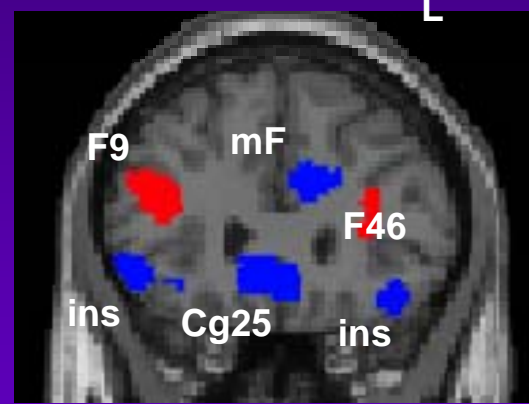
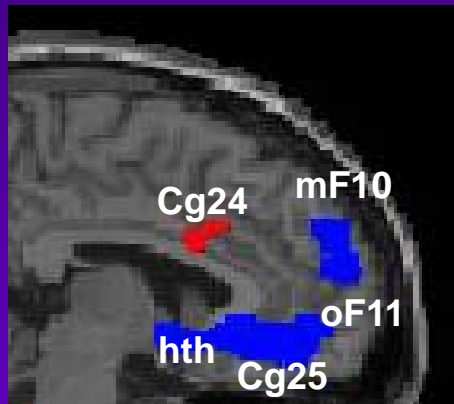
Treatment-resistant depression is a severely disabling disorder with no proven treatment options once multiple medications, psychotherapy, and electroconvulsive therapy have failed. Based on our preliminary observation that the subgenual cingulate region (Brodmann area 25) is metabolically overactive in treatment-resistant depression, we studied whether the application of chronic deep brain stimulation to modulate BA25 could reduce this elevated activity and produce clinical benefit in six patients with refractory depression. Chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in four of six patients. Antidepressant effects were associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites, measured using positron emission tomography. These results suggest that disrupting focal pathological activity in limbic-cortical circuits using electrical stimulation of the subgenual cingulate white matter can effectively reverse symptoms in otherwise treatment-resistant depression.

# DBS Effect on Cerebral Blood Flow

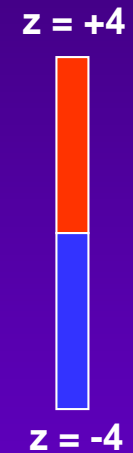
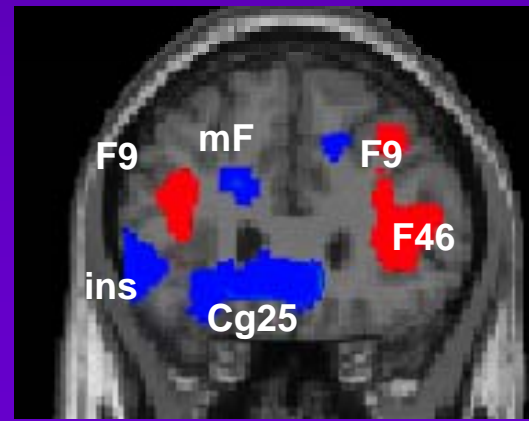
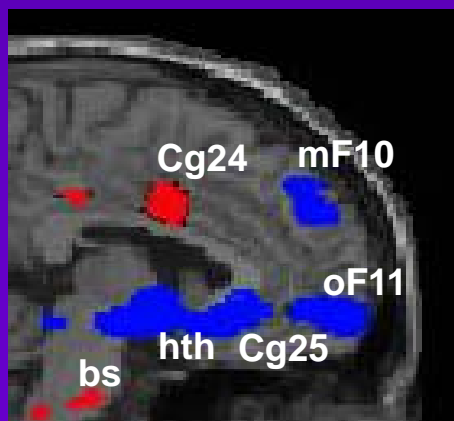
Baseline  
CBF PET  
N=5



3 months  
DBS  
R=3



6 months  
DBS  
R=3



x = -4

y = +28

# DBS to SCG-25 for TRD: *Individual Patient HRSD Scores*



Modified from Lozano et al, 2008

# Medication Status

- Pre-surgery

- 11: 2 antidepressants + atypical or lithium + BZD
- 5 : 1 antidepressant + atypical + BZD
- 2 : 1 antidepressant only
- 2 : No antidepressant, BZD only

- Post-surgery

- No new antidepressants were prescribed
- 10 patients received dose decrement or discontinued of an antidepressant

# Subcallosal Cingulate DBS : Adverse Effects

<b>Adverse Effect</b>	<b># of Occurrences</b>
<b>Wound infection</b>	<b>4</b>
<b>Peri-operative seizure</b>	<b>1</b>
<b>Headache</b>	<b>5</b>
<b>Pain at generator site</b>	<b>1</b>
<b>No adverse events</b>	<b>9</b>

# Neuroanatomical Targets for DBS-TRD

## SITE

## RATIONALE

- Subcallosal cingulate cortex – BA25
- 

- Theoretically driven by FDG-PET results in sadness, MDD and pharmacotherapy
- 

- Ventral internal capsule/ventral striatum
- 

- Mood benefits in comorbidly depressed OCD patients
- 

- Ventral Striatum/Nucleus Accumbens

- Dopamine rich reward pathways

# The Psychiatrist's Role in the DBS Team

- Assessment Diagnostic and Longitudinal

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- Stimulator adjustments Avoid excessive changes

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- Pharmacotherapy Aim for Reductions

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- Psychosocial Interventions Better use of CBT  
Involvement of spouse  
Workplace reentry

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- Team approach Integrated follow-up with  
neurosurgery and health care  
team in the community

# DBS-Scientific and Ethical Issues: Consensus Statement

- Support for continuing research
- Currently an investigational therapy
- Need for Comparative trials including vs ablation
- Perform only at expert centres
- Interdisciplinary team is essential
- Limited at this stage to adults
- Extensive pre surgical assessment is essential
- Expand measures into Quality of life and function
- Standardize Consent process
- No evidence to question ability of patients to consent
- Funding for 5-10 year follow up required

# Future of Neuromodulation Therapies

- Enhancing patient care
- Reducing marginalization of neuromodulation and surgical interventions
- Reinforces the link between Psychiatry and Neurosciences
- Building interdisciplinary collaborations
- Changing public perceptions of Psychiatry
- Challenge to identify optimal endophenotypes