Neuropsychiatric disorders and Deep Brain Stimulation

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Introduction

- DBS
- neuropsychiatric disorders
  - Tourette
  - OCD
  - “Depression"

DBS

History

1987: Benabid introduced Deep Brain Stimulation DBS as a treatment of movement disorders

- Widely applied for movement disorders, e.g Parkinson
- Influence of neuronal activity in basal ganglia
- New indication: psychosurgery / neuropsychiatry

1952-1953: first DBS experiments in humans by different groups.
Improvement compared to leucotomies (Monitz & Hess)

Mayo Clinic Proceedings 28(6), 1953.

OBSERVATIONS ON DEPTH STIMULATION OF THE HUMAN BRAIN THROUGH IMPLANTED ELECTROGRAPHIC LEADS

Reginald G. Bickford, M.B., M.R.C.P., Section of Physiology, Magnus C. Petersen, M.D., Rochester State Hospital, Henry W. Dodge, Jr., M.D., Section of Neurologic Surgery, and

An observation that may have some practical significance was that several of our psychotic patients seem to improve and become more accessible in the course of stimulation studies lasting several days. While it is possible that this effect was related to the unusual amount of attention paid to them during the studies, a more likely explanation is that the local stimulation was having a therapeutic effect comparable to that of electroshock. This aspect of localized stimulation studies requires further investigation since it may lead to a more specific, less damaging, and more therapeutically effective electrostimulation technic than can be achieved by the relatively crude extracranial stimulation methods in use at present.

by courtesy of Prof. M. Hariz

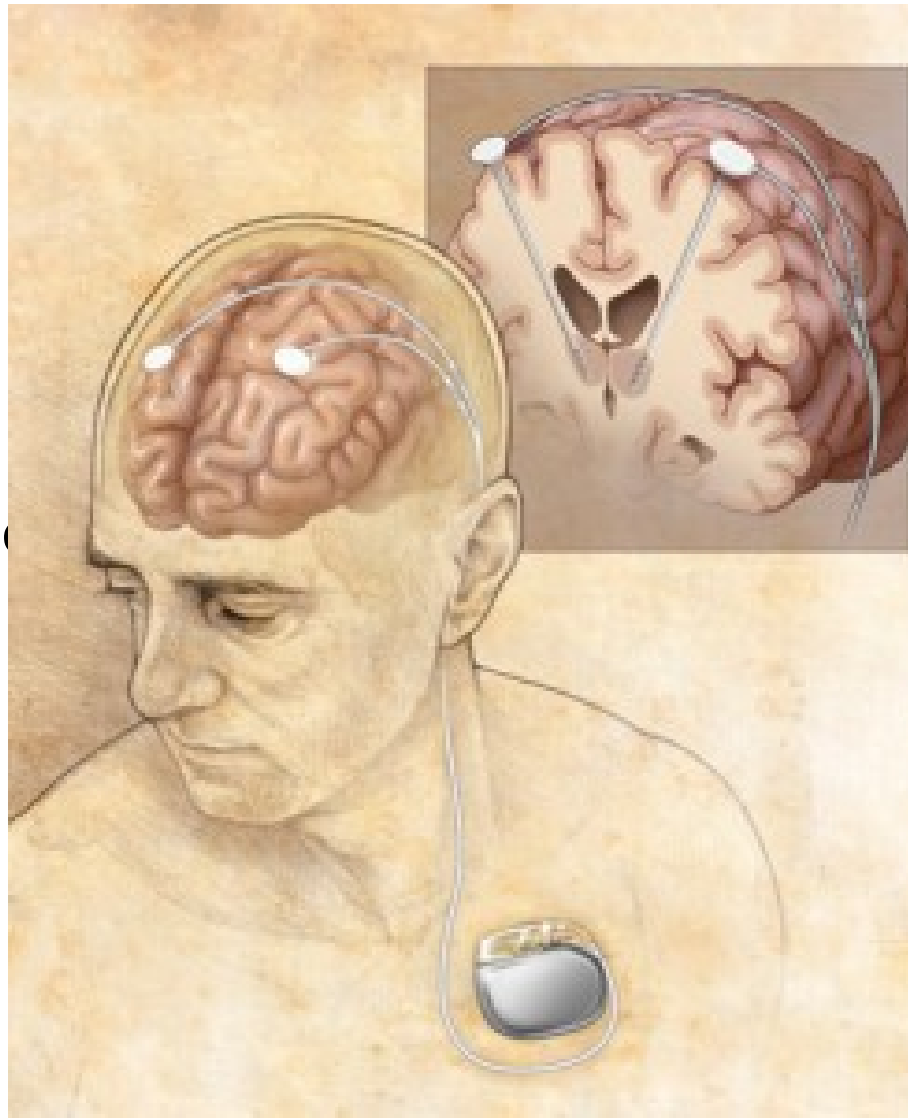
DBS

Uniform Selection criteria for DBS

- No other conservative treatment options
- Good physical and mental health

DBS

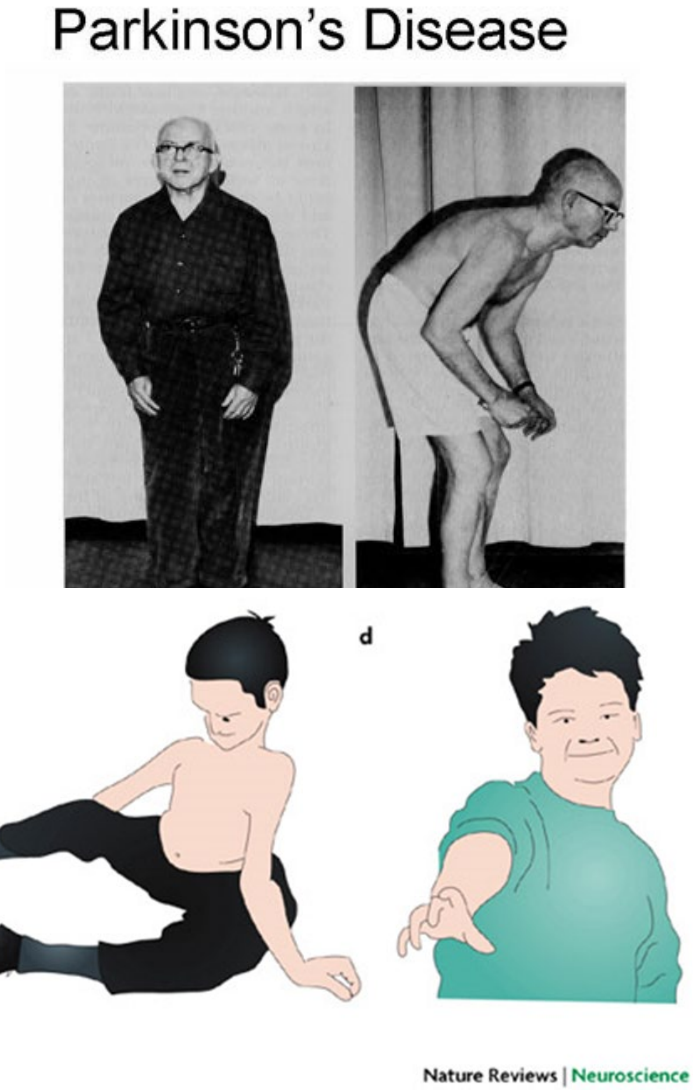
- Deep brain stimulation
  - Delivery of current (mA)
  - Brain parenchyma
  - Implanted electrodes
  - >160 000 patients implante
  - 2017:
    - 30 years anniversary



DBS

Movement Disorders

- Parkinson's disease
- Tremor
- Dystonia



DBS

Psychiatric Disorders

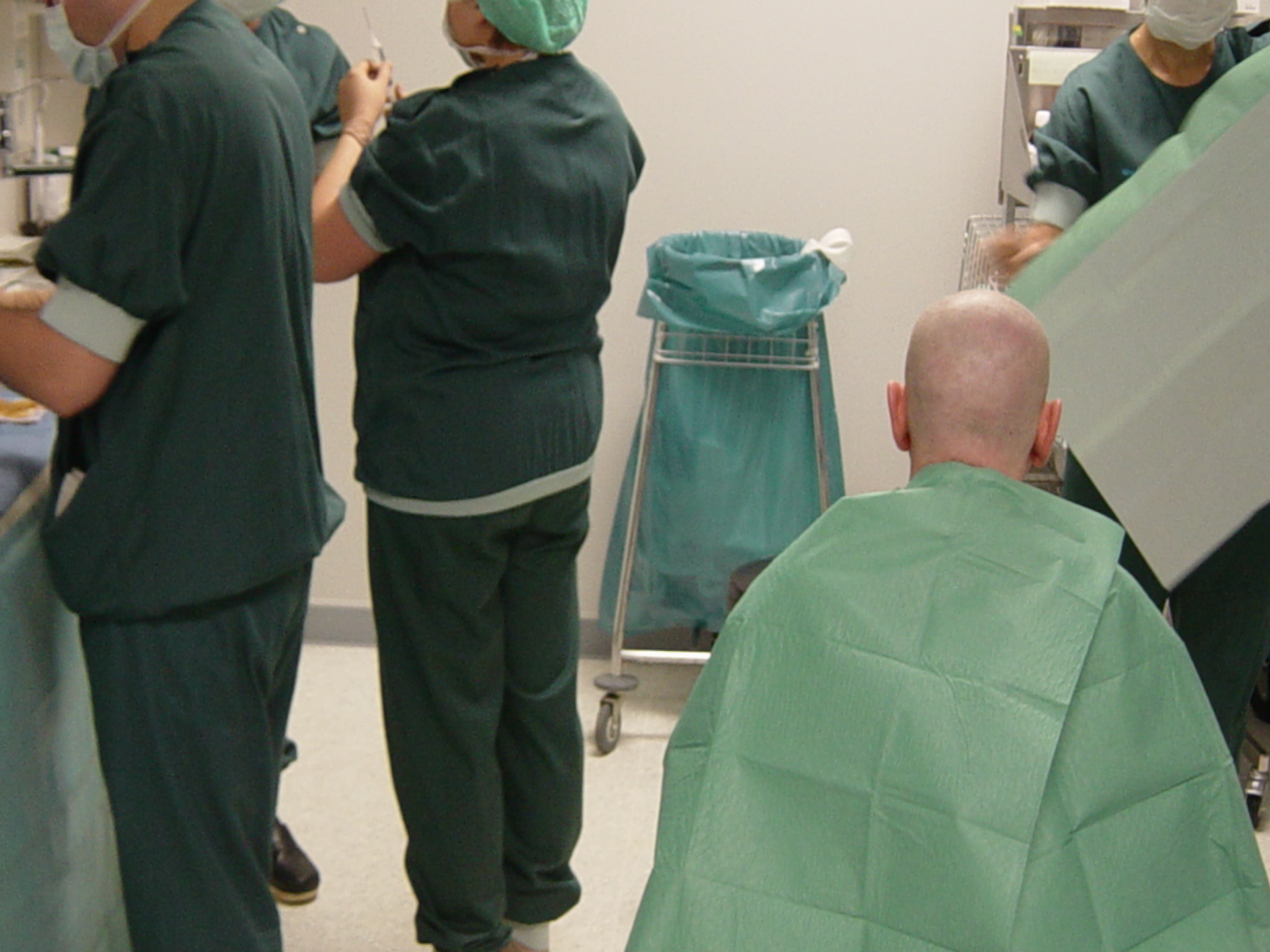
- Tourette syndrome
- Obsessive-Compulsive disorder
- *Depression, ADHD, Anorexia Nervosa, Alzheimer's disease etc*

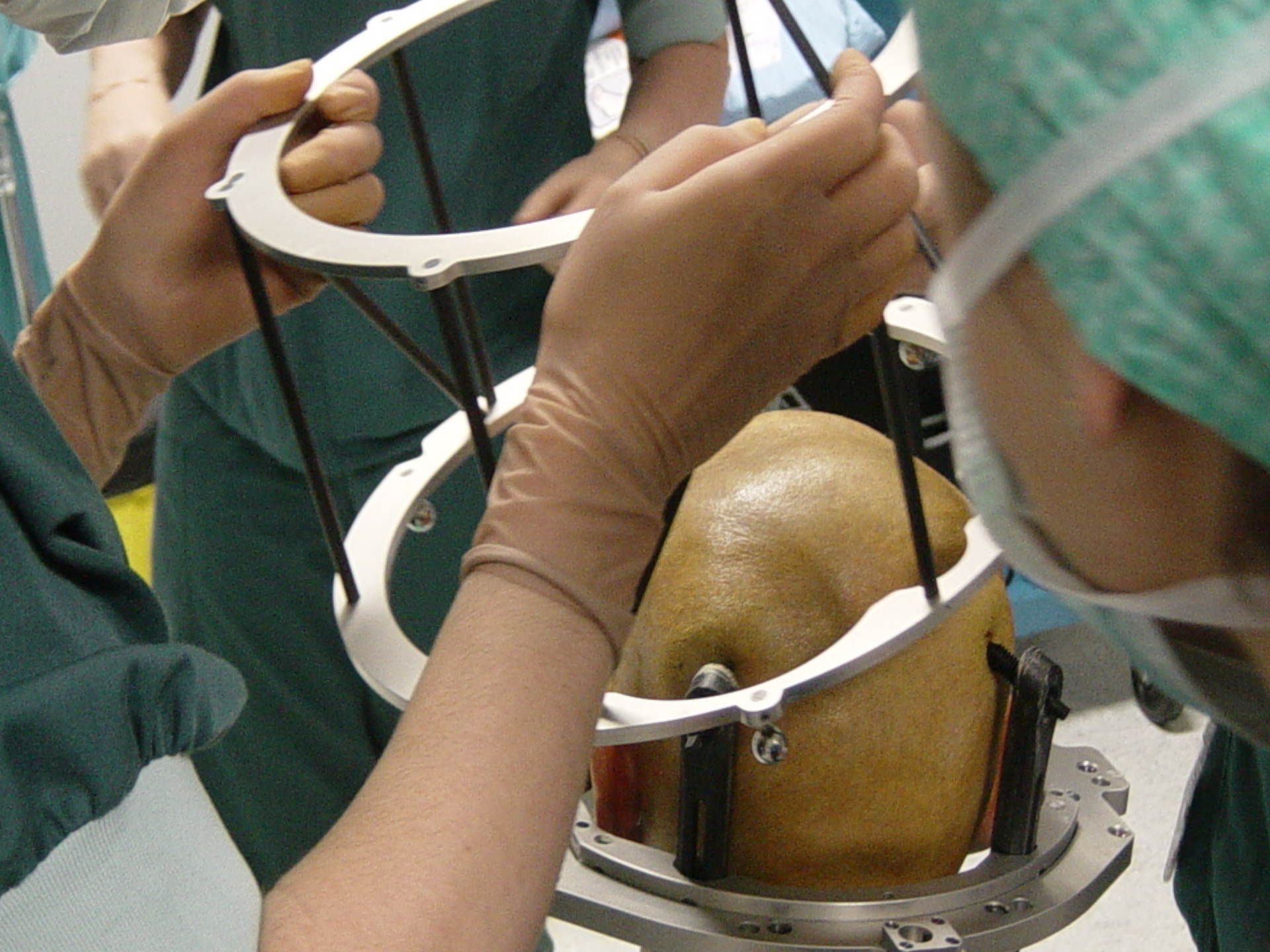
DBS

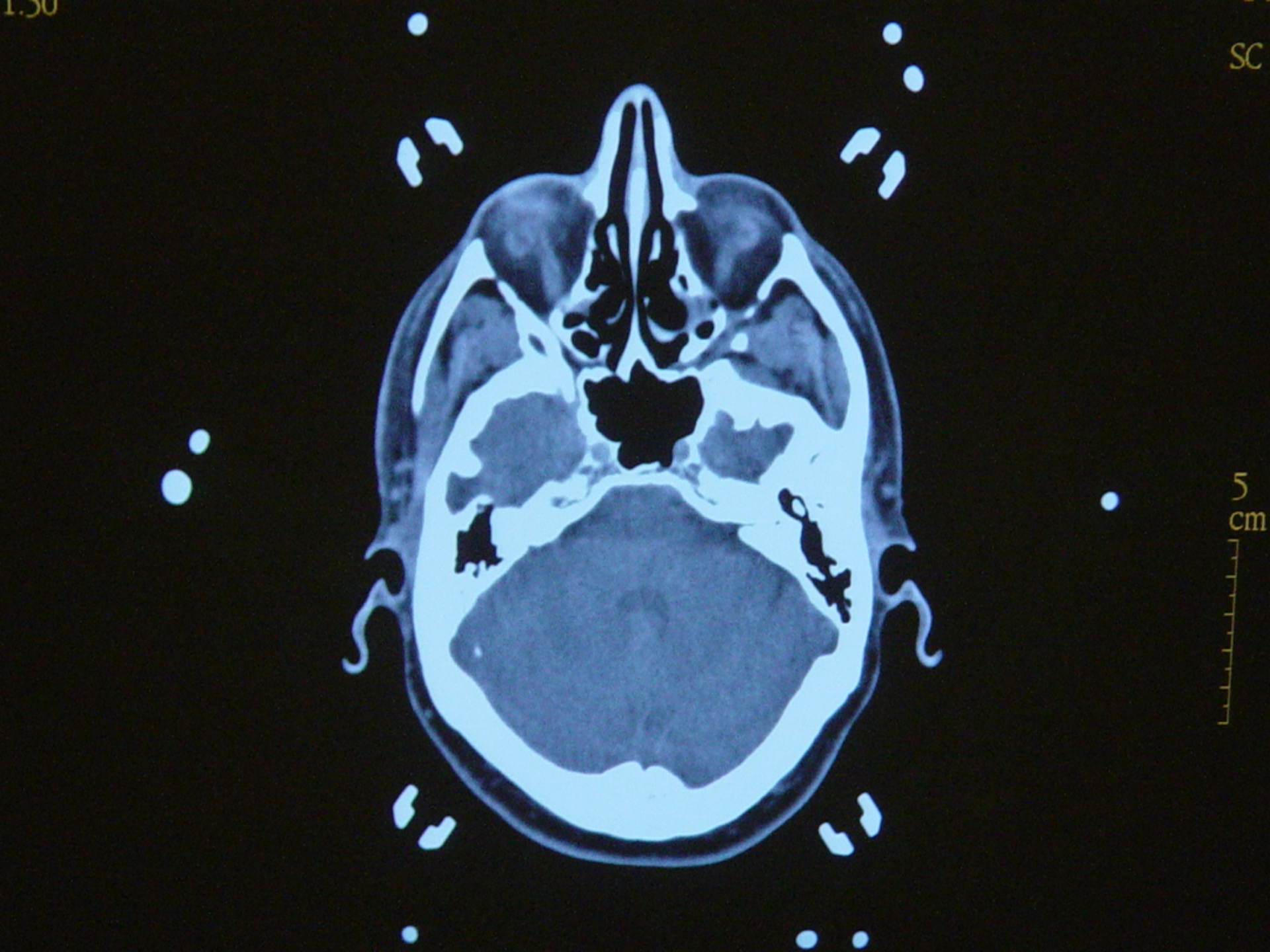
1. Stereotactic implantation of electrodes
   - local anesthesia
   - varying imaging techniques

2. Test period

3. Implantation of pulse generator



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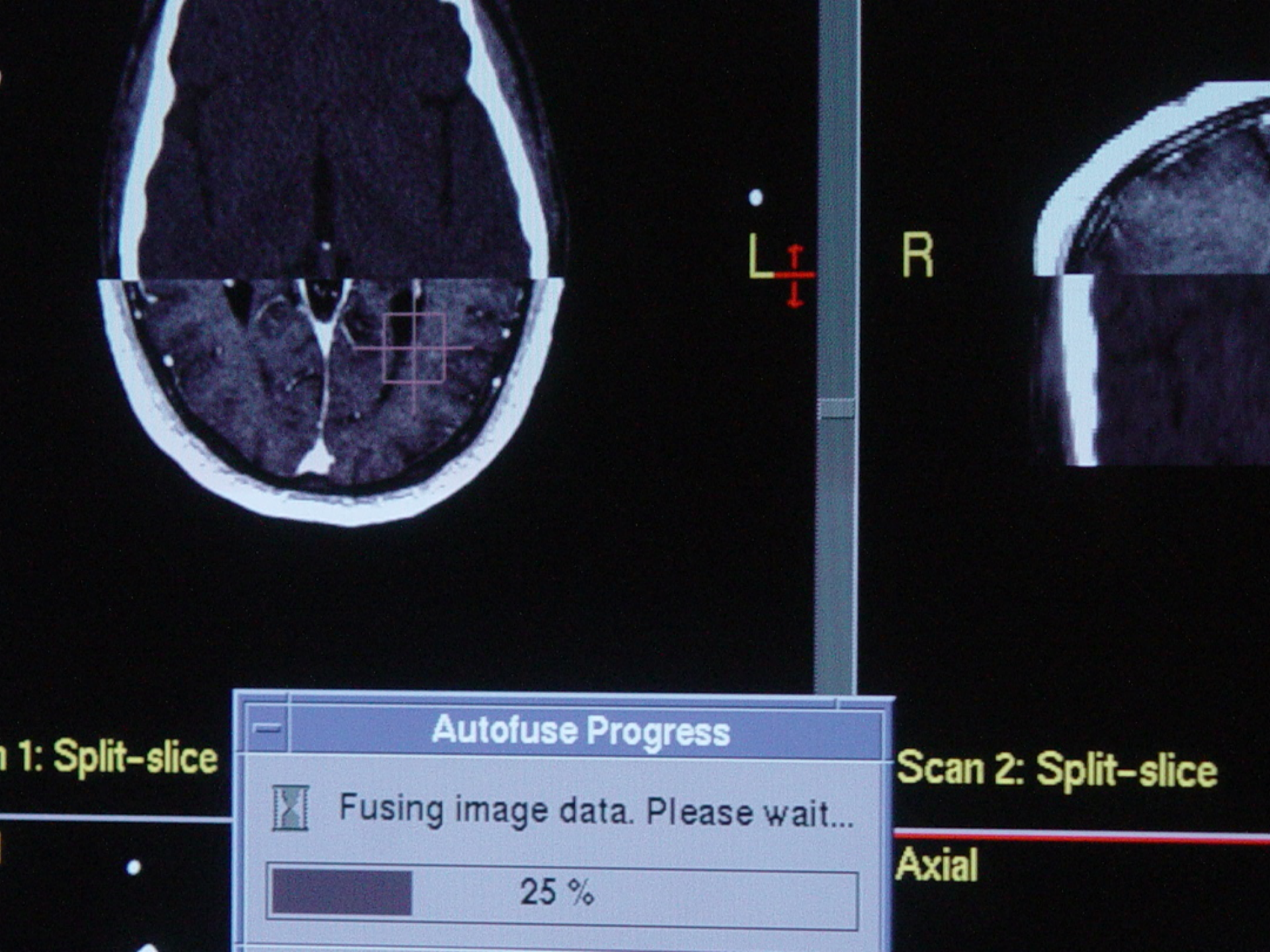
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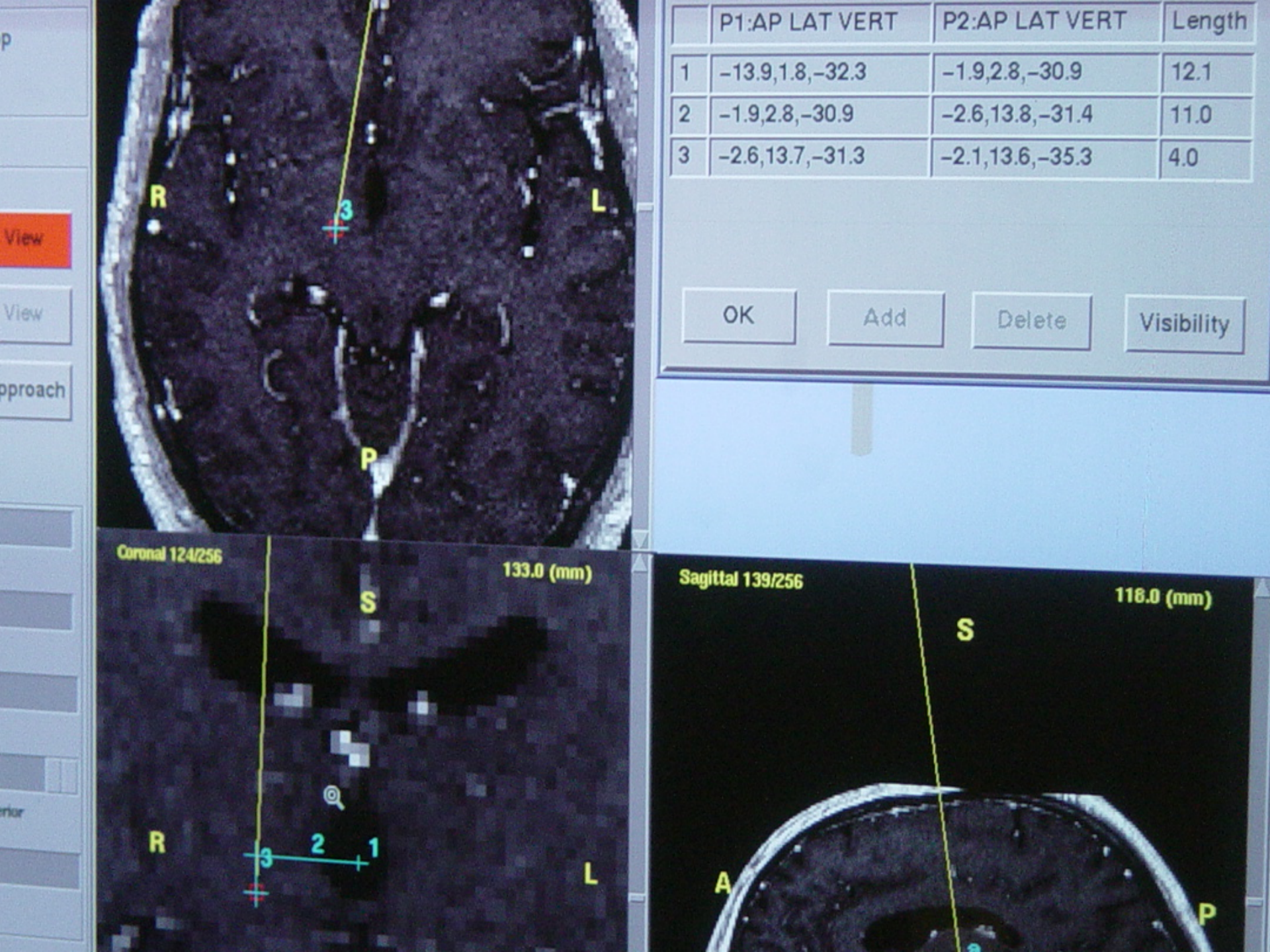

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2	-1.9,2.8,-30.9	-2.6,13.8,-31.4	11.0
3	-2.6,13.7,-31.3	-2.1,13.6,-35.3	4.0

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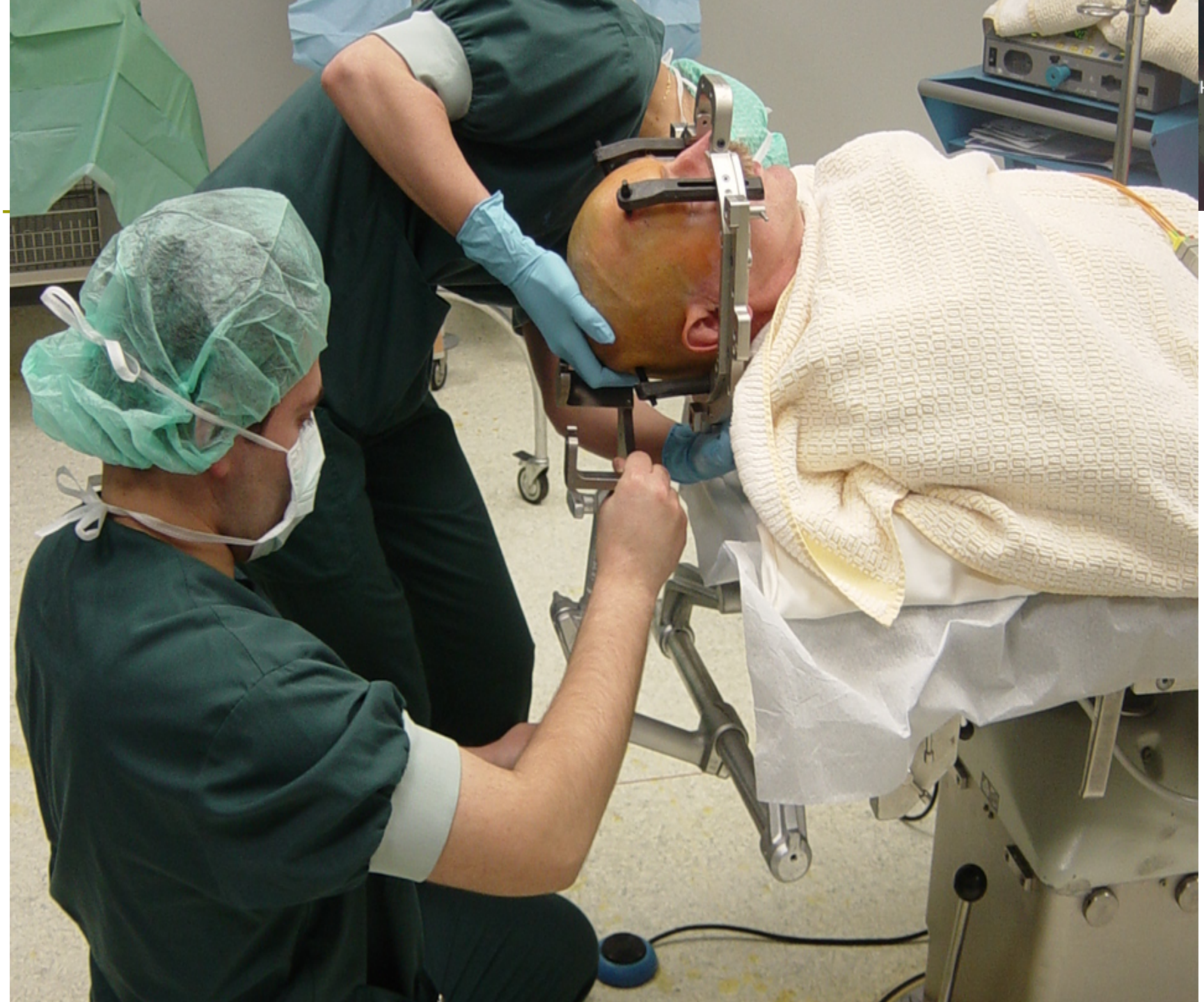
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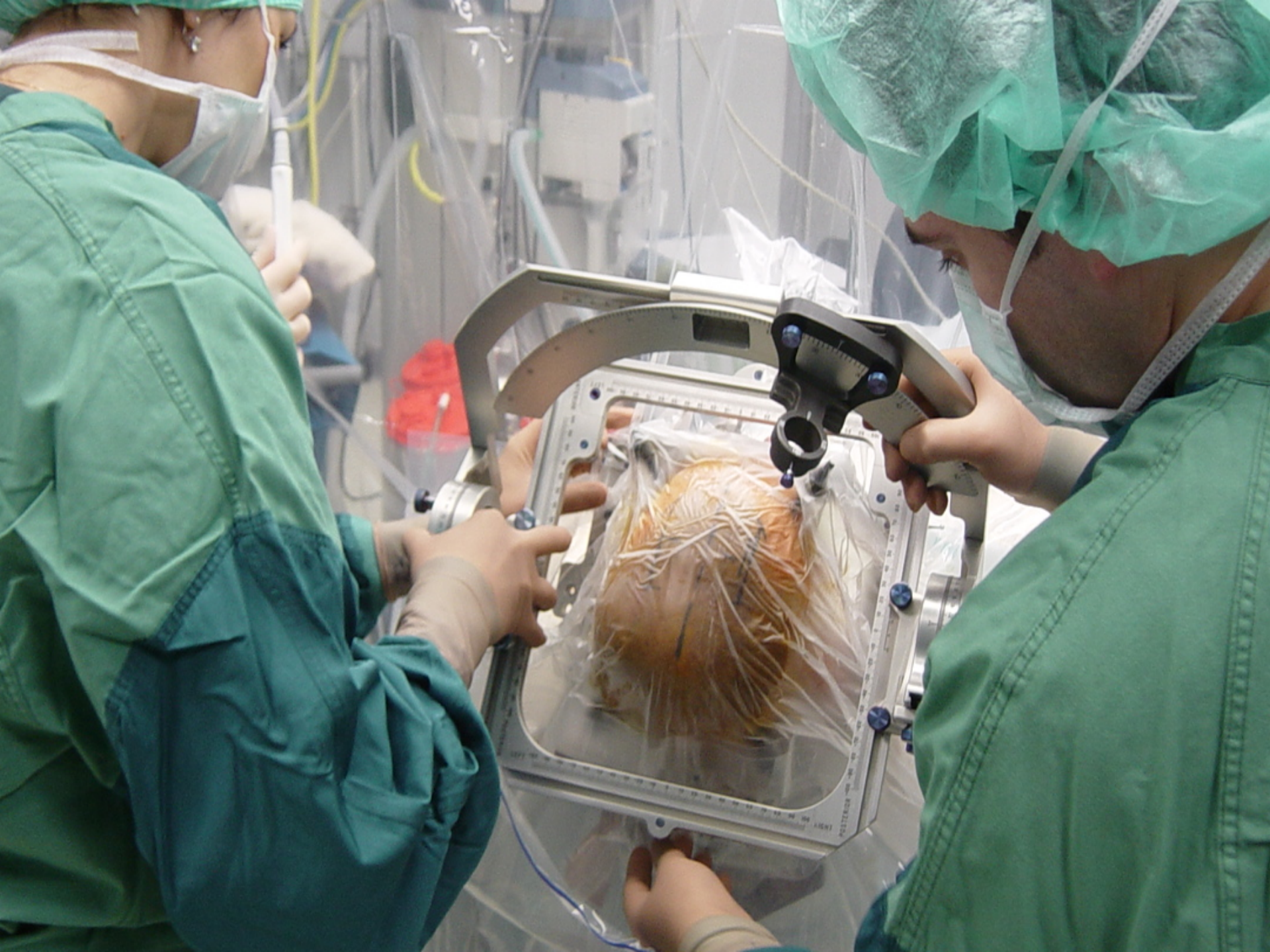

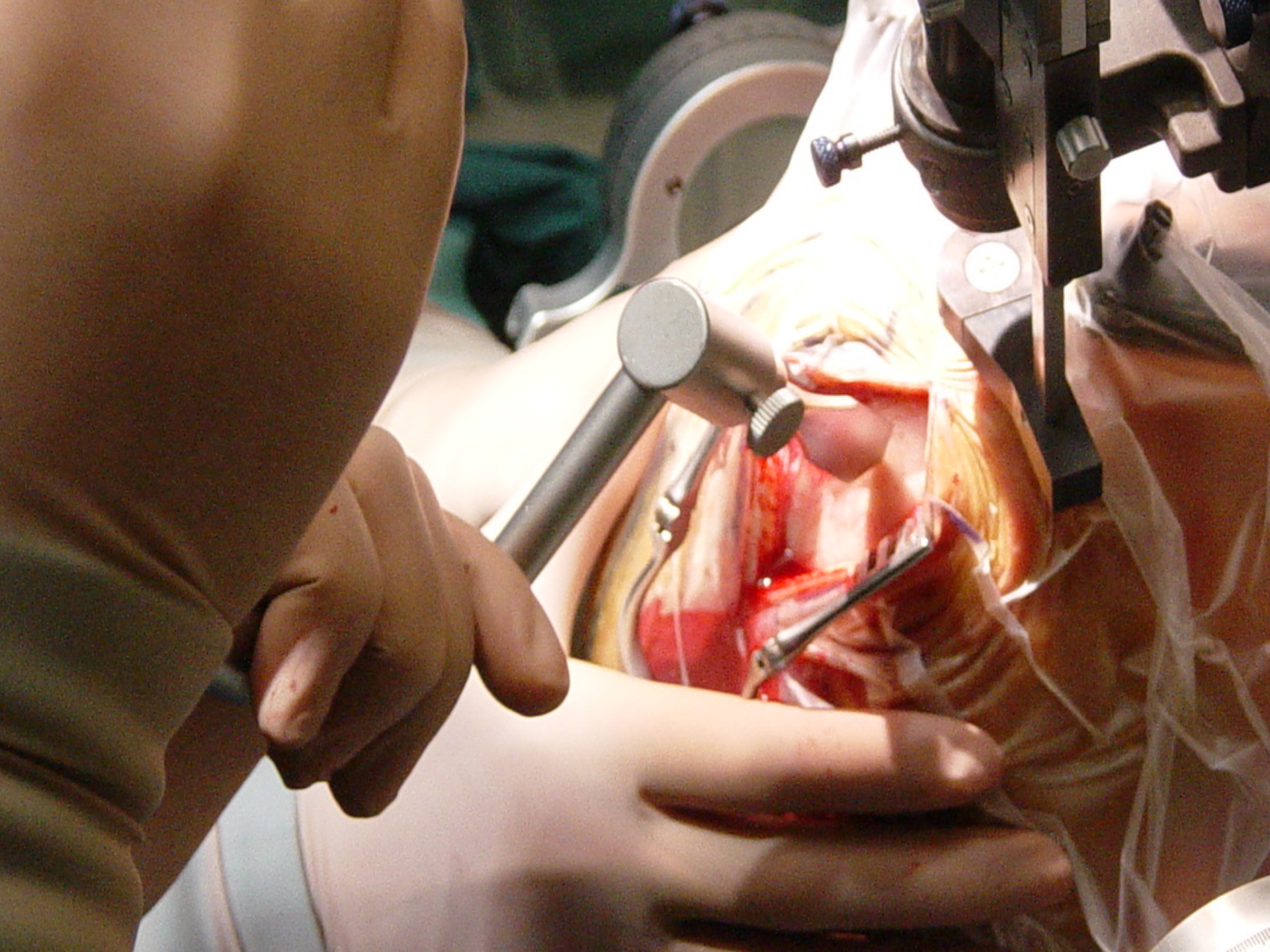

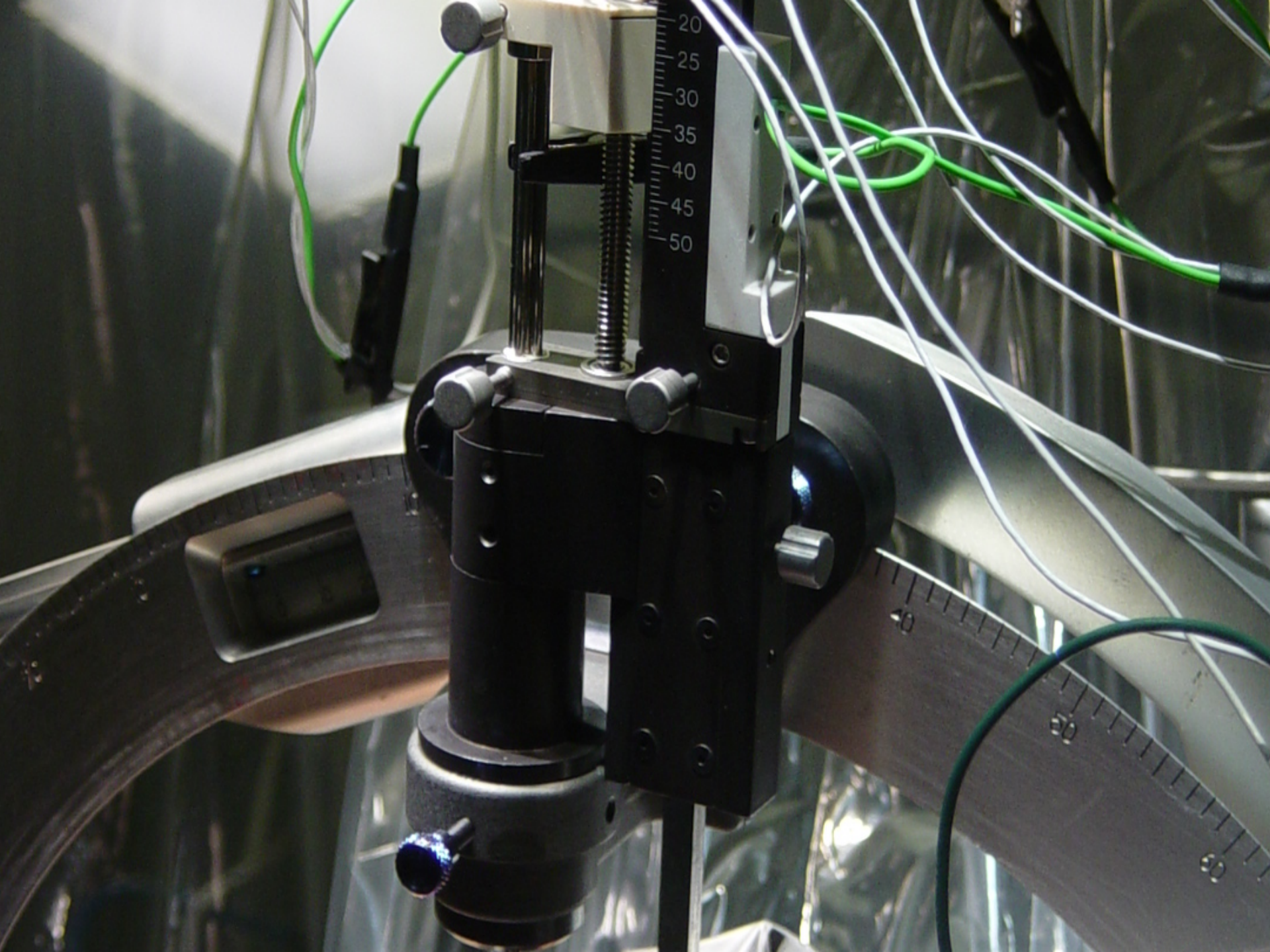
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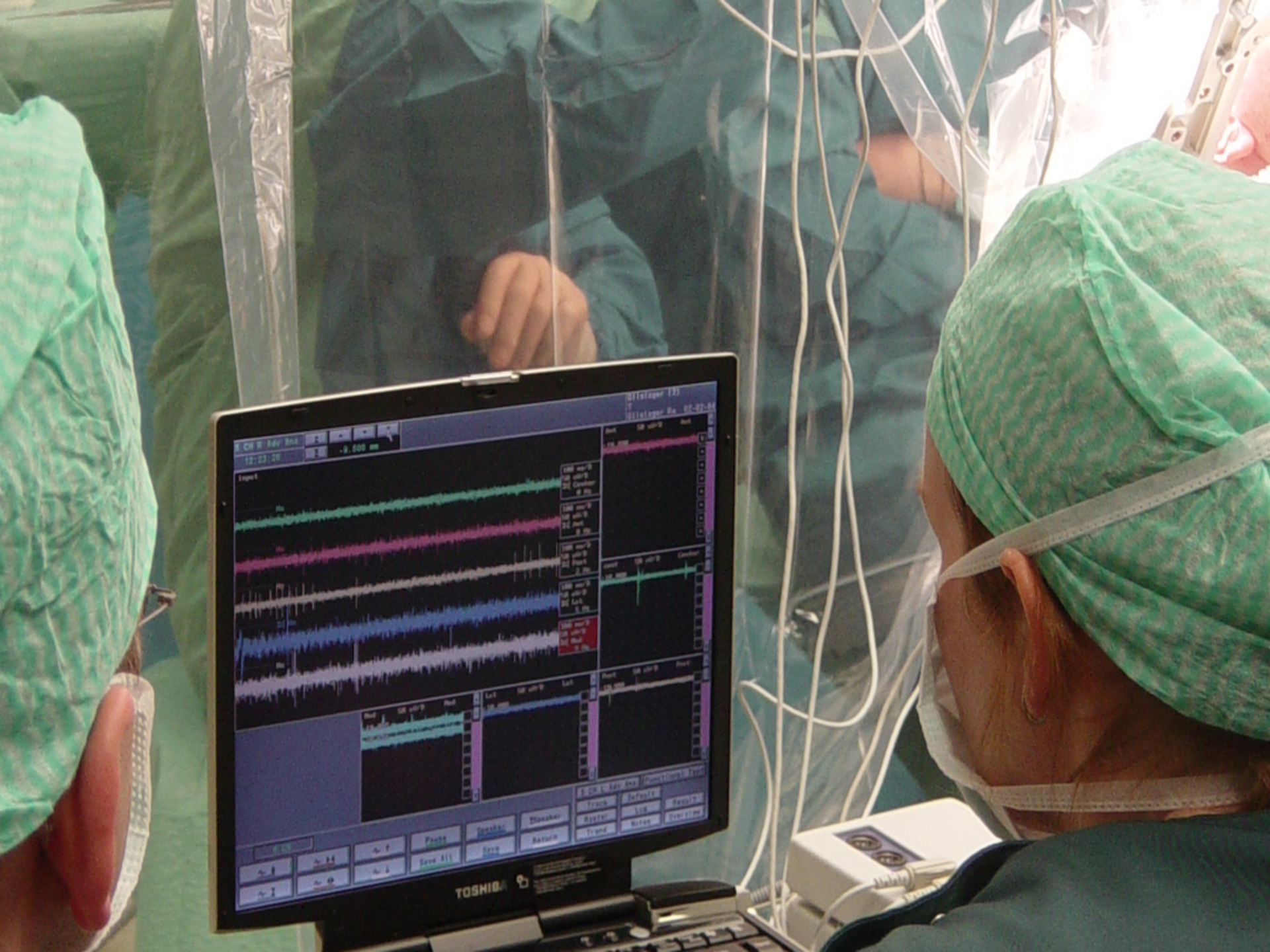
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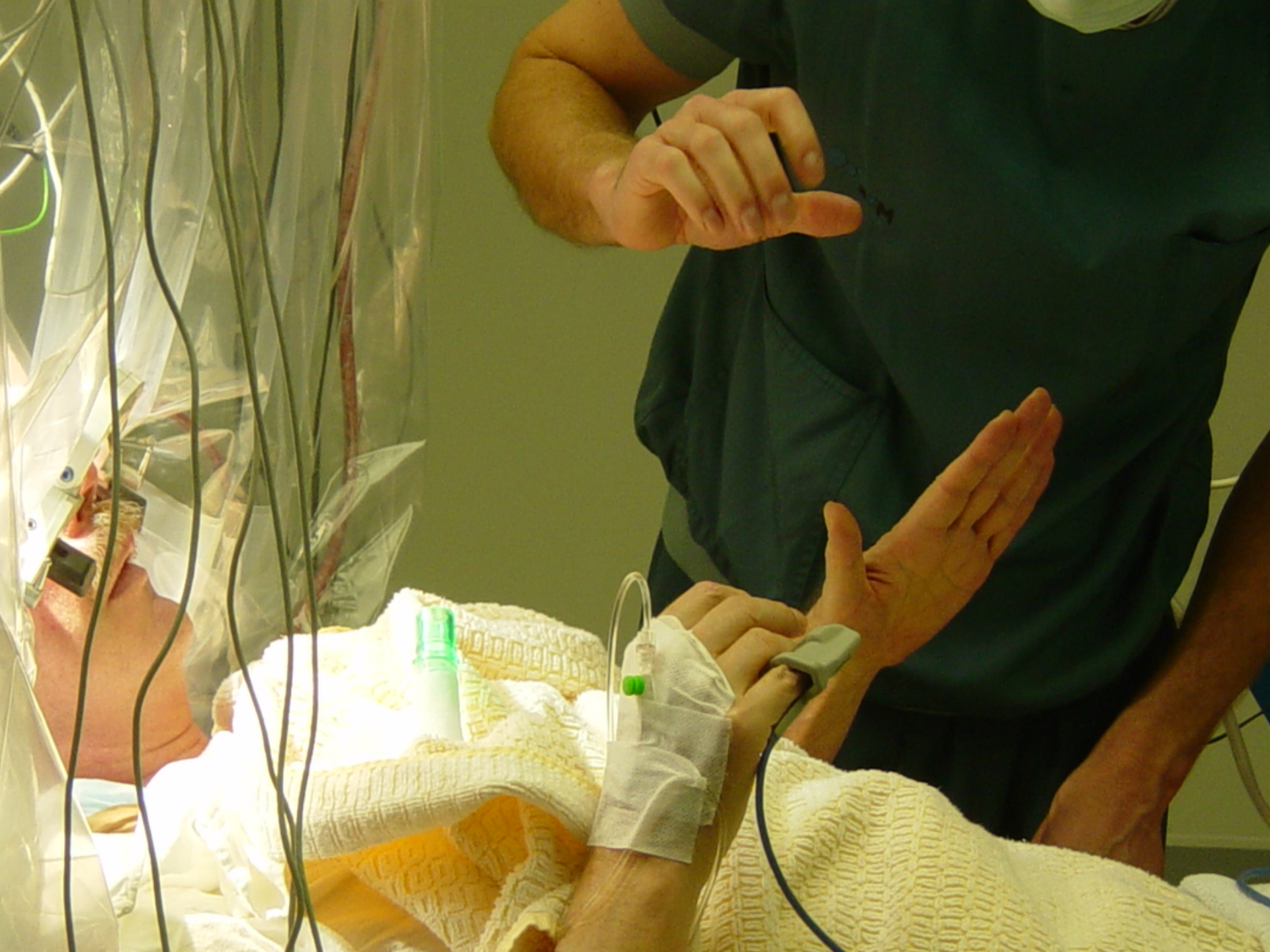

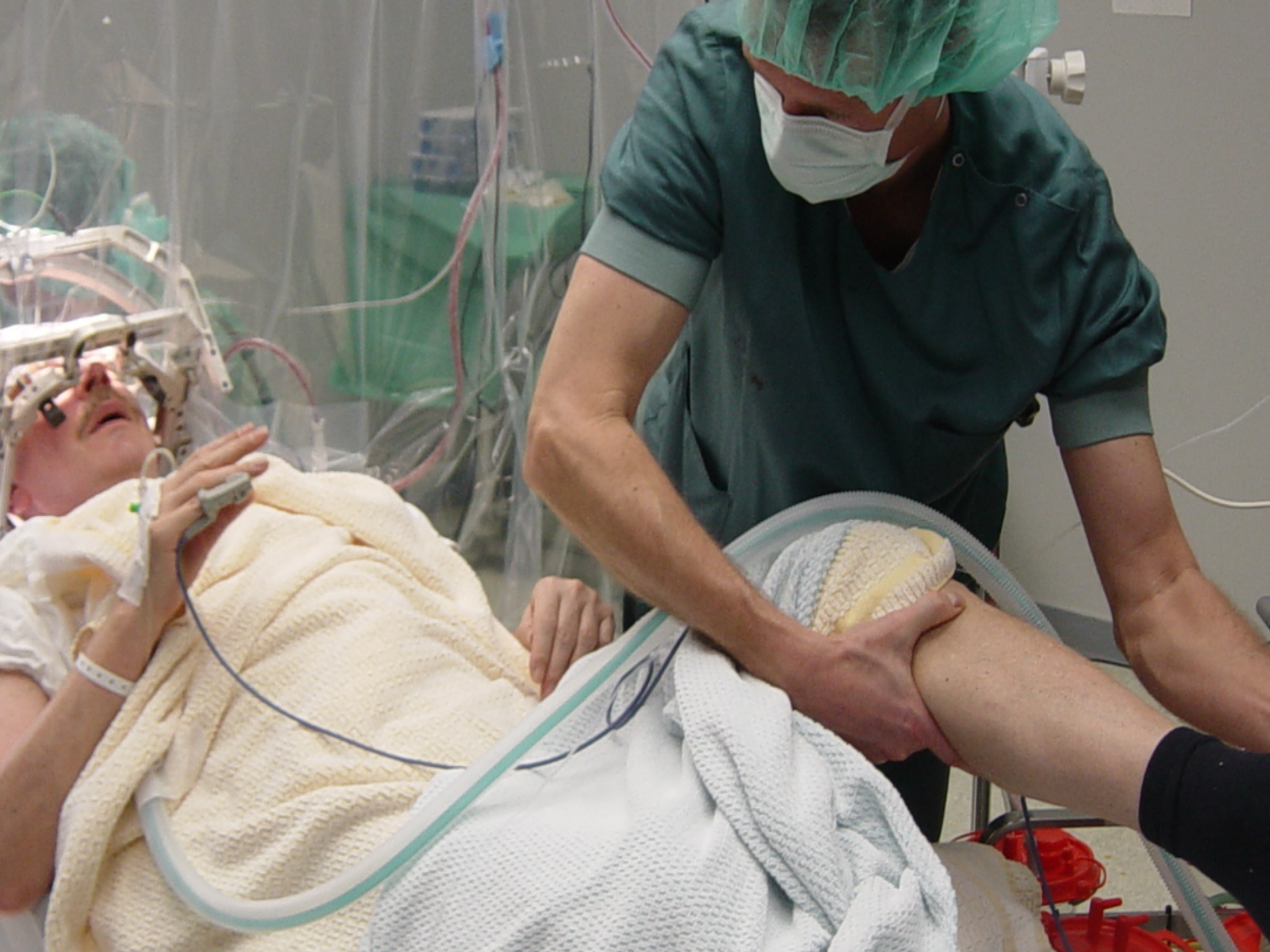

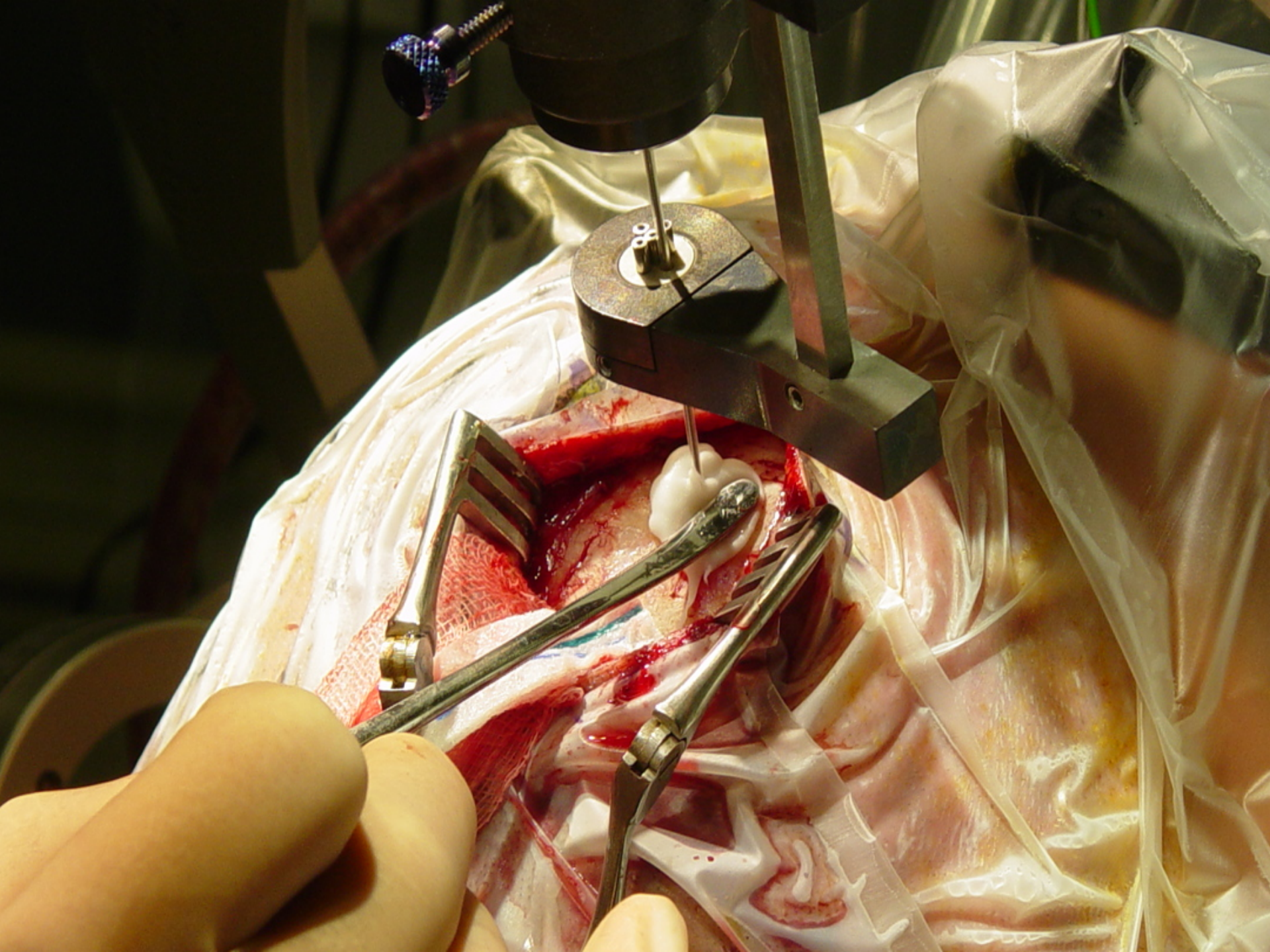

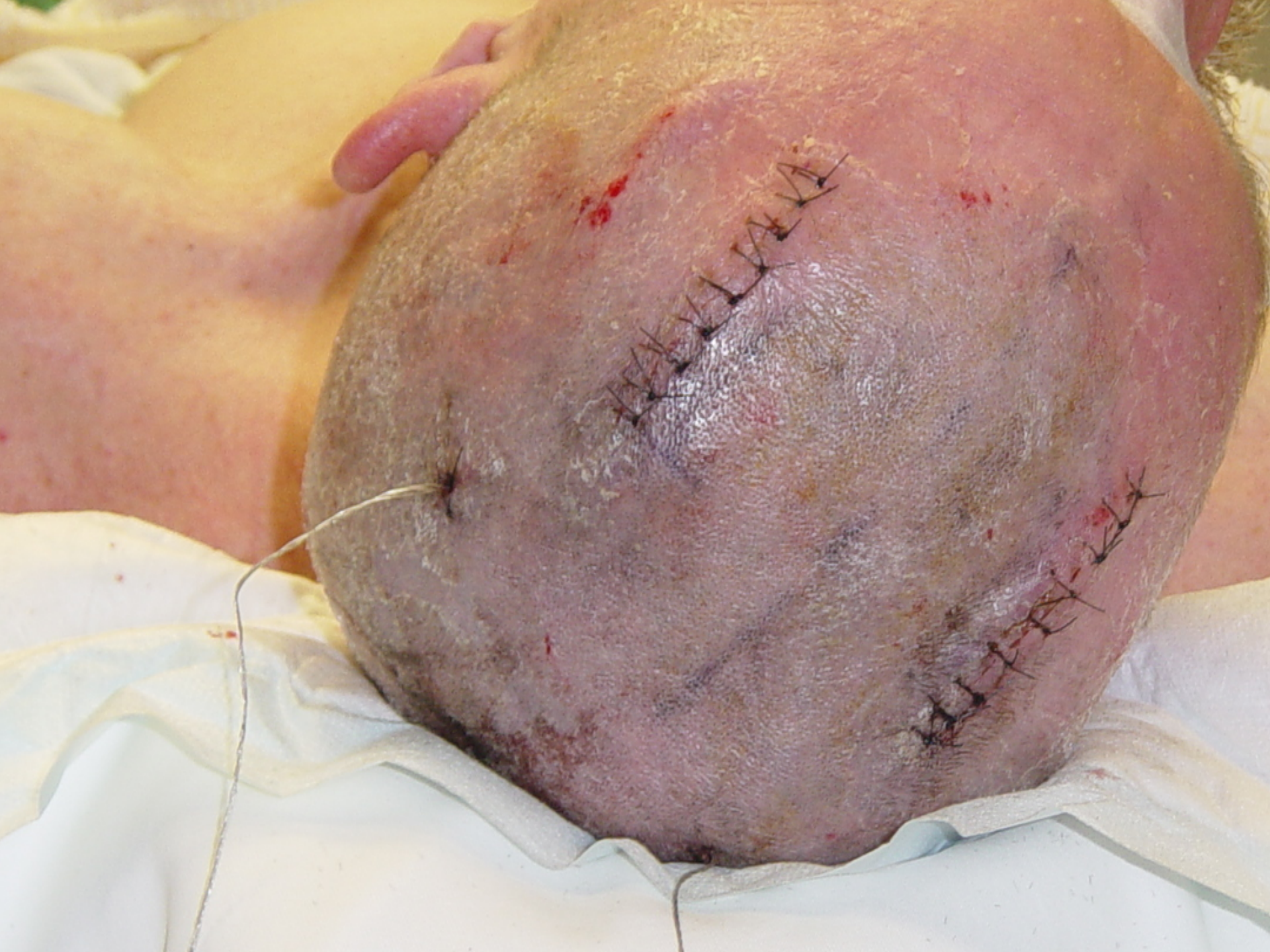

Complications

- Implantation related complications

  Symptomatic bleed: < 2%
  Infection: 0-10%

Tourette Syndrome

Tourette Syndrome

George Albert Edouard Brutus Gilles de laTourette (1857-1904)

- 1885: neuropsychiatric disease characterized by involuntary, stereotyped movements (*motor tics),* or sounds *(vocal tics)*

Tourette Syndrome

- Tics
  - start with facial tics
  - before the age of 11
  - wax and waning
  - coprolaly (swearing) 20-30%

Tourette Syndrome

- Associated co-morbidity:
  - Obsessive-Compulsive behaviour
  - ADHD
  - Self-injurious behaviour (SIB)
  - Autism related disturbances
- Prevalence: 0,05 – 0,5 % of population*
- Male : Female = 4:1

Therapy

- Behaviour therapy

- Medication
  - Classic: haloperdol, clonidine
  - Modern: risperidon, tiapride, olanzapine
  - Atypical: pergolide, quetiapine

- **Surgery**
  - → **Deep Brain Stimulation (DBS)** (Vandewalle. Lancet 1999)

Patient selection

Inclusioncriteria	Exclusioncriteria
Primary diagnosis TS	Tics not related to TS
Minimum score of 80 on the DCI	Severe psychiatric disorder
> 25 years	Drug abuse/dependence (exception: nicotine)
Minimum score of 25 on the YGTSS	Severe cognitive disorder
Minimum of 10 sessions of behavioural therapy	Structural abnormalities on brain MRI
No respons or intollerable side-effects on 3 month trials of classic, modern and experimental antipsychotics	General contra-indications for surgery or anestheasia

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DBS in **Tourette syndrome**: where are we standing now?

Andrade P, Visser-Vandewalle V.

J Neural Transm (Vienna). 2016 Jul;123(7):791-796. doi: 10.1007/s00702-016-1569-7. Epub 2016 May 21. **Review**.

Sixteen years of deep brain stimulation in **Tourette's Syndrome**: a critical **review**.

Servello D, Zekaj E, Saleh C, Zanaboni Dina C, Porta M.

J Neurosurg Sci. 2016 Jun;60(2):218-29. Epub 2016 Jan 20. **Review**.

Tourette syndrome deep brain stimulation: a **review** and updated recommendations.

Schrock LE, Mink JW, Woods DW, Porta M, Servello D, Visser-Vandewalle V, Silburn PA, Foltynie T, Walker HC, Shahed-Jimenez J, Savica R, Klassen BT, Machado AG, Foote KD, Zhang JG, Hu W, Ackermans L, Temel Y, Mari Z, Changizi BK, Lozano A, Auyeung M, Kaido T, Agid Y, Welter ML, Khandhar SM, Mogilner AY, Pourfar MH, Walter BL, Juncos JL, Gross RE, Kuhn J, Leckman JF, Neimat JA, Okun MS; **Tourette Syndrome** Association International Deep Brain Stimulation (**DBS**) Database and Registry Study Group.

Mov Disord. 2015 Apr;30(4):448-71. doi: 10.1002/mds.26094. Epub 2014 Dec 5. **Review**.

Deep brain stimulation for psychiatric disorders: where we are now.

Cleary DR, Ozpinar A, Raslan AM, Ko AL.

Neurosurg Focus. 2015 Jun;38(6):E2. doi: 10.3171/2015.3.FOCUS1546. **Review**.

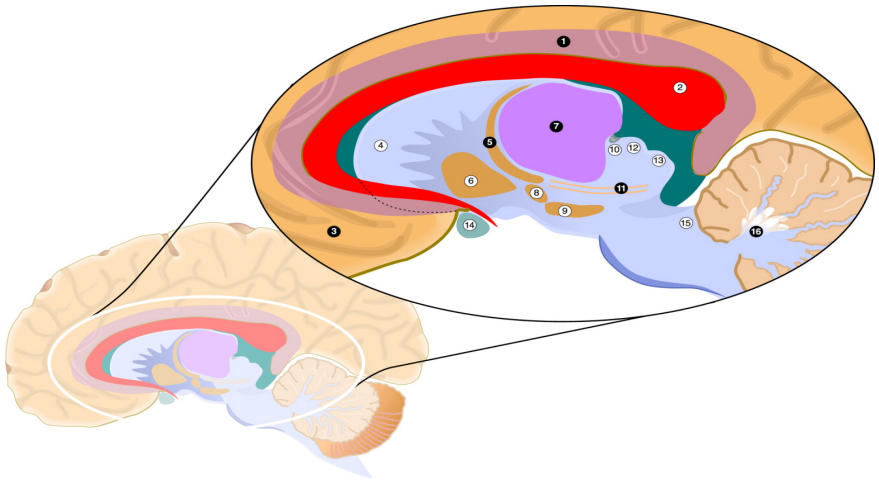
Where are we now?

1. precise pathophysiology unknown

2. which target?

* Based on effects of lesions
* Based on comparable disorders
* Based on pathogenesis of TS

- 1. Based on the effect of Lesions



Thalamotomies
⇓
Thalamic DBS

Hassler and Dieckmann, Rev Neurol Paris 1970

Vandewalle et al, Lancet 1999

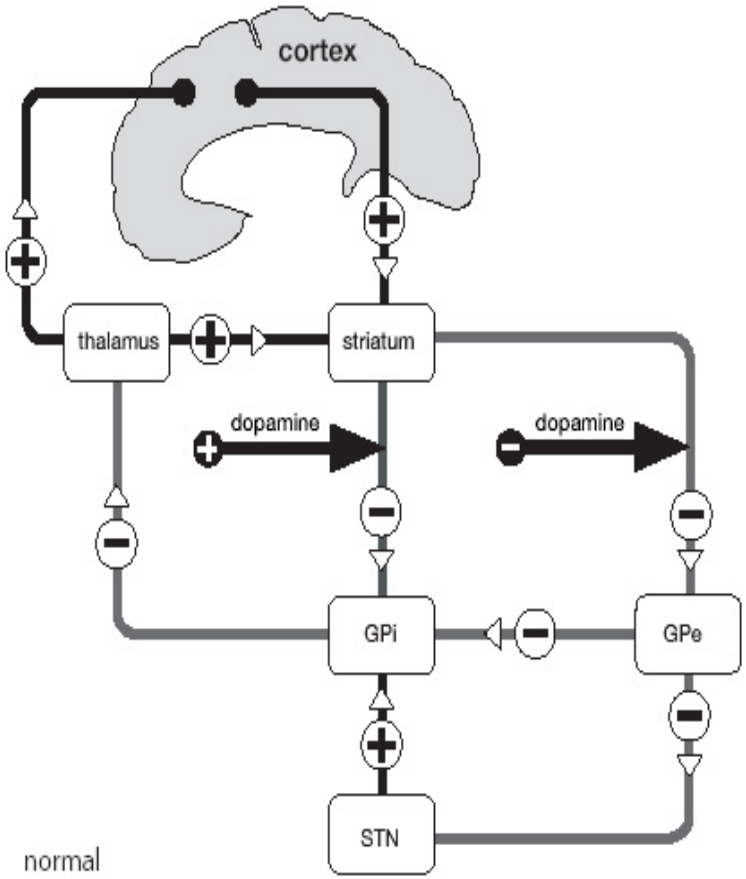
2. Based on study the effects on "comparable" disorders

Pallidal stimulation for dyskinesias

⇓

Pallidal stimulation in TS *Diederich et al, Mov Disord 04*

3. Based on pathogenesis of TS



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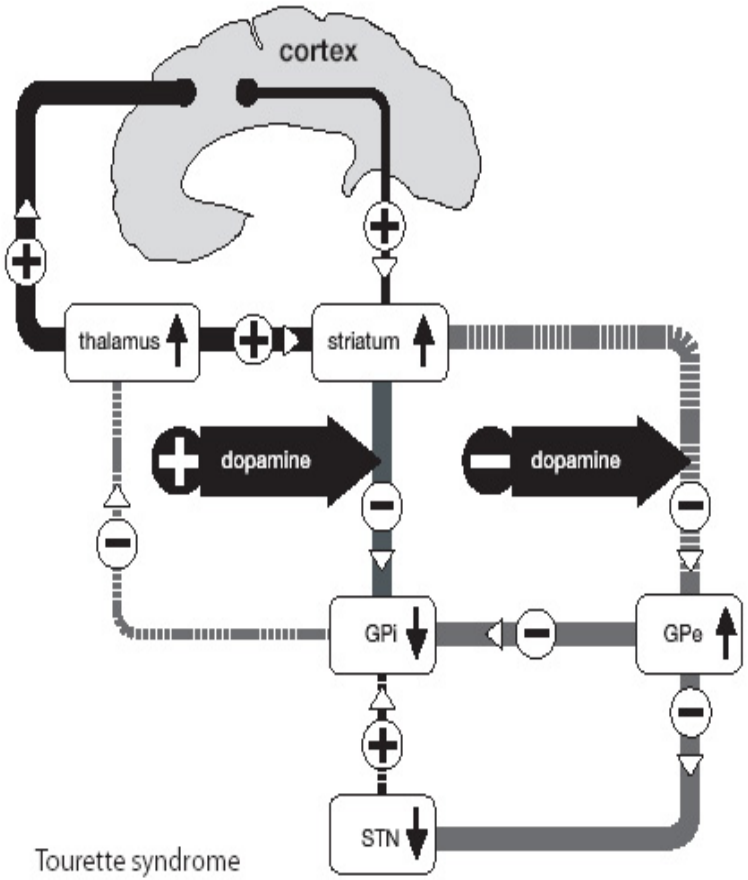

Tourette syndrome

Inclusion criteria

Patient selection and assessment **recommendations** for deep brain stimulation in **Tourette syndrome**.

Mink JW, Walkup J, Frey KA, Como P, Cath D, Delong MR, Erenberg G, Jankovic J, Juncos J, Leckman JF, Swerdlow N, Visser-Vandewalle V, Vitek JL; **Tourette Syndrome** Association, Inc.

Mov Disord. 2006 Nov;21(11):1831-8.

An approach to deep brain stimulation for severe treatment-refractory **Tourette syndrome**: the UK perspective.

Cavanna AE, Eddy CM, Mitchell R, Pall H, Mitchell I, Zrinzo L, Foltynie T, Jahanshahi M, Limousin P, Hariz MI, Rickards H.

Br J Neurosurg. 2011 Feb;25(1):38-44. doi: 10.3109/02688697.2010.534200. Epub 2010 Dec 15. Review.

Neurosurgical treatment for Gilles de la **Tourette syndrome**: the Italian perspective.

Porta M, Sassi M, Ali F, Cavanna AE, Servello D.

J Psychosom Res. 2009 Dec;67(6):585-90. doi: 10.1016/j.jpsychores.2009.06.001. Epub 2009 Oct 2. Review.

European clinical guidelines for **Tourette syndrome** and other tic disorders. Part IV: deep brain stimulation.

Müller-Vahl KR, Cath DC, Cavanna AE, Dehning S, Porta M, Robertson MM, Visser-Vandewalle V; ESSTS Guidelines Group.

Eur Child Adolesc Psychiatry. 2011 Apr;20(4):209-17. doi: 10.1007/s00787-011-0166-4. Erratum in: Eur Child Adolesc Psychiatry. 2011 Jul;20(7):377.

9 Targets in literature

- Thalamus
  1. thalamic centromedian parafascicular complex
  2. crosspoint CM-Spv-Voi
  3. Vop-Voa-Voi complex
- Globus Pallidus interna
  4. anteromedial
  5. posteroventral
6. nucleus accumbens
7. anterior limb interna capsule
8. STN
9. GPe

> 38 case reports

only 6 double blinded randomised trials

n = 200

Study	Target	Sample Size, Sex (Age, Years)	Follow up	Stimulation Parameters	Effect on Tics Severity/YGTSS or MRVRS
Maciunas et al. 2007 [39]	CMPf, Voi	Five males (18–34)	3	Variable polarity 3.5–3.6 V, 90–210 μs,130–180 Hz	Double blind comparison during first 4 weeks showed a 17% improvement. At 3 months 44% (mean) Non-responders with 4.3%–260% tic exacerbation
Houeto et al. 2005 [62], Welter et al. 2008 [63]	CMPF and anteromedial GPi	Two females, one male (36, 30, 30)	60, 27, 20	CMPf: double monopolar 1.5–1.7 V, 60 μs, 130 Hz, Gpi: Single or double monopolar 1.5–3.5 V, 60 μs, 130 Hz	YGTSS cross-over period, (a)-AmGPi: (65%, 96%, 74%, (b)-CMPf: 30%, 40%, 64%, (c)-Gpi and CMPF 43%, 60%, 76% (after 60 months)
Ackermans et al. 2011 [40]	CM-Spv-Voi	6 males (completed full trial) (35–48 years)	36	1.3–7 V, 60–210 μs, 70–130 Hz. Monopolar stimulation in three patients and bipolar stimulation in the other three patients.	YGTSS at blinded ON compared to OFF stimulation was significantly lower (37%). After one year 49% and MRVRS 35%.
Kefalopoulou et al. 2015 [64]	AmGPi (13 patients), pvGPi (2 patients due to dystonic features).	11 males 4 females (25–55 years), 14 randomly assigned 13 completed assessments in both blinded periods. All 15 received stimulation in open-label phase	20–60	In blinded phase, 9 patients had monopolar and double monopolar in 4	YGTSS from off to on stimulation during blinded crossover period was 15.3%. Increased to 40.1% in open label phase

Thalamic DBS

Comparison of thalamic and mGPi in 2 patients

(Ackermans et al. Mov. Dis 2006)

Thalamic stimulation

- 53% tic reduction
- Compulsions resolved
- Reduced energy

mGPi stimulation

79% tic reduction

Compulsions resolved

reduced energy

Conclusion:

- No defintive conclusion considering best target?
- Double blinded randomised controlled trial with thalamic dbs

Thalamic DBS

doi:10.1093/brain/awq380 Brain 2011: 134; 832–844 | 832

BRAIN
A JOURNAL OF NEUROLOGY

Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome

Linda Ackermans,[1,2,*] Annelien Duits,[2,3,4,*] Chris van der Linden,[5,*] Marina Tijssen,[6,*] Koen Schruers,[2,4,7,*] Yasin Temel,[1,2,8,*] Mariska Kleijer,[9,*] Pieter Nederveen,[10,*] Richard Bruggeman,[11,*] Selma Tromp,[12] Vivianne van Kranen-Mastenbroek,[2,13] Herman Kingma,[14] Danielle Cath[15,*] and Veerle Visser-Vandewalle[1,2,8,*]

Thalamic DBS

Results after 1 year thalamic stimulation (n= 6)

	pre-operative	post-operative (1 year)	p-value
YGTSS	42.2 (3.1)	21.5 (11.1)	P = 0.028*
video-tics	233.3 (82.1)	65.3 (81.6)	p = 0.028*
mRVRS	12.1 (1.1)	7.8 (3.2)	p = 0.046*
OCb	8.3 (5.6)	2.5 (3.5)	p = 0.249

* Indicates a significant difference ($p < 0.05$)

Thalamic DBS

Side-effects:

- visual disturbances
- lack of energy
- frequent replacements of battery
- erectile changes

Thalamic DBS

Patient	Sex	Age	Follow-up (months)	DBS on/off/explanted	tic reduction %
6	M	40	26	OFF	34
2	M	39	36	OFF	50
3	M	40	78	ON	89
5	M	40	12	OFF (thal) ON (mGPi)	27 lost to follow-up
4	M	35	16	Explanted ON (lGPi)	34 64
1	M	48	60	ON (thal) OFF (lGPi)	81 -
7	M	45	108	Explanted ON (lGPi)	9 80.4

Lessons learned

* Difference in opinion of satisfactory outcome
(tics vs side effects)

* Satisfaction is individualised based

* Relief of tic improvement may distract from essential other premorbid problems and side effects —> loss of burden.

* Side effects, though based on self-report, became more pronounced with increasing treatment duration.

Neuromodulation: Technology at the Neural Interface

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(onlinelibrary.wiley.com) DOI: 10.1111/ner.12556

Thalamic Deep Brain Stimulation for Refractory Tourette Syndrome: Clinical Evidence for Increasing Disbalance of Therapeutic Effects and Side Effects at Long-Term Follow-Up

Anouk Y.J.M. Smeets, MD*; Annelien A. Duits, MD, PhD†; Albert F.G. Leentjens, MD, PhD†; Koen Schruers, MD, PhD‡; Vivianne van Kranen-Mastenbroek, MD, PhD§; Veerle Visser-Vandewalle, MD, PhD¶; Yasin Temel, MD, PhD*; Linda Ackermans, MD, PhD*

Lessons learned

* TS patients tend to blame the stimulator for almost all negative symptoms

* Professionals reinforce them by frequent adjustments of stimulation

* Guidance in problems coping the postoperative situation

* Study outcomes have focused on tic reduction and rating scales, not always accurate reflection of tic impact on self-esteem and socio-professional life.

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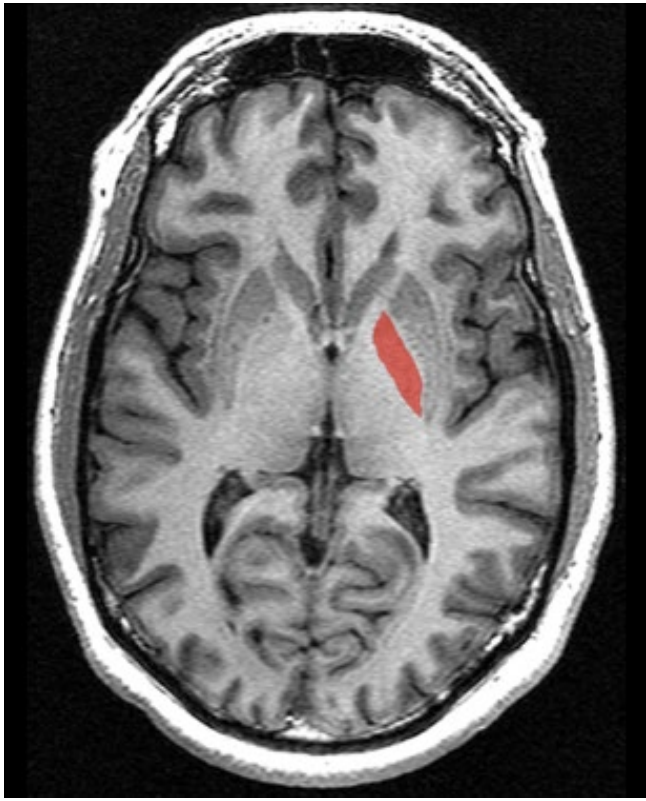
Thalamic vs Pallidal

Promising reports of pallidal stimulation

Side –effects of thalamic stimulation

anatomic / physiological



Pallidal DBS

Internal globus pallidus (GPi)

- Anteromedial limbic part
- Posteroventrolateral motor part

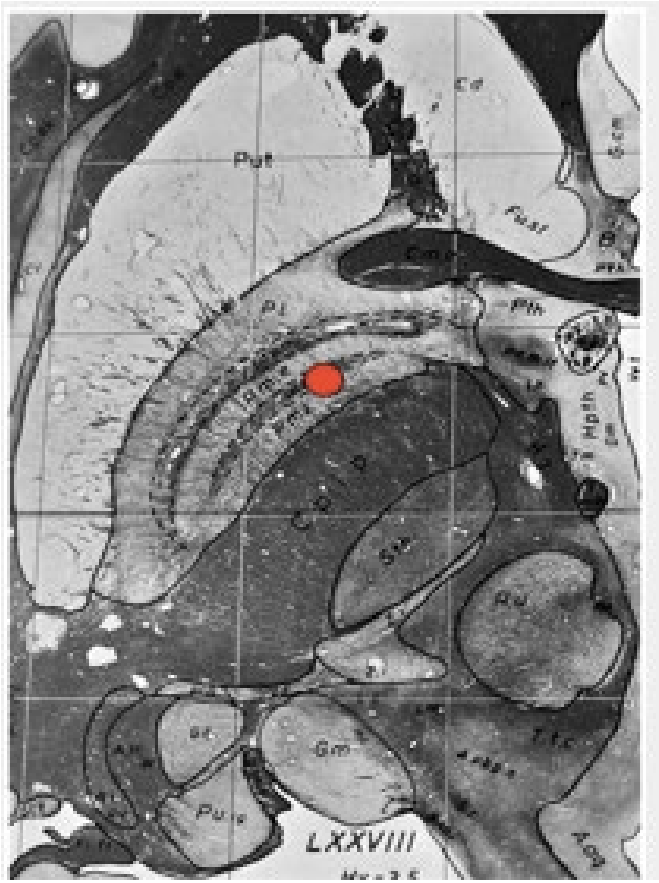
- Hyperkinesia Parkinson en dystonia
- TS: disinhibition limbic circuits

- Welter et al (2008): double blind, RCT, 3 pt
- Martinez-Fernandes et al (2011): open label, 5 pt

Pallidal DBS

Clinical characteristics

- 3 ♂, 2 ♀
- Follow-up: 7 – 38 months (SD 13.7)
- Mean age: 41.6 years (SD 9.7)
- 3 patients thalamic DBS in the past
- 4 patients OCb



Pallidal DBS

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Deep Brain Stimulation of the internal globus pallidus in refractory Tourette Syndrome

A.Y.J.M Smeets[a,b,*], A.A Duits[c], B.R Plantinga[f], A.F.G Leentjens[c], M. Oosterloo[d], V. Visser-Vandewalle[e], Y. Temel[a,b], L. Ackermans[a]

Primary outcomes

	Preoperative	Postoperative	% improvement	P-value
YGTSS tot	42.4 (4.5)	13.8 (5.2)	67.5 (13.3)	0.043*
Video-tics	259.6 (107.3)	56.0 (36.2)	78.4 (10.3)	0.043*
mRVRS	13.0 (2.0)	7.0 (1.6)	46.2 (7.9)	0.041*

* Indicates a significant difference ($p < 0.05$)

Pallidal DBS

Secondary outcomes

	Preoperative	Postoperative	P-value
Behavioural disorders			
Y-BOCS	15.4 (11.5)	5.4 (7.4)	0.068
CAARS	52.3 (43.7)	65.5 (29.5)	0.465
Mood			
BAI	37.0 (16.2)	34.0 (12.3)	1.000
BDI	10.5 (6.6)	9.6 (8.6)	0.581

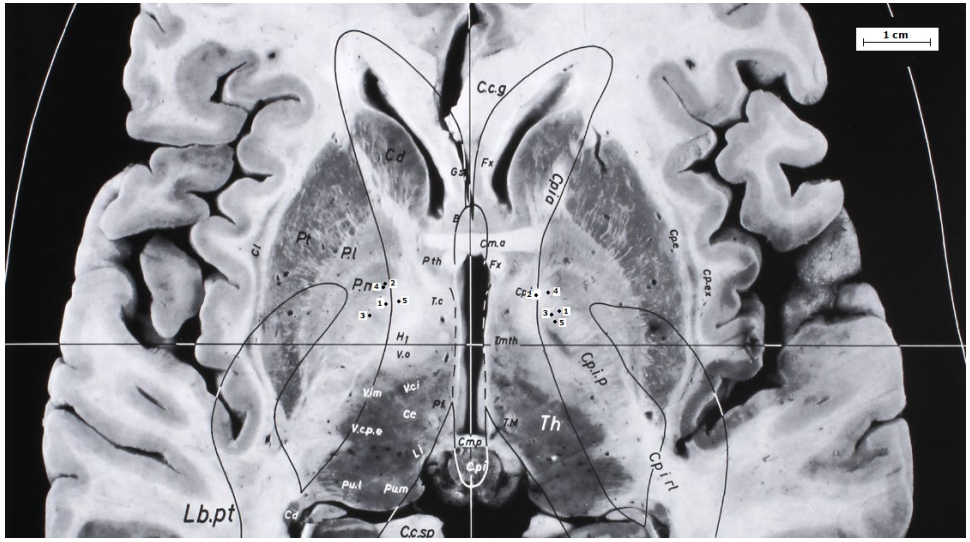
Pallidal DBS

Side-effects

- 2 x apathy and passive behaviour
- 1 x agitation and weight loss

Complications

- 1 x infection pulse generator

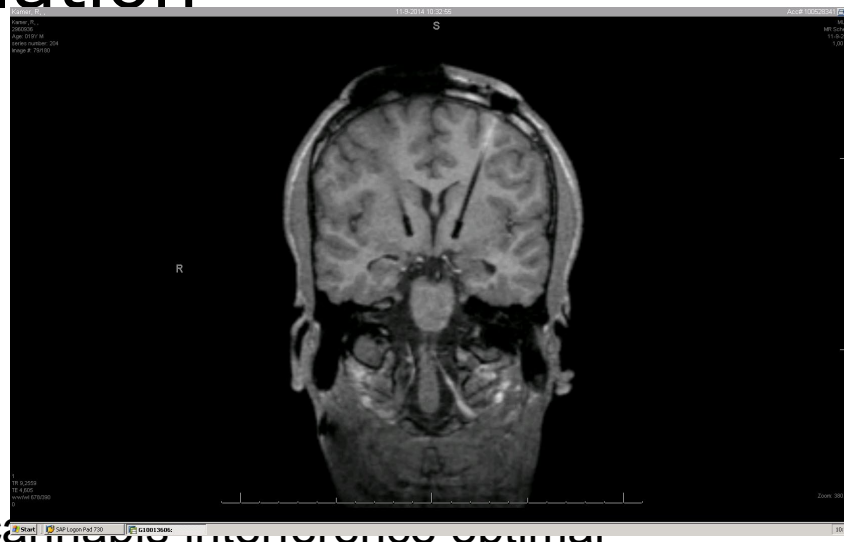


Pallidal DBS

Male, 17y old

Only side-effects of stimulation

- Depression like thoughts
- Hyperkinetic movements of legs
- Low stimulation –settings



Follow-up 2y > 50% tic reduction

Male, 17y old

Post-op behavioural disturbances/aggresion/cannabis interference optimal programming

Follow-up 1y >70% tic reduction

Lessons learned

DBS in TS <25y without attention to ethical aspects

(Smeets A, et al, submitted)

Ethics of Deep Brain Stimulation in adolescent patients with refractory Tourette Syndrome: a systematic review and two case discussions

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Spontaneous remission

Chronicity cannot be predicted

Reduce compliance in this age?

→ Ethical discussion: submitted

How we do it!

(in)direct targetting T2 W planning mri

L-Gpi coordinates

- x : 12 mm lateral,
- y : 6-9 mm anterior midcommisural point
- z : 0-3 mm superior midcommisural point

>18 Y

Lead 3389

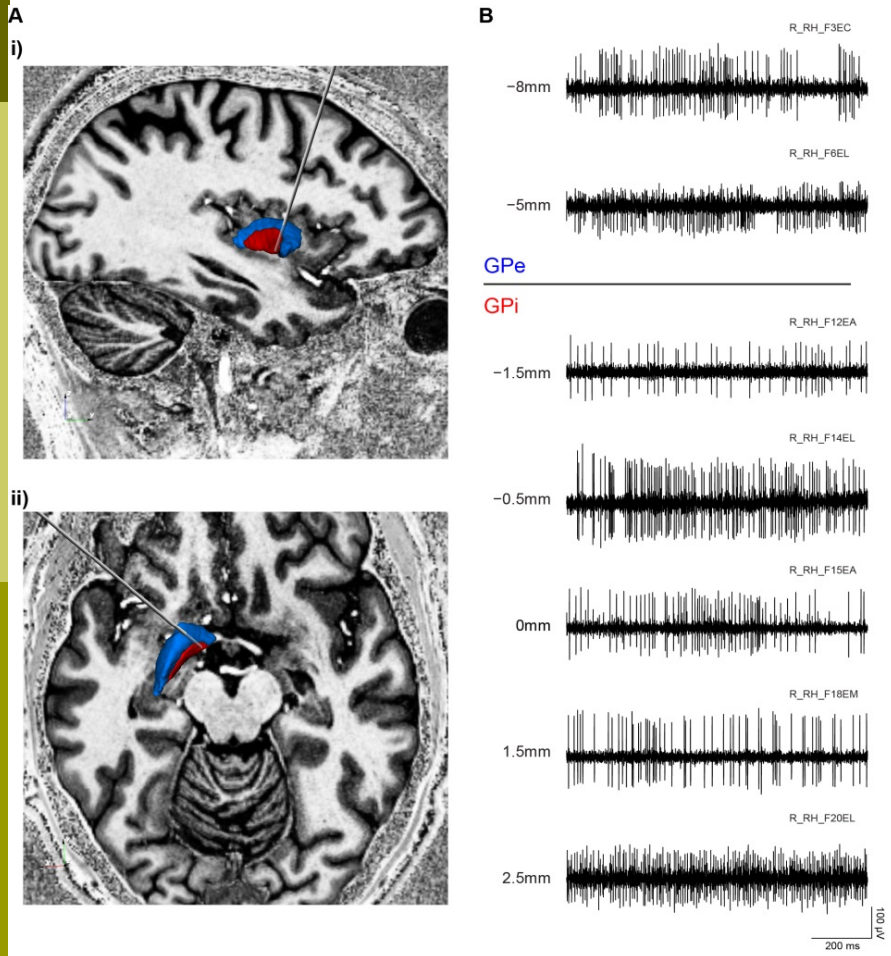
Generalised anesthesia

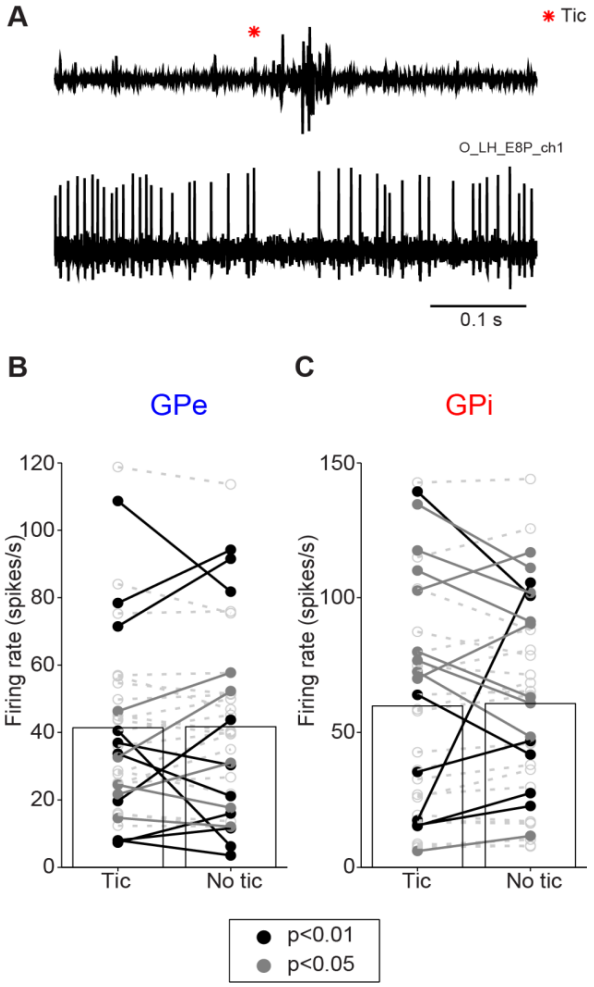
MER*

Psychiatric ward

Pallidal DBS

MER: Israelashvili M, et al. Mov Dis 2017

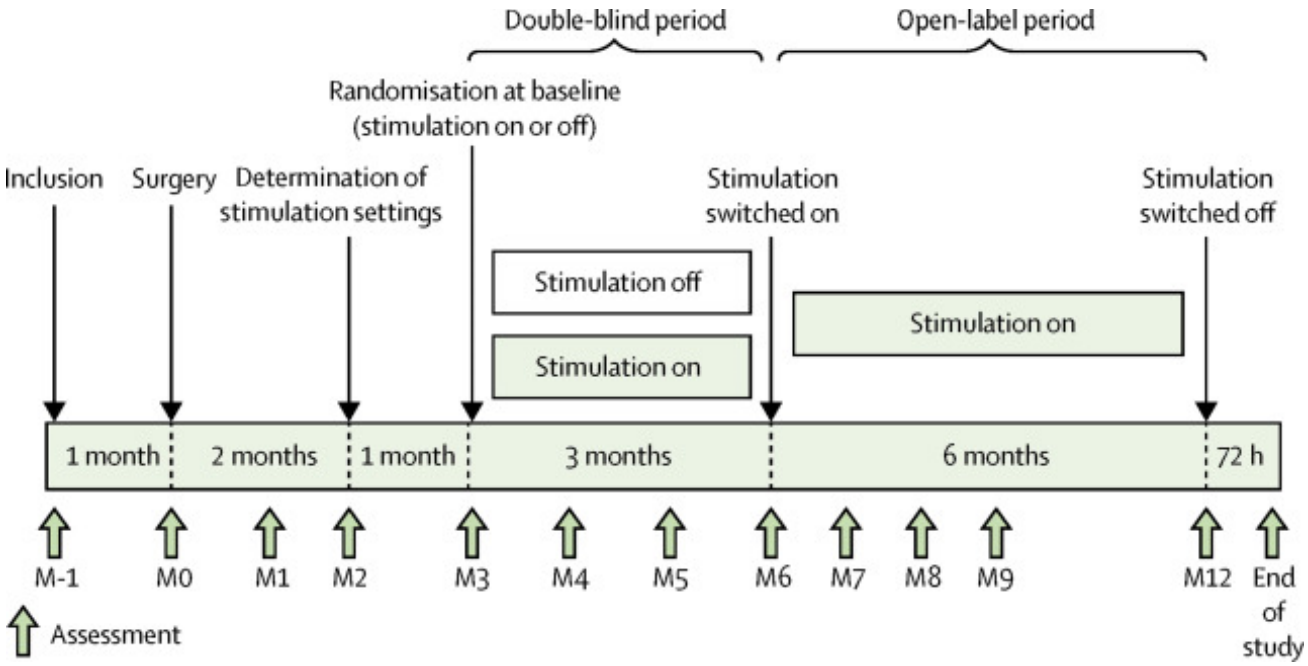




Pallidal DBS

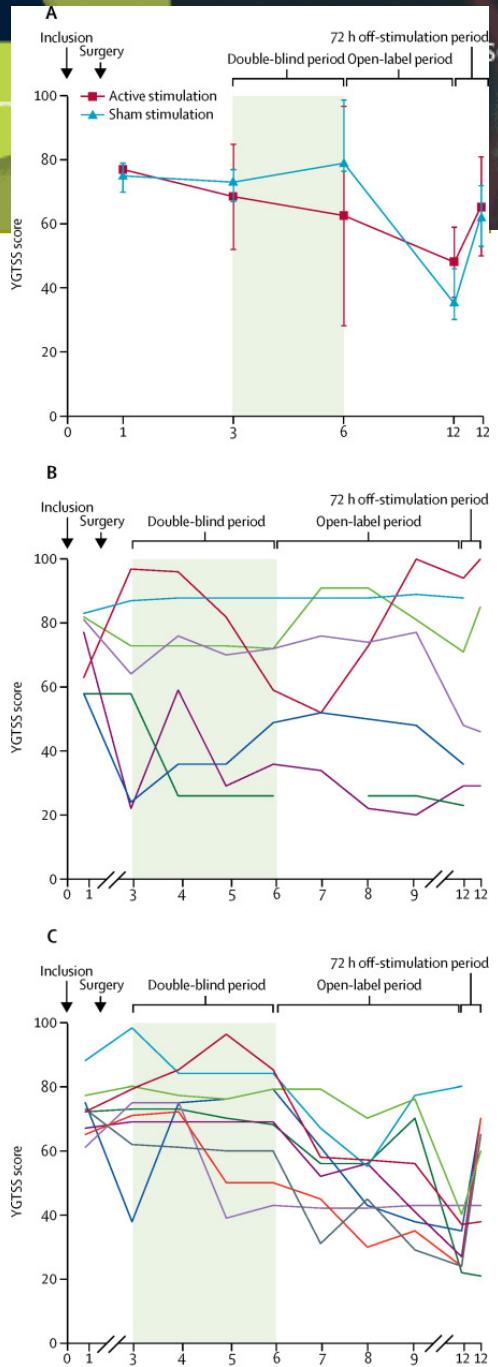
Recent publication: Lancet Neurology 2017

- aGPi in TS: randomised, double blinded, controlled
- 2007-2013, inclusion N = 19
- N = 16



Pallidal DBS

- No significant effect after 3 month
- Data from open-label suggest possible benefit
- 6/11 unemployed returned work/school
- High infection rate (21% removal stimulator)
- IPG implantation after 1-5 days
- 15 SAE in 13 pts



Conclusions (1)

- Possible explanation:
  1. stimulation settings during blinded phase was below side-effect treshold (preserve masking)
  2. Cerebral plasticity
  3. Complex of TS
  4. N = 4 non responders → N = 2, contacts not in aGPi

Conclusions (2)

High levels of satisfaction → YGTSS suitable marker?

Pallidal vs Thalamus or even more targets might be effective

Meta-analysis

neuropsychiatric disorders such as attention deficit hyperactivity disorder and OCD is common in patients with TS, further complicating treatment. To address some of this ongoing uncertainty, the Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group issued updated recommendations for the treatment of TS with DBS in December 2014, highlighting the need for a multidisciplinary approach, emphasizing pre- and postoperative outcome measures, and proposing inclusion and exclusion criteria for DBS in patients with TS.[254]

Conclusions (3)

frontiers in Neuroscience

euron EUROPEAN GRADUATE SCHOOL OF NEUROSCIENCE

PERSPECTIVE
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The International Deep Brain Stimulation Registry and Database for Gilles de la Tourette Syndrome: How Does It Work?

Wissam Deeb[1], Peter J. Rossi[1], Mauro Porta[2], Veerle Visser-Vandewalle[3], Domenico Servello[4], Peter Silburn[5,6], Terry Coyne[6,7], James F. Leckman[8], Thomas Foltynie[9], Marwan Hariz[9], Eileen M. Joyce[9], Ludvic Zrinzo[9], Zinovia Kefalopoulou[9], Marie-Laure Welter[10], Carine Karachi[11,12], Luc Mallet[11,13,14], Jean-Luc Houeto[15], Joohi Shahed-Jimenez[16], Fan-Gang Meng[17], Bryan T. Klassen[18], Alon Y. Mogilner[19], Michael H. Pourfar[19], Jens Kuhn[20], L. Ackermans[21], Takanobu Kaido[22], Yasin Temel[23,24], Robert E. Gross[25], Harrison C. Walker[26], Andres M. Lozano[27], Suketu M. Khandhar[28], Benjamin L. Walter[29], Ellen Walter[30], Zoltan Mari[31], Barbara K. Changizi[32], Elena Moro[33], Juan C. Baldermann[34], Daniel Huys[34], S. Elizabeth Zauber[35], Lauren E. Schrock[36], Jian-Guo Zhang[37], Wei Hu[1], Kelly D. Foote[1,38], Kyle Rizer[1], Jonathan W. Mink[39], Douglas W. Woods[40], Aysegul Gunduz[1,41] and Michael S. Okun[1]*

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Conclusions (4)

Future studies might focus on a better characterization of the clinical effects of distinct regions, rather than searching for a unique target.

(Baldermann et al. 2016)

OCD

- obsessions (thoughts) and compulsions (actions)
- > 1h day
- quality of life

- less respons on medication and therapy

OCD

- non responders
  - 1. medication
  - 2. cognitive/behavioural therapy CBT
  - YBOCS >30
  - multidisciplinairy team

OCD

- 1999
- orbiotofronto-striatio-thalamocortical network
  - 1. anterior limb of internal capsule (ALIC)
  - 2. ventral capsule and ventral striatum (VC/VS)
  - 3. nucleus accumbent (Nac)
  - 4. nucleus subthalamicus (STN)

OCD

- mechanism unknown
- neuronal inhibition vs neuronal exitation

- no best target yet
- respons >30%

- infection rate 5-25%!!

OCD

- promising therapy
- more research and follow-up —> larger studies are necessary

Depression

- although hypothesis no randomised trials confirmed
- DBS not (yet) suitable for depression

DBS and neuropsychiatry

DBS may show promise for OCD and depression
but,
the results are limited:
- small sample size
- insufficient randomized controlled data

DBS by OCD has FDA approval.

Other psychiatric indications (like Tourette) are currently of a purely experimental nature.

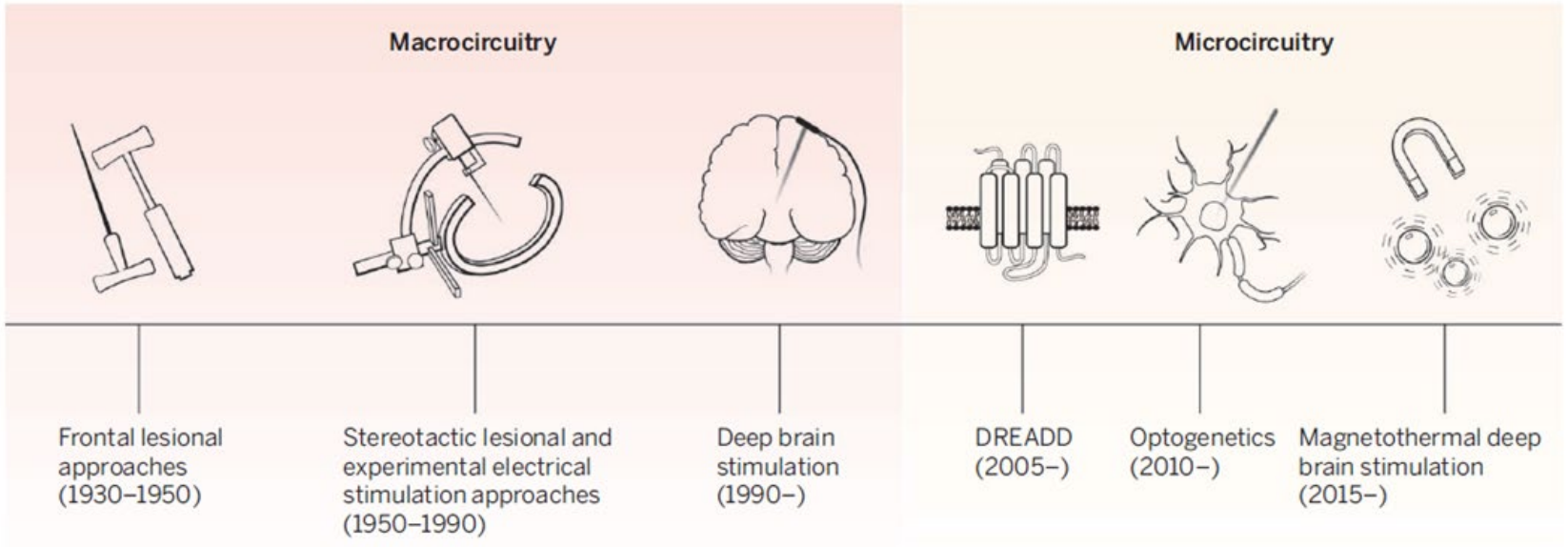
Trends

NEUROSCIENCE

Treating brain disorders with neuromodulation

By **Yasin Temel** *and* **Ali Jahanshahi**
Science, 2015

Key neuromodulation approaches



Trends in treatment. Techniques to alter neuron activity in the brain shifted from a macrocircuitry focus to one that now concentrates on modulating specific populations of neurons. The time periods indicate the global course of development.

- Team

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