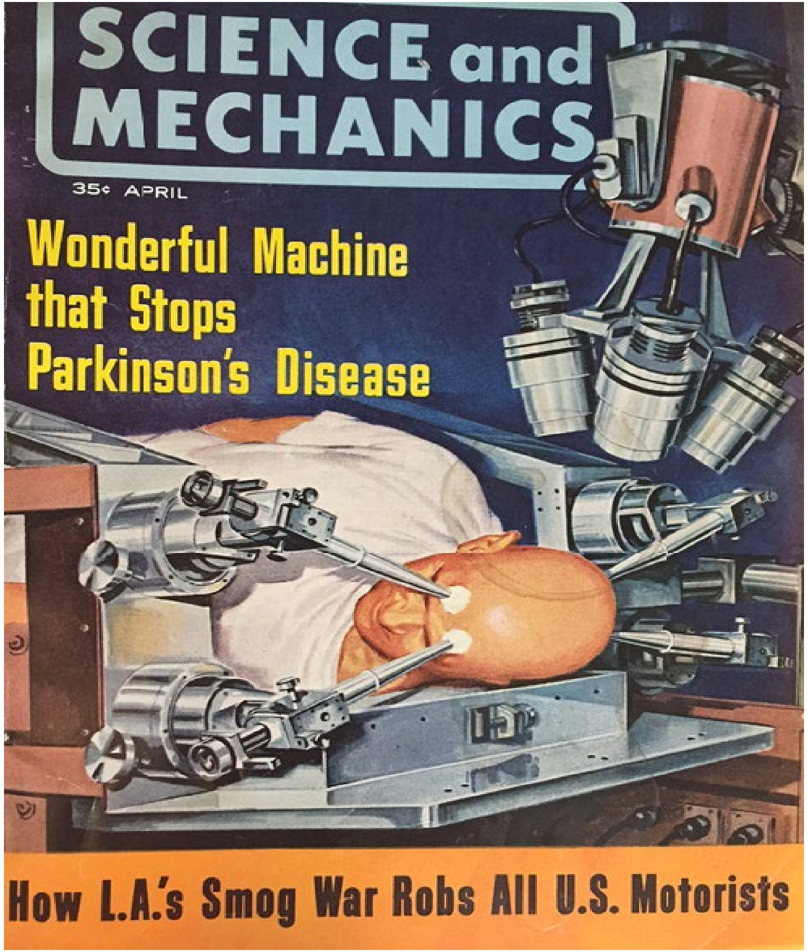
Terapia lesionale con ultrasuoni ad alto campo (MRgFUS)

Roberto Eleopra
UOC Neurologia I

Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

Sistema Socio Sanitario
Regione Lombardia



Science and Mechanics magazine, April 1963

Year	Description
1880	Piezoelectric effect (Curie)
1907	Electronic vacuum tube (de Forest)
1918	Sonar (Langevin)
1927	Effects on biologic tissues (Looms and Wood)
1942	HIFU effects in animals (Lynn and Putnam; Lynn et al.[54])
1950–1969	Molecular studies on HIFU effects (Francis and William Fry; Fry and Meyers[29])
1951–1960	Radiofrequency generator and electrode development (Bernard Cosman, in light of FUS developments)
1951–1967	Radiosurgery and Gamma Knife development (Lars Leksell after ultrasound investigation)
1960–1980	Clinical studies on HIFU surgery with open skull (Fry and Heimburger)
1980s–present	MRI technology
Early 1990s	Ultrasound phased arrays (Hynyen)
Mid-1990s	MR thermometry (Jolesz)
2001	The first integrated MRgFUS machine (InSightec Ltd.)
2006	Report on MRgFUS for treatment of GBM after craniotomy (Ram et al.[60])
2009	tcMRgHIFU for chronic neuropathic pain (Martin et al.[56])
2009	In vitro study for thrombolysis by histotripsy using HIFU (Maxwell et al.[57])
2010	Phase I clinical trial for noninvasive tumor ablation; to prevent heating of the skull, a water cooling, circulating, and degassing was used (McDannold et al.[58])
2011–2013	Use of tcMRgHIFU for ET (Elias et al.[22] and Lipsman et al.[53])
2013–2014	In vitro and in vivo studies for sonothrombolysis of ICH (Monteith et al.[64] and Harnof et al.[38])
2014	Report on the first experience with tcMRgHIFU for PD (Magara et al.[55])
2016	Randomized controlled trial of tcMRgFUS thalamotomy for ET (Elias et al.[23])
2016	Preliminary report on randomized controlled trial of MRgFUS thalamotomy for PD (Bond et al.)[4]

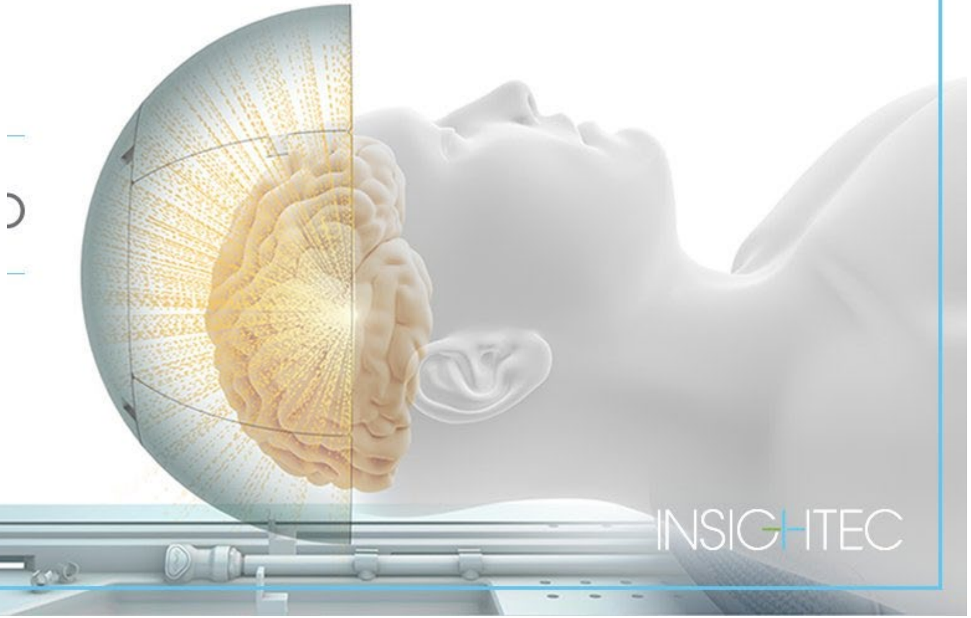
ICH = intracerebral hemorrhage.

Magnetic Resonance guided Focused UltraSound (MRgFUS)

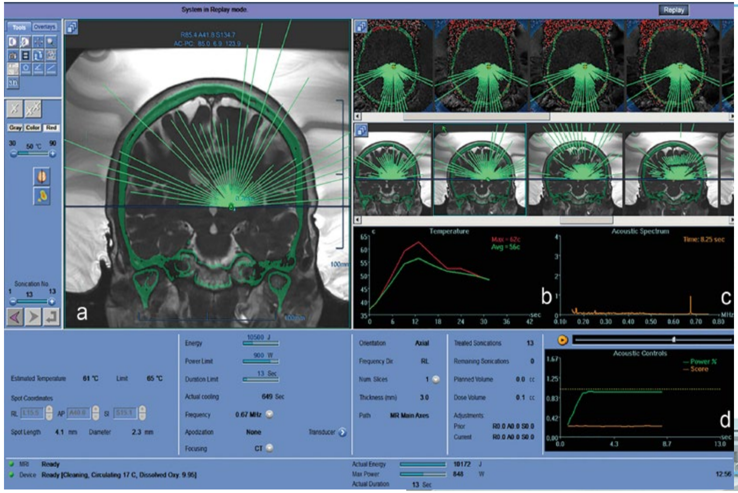
Principio funzionamento:

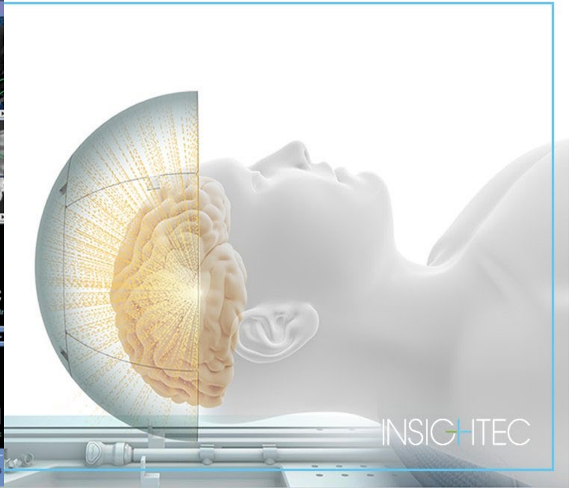
- **fascio di ultrasuoni emesso da un elevato numero di trasduttori su un bersaglio (concentrati) → aumento rapido temperatura del tessuto tale da distruggerlo o causare una lesione permanente.**

- **Il processo è monitorato in tempo reale utilizzando immagini di Risonanza Magnetica (RM) che permettono:**
  - **Visualizzare le strutture anatomiche**
  - **Rilevare variazioni di temperatura all'interno del cervello (imaging termometrico).**



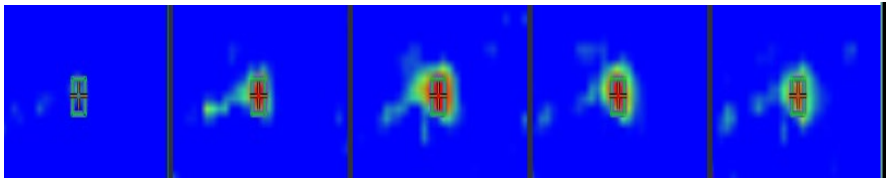
Magnetic Resonance guided Focused UltraSound MRgFUS

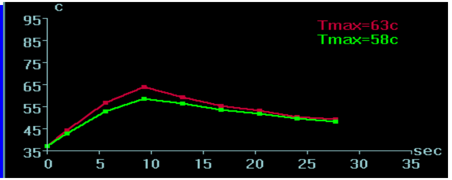




Combination of two well known technologies:

High intensity focused ultrasound **Magnetic resonance imaging (MRI)**

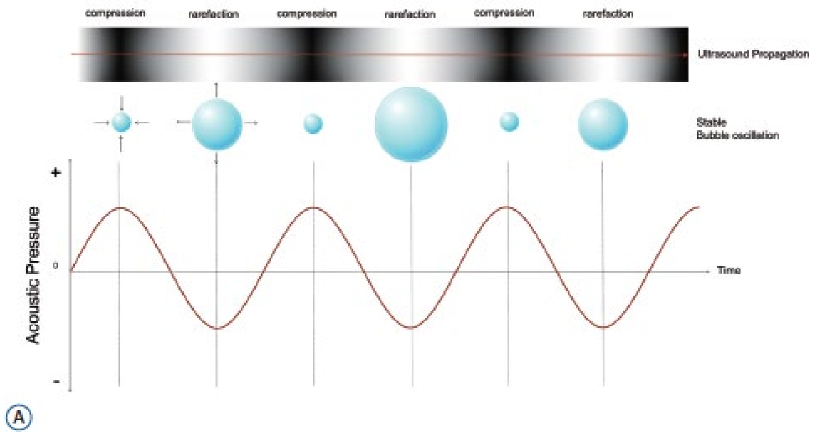




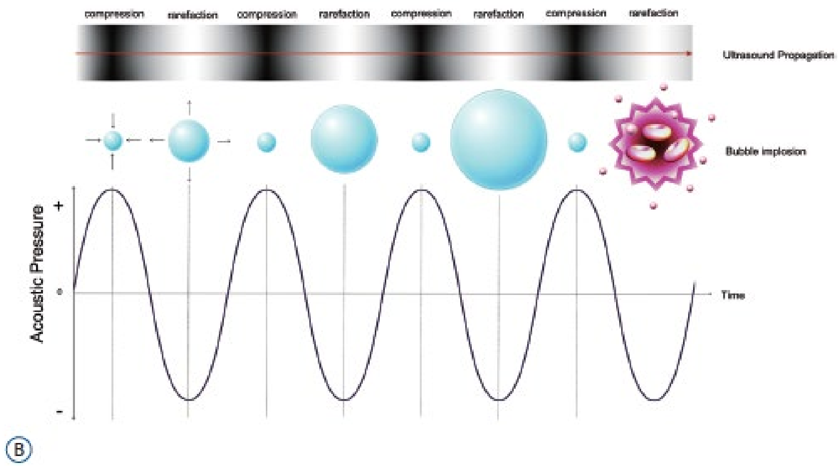
- Ultrasound is defined as an acoustic wave with fundamental frequency above the upper limit of human hearing (>20 kHz). Ultrasound frequencies for medical imaging range between 2–20 MHz, while those for therapeutic applications are lower (0.2–2 MHz)

- HIFU requires an intensity greater than 1000 W/cm^2 in continuous mode induces frictional energy in the target area so that the target tissue is heated, causing protein denaturation, DNA fragmentation, coagulative necrosis, and cellular death

- In contrast, low intensity focused ultrasound (LIFU) has been shown to modulate activity of neurons and glial cells, and is typically pulsed, with FDA limits of time-averaged intensities ≤ 94 mW/cm^2 and pulse-averaged intensities <190 W/cm^2. Depending on key pulsing parameters (repetition frequency, duty cycle, etc.) pulsed LIFU can either suppress or evoke neuronal activity



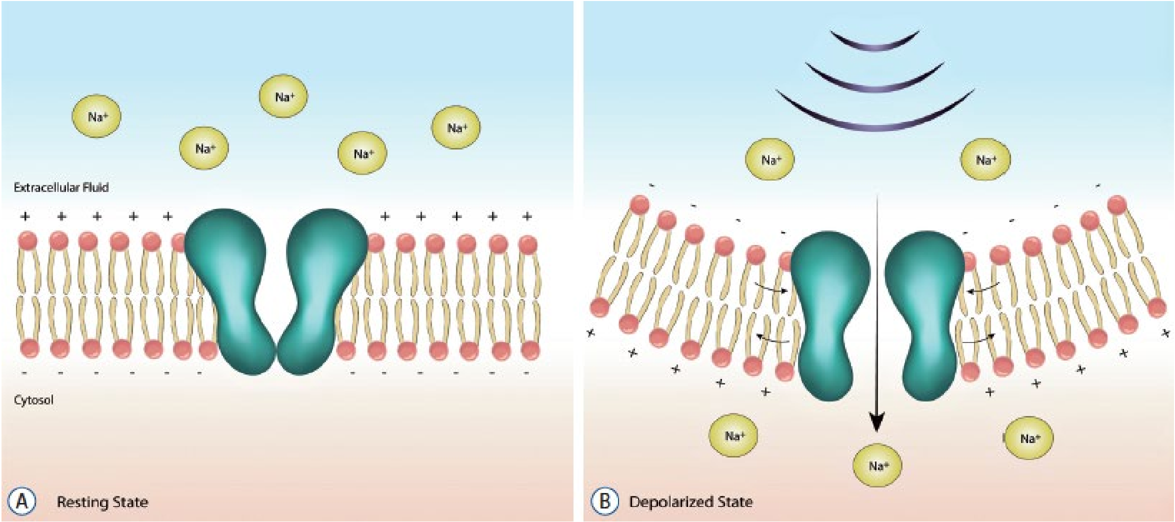
LIFU



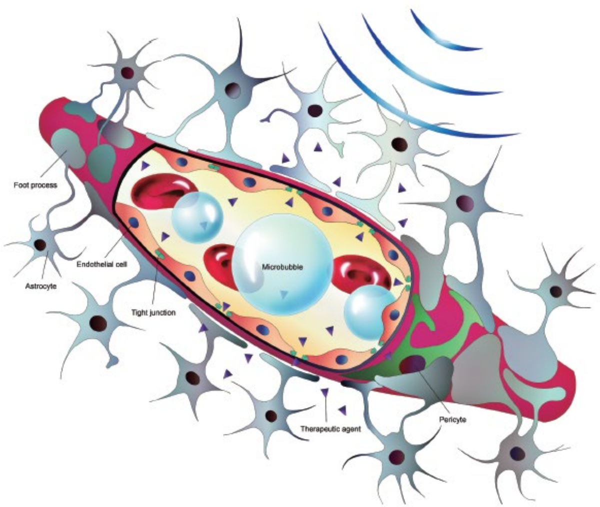
HIFU

Hynynen K et al. Radiology, 2001

Low Intensity Focal Ultrasound (LIFU)



MRgFUS-Mediated Thermal Ablation and BBB Opening | Lee EJ, et al.



JKNS, 2019

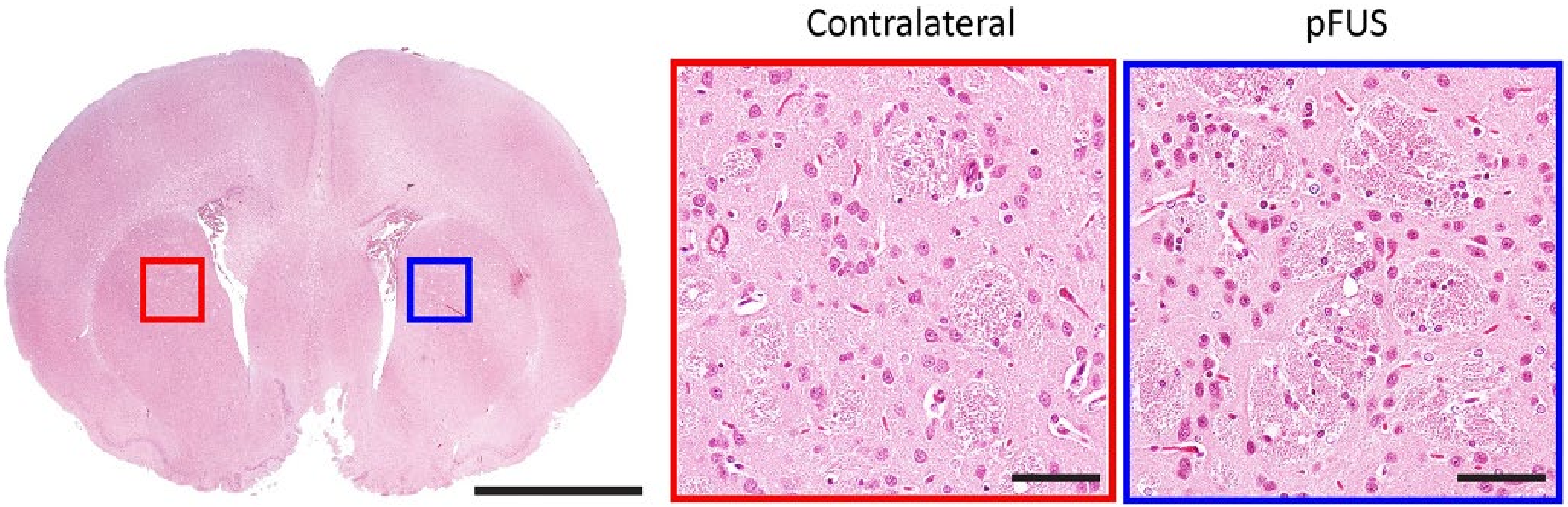


Fig 6. Histological analysis of MRgFUS-treated brains. A representative brain slice obtained 2 hours following MRgFUS treatment of the left striatum indicating a lack of visible differences between the treated (blue) and untreated (red) regions. Left scale bar = 250 μm, center and right scale bars = 25 μm.

Hersch et al, PLOS One 2018

CE approval content (2012)

Intended Use
The ExAblate System is intended for thermal ablation of targets in the thalamus, sub-thalamus and pallidum regions of the brain

Indication for Use
ExAblate 4000 transcranial MR guided focused ultrasound (TcMRgFUS) system is accurate and safe for the treatment of neurological disorders in the brain e.g.

- Essential Tremors “ET”
- Tremor Dominant Idiopathic Parkinson’s Disease “PD”,
- Neuropathic Pain “NP”

By heat induced focusing using ultrasound energy under full MR planning and thermal imaging control. This claim is derived from clinical treatments performed in the thalamus, sub-thalamus and pallidum regions


DEKRA

ADDENDUM

Belonging to certificate: 2110597CE01 1/1

CE MARKING OF CONFORMITY
MEDICAL DEVICES

Focused Ultra Sound Therapy Devices for Tissue Ablation

Issued to:

InSightec, Ltd.
5 Nachum Heth St.
PO Box 2059
Tirat Carmel 39120
Israel

This certificate covers the following product(s):

ExAblate 2000 UF and ExAblate 2100 UF:
Indication for use: Ablation of soft tissue for treatment of benign tumors, including uterine fibroids and adenomyosis through focused heating of sections by means of ultrasound energy under MRI control.

ExAblate 2000 Bone application and ExAblate 2100 Bone application:
Indication for use: Ablation of soft tissue and palliative treatment of cancerous tumors, including bone tumors through focused heating of sections by means of ultrasound energy under MRI control.

ExAblate 4000 transcranial MR guided focused ultrasound system (Type 1) intended for thermal ablation of targets in the thalamus, sub thalamus and pallidum regions of the brain.
Indication for Use: ExAblate 4000 transcranial MR guided focused ultrasound can be used for the treatment of neurological disorders (Essential Tremors, Tremor Dominant Idiopathic Parkinson's Disease - Unilateral) and Neuropathic Pain) in the brain by heat induced focusing using ultrasound energy under full MR planning and thermal imaging control.

Initial date: 27 January 2009
Revision date: 29 November 2012

DEKRA Certification B.V.

drs. G.J. Zoetbrood
Managing Director

ing. A.A.M. Laan
Certification Manager

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Problema ossa cranio

(valore SDR)

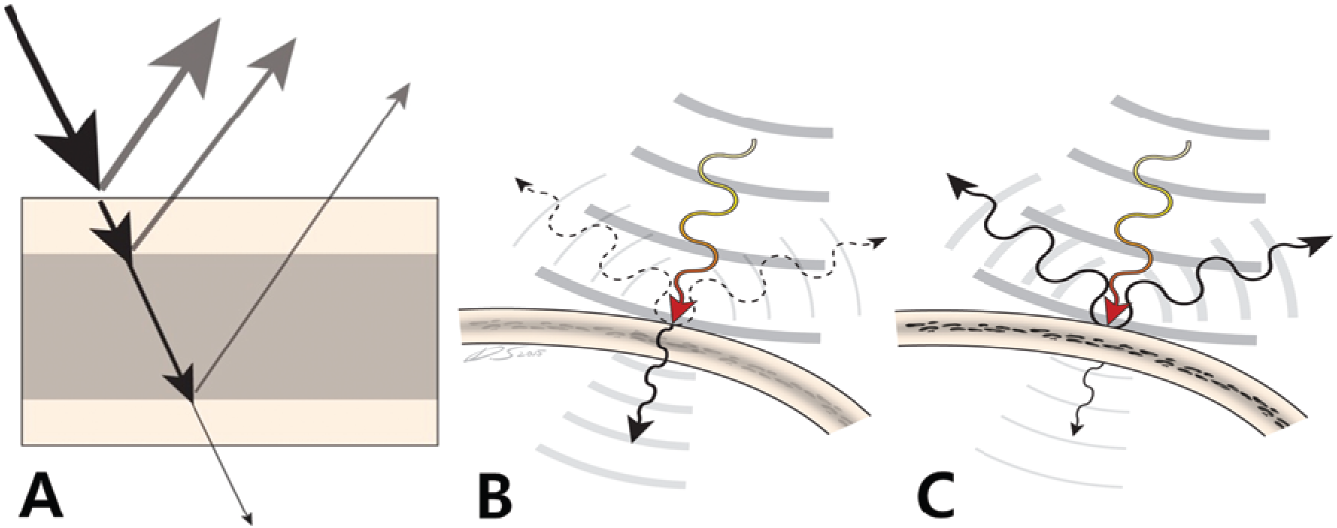
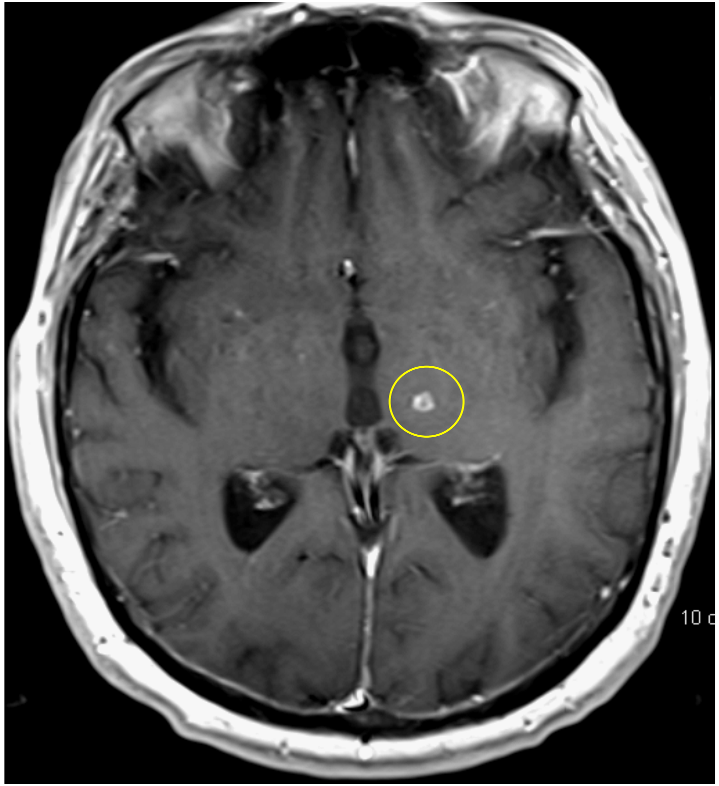


FIG. 4. Ultrasonic energy transmission across skull. **A:** Ultrasonic energy attenuation and reflection at cortical and marrow bone. **B:** Higher energy transmission across skulls with higher SDR. **C:** Lower energy transmission across skulls with lower SDR. Copyright Jin Woo Chang. Published with permission. Figure is available in color online only.

J Neurosurg Volume 124 • February 2016

Precisione bersaglio inferiore al millimetro !!!



	Mean +/- SD (mm)
Dorsoventral	0.72+/-0.39
Anteroposterior	0.54+/-0.34
Mediolateral	0.72+/-0.42

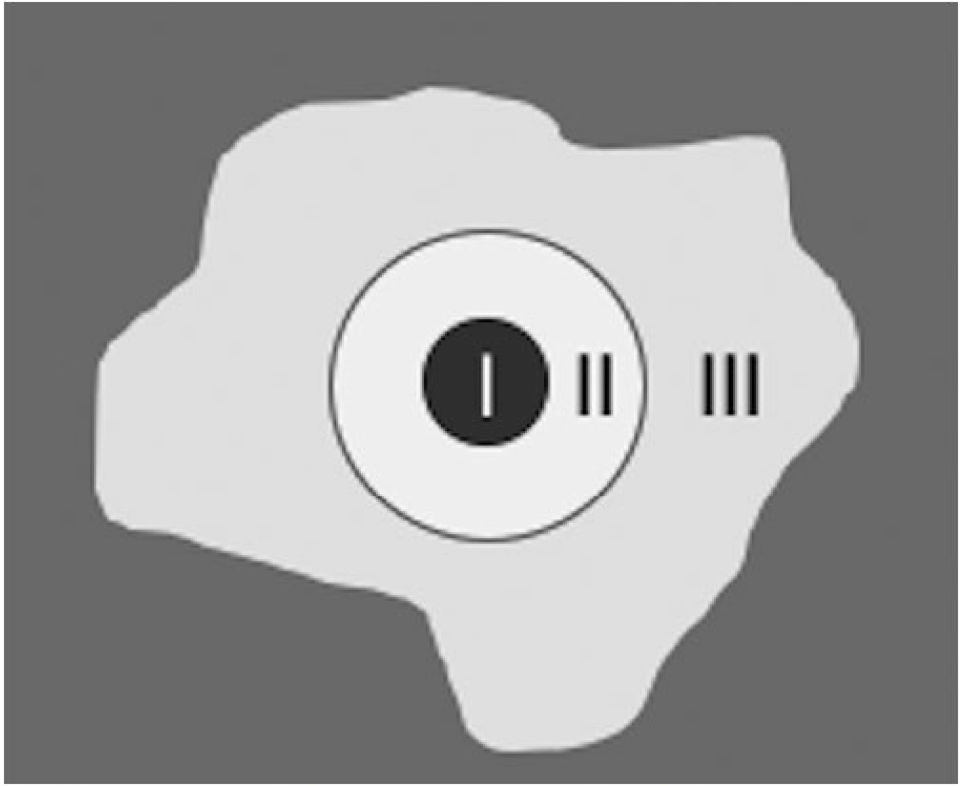


FIG. 1. Lesion zones. Zone I, necrotic core. Zone II, cytotoxic edema. Zone III, vasogenic edema. Based on a representation by Wintermark et al.[28]

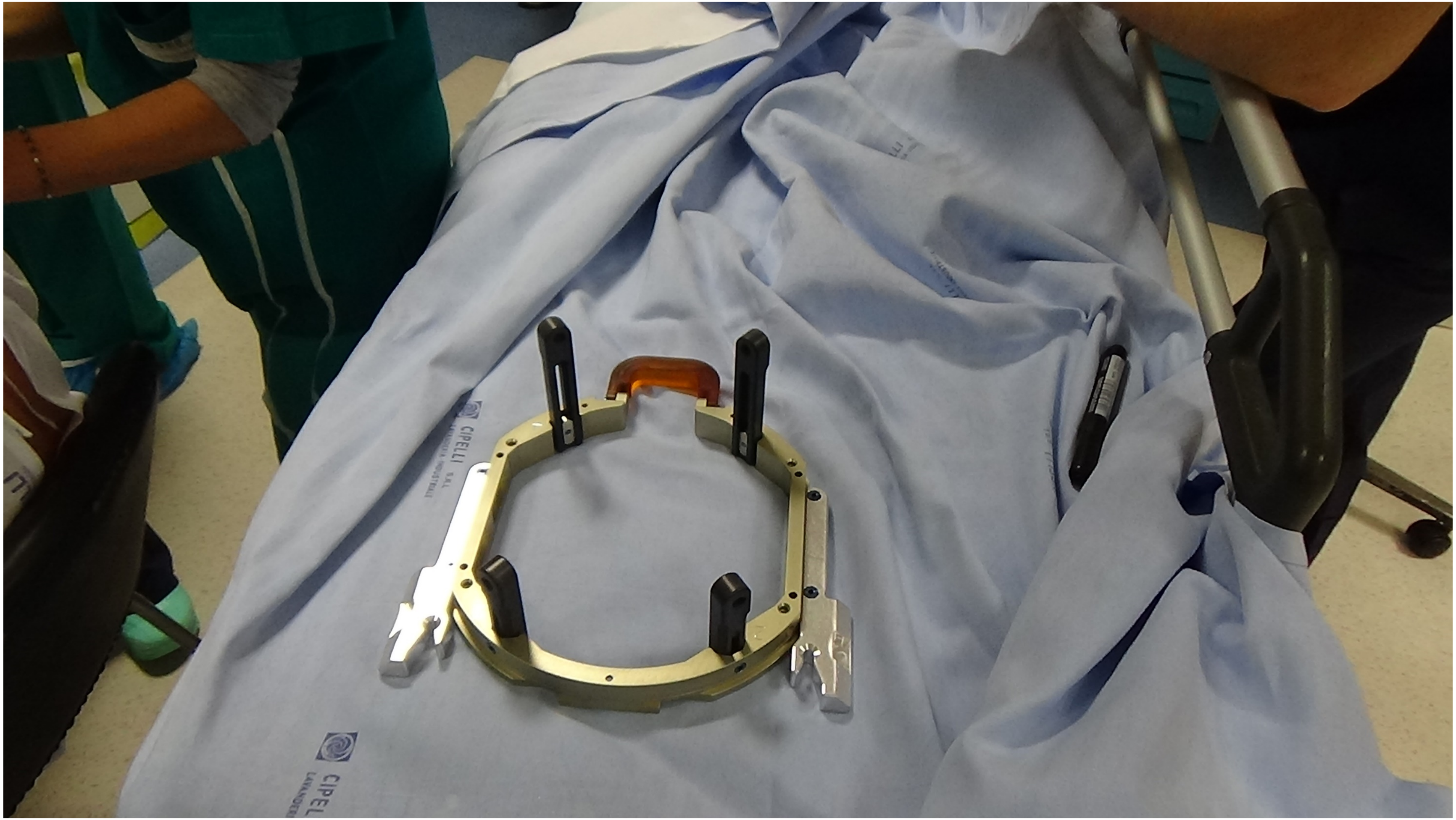
Procedura trattamento

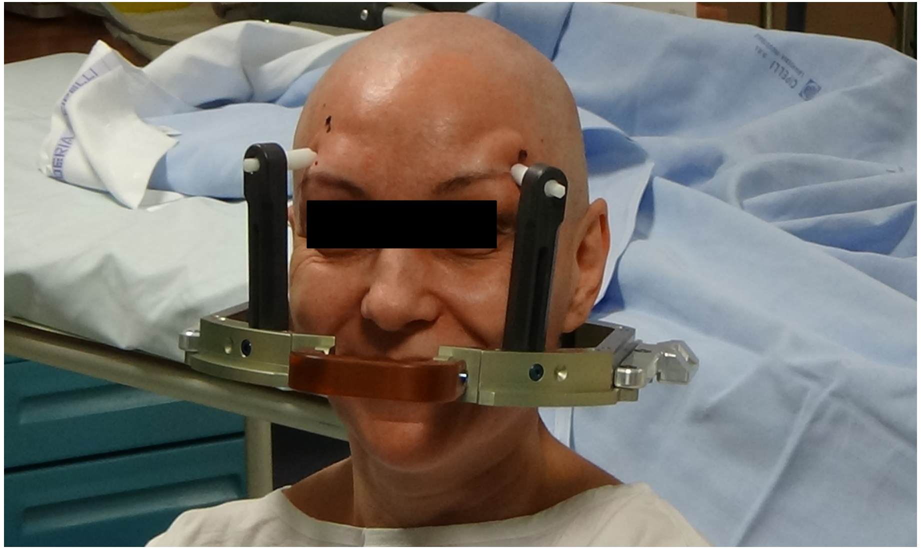
Preparazione paziente

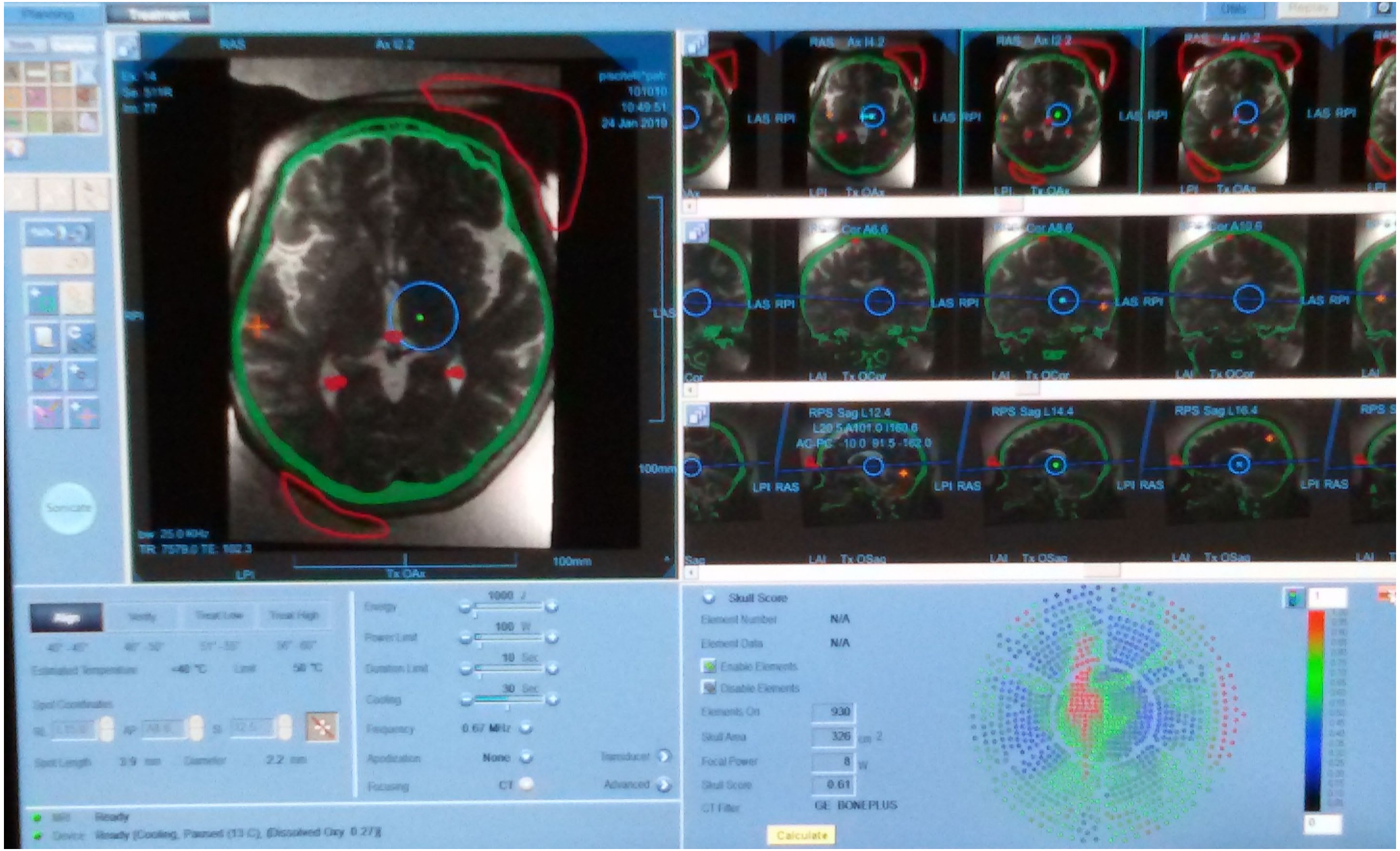
Calcolo posizione bersaglio (target)

Trattamento
(sonificazione)

Verifica clinica durante procedura






RAS
Ax I2.2
LPI
Tx OAx
100mm
LAS RPI
RPS Sag L12.4
RPS Sag L14.4
RPS Sag L16.4
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Skull Score
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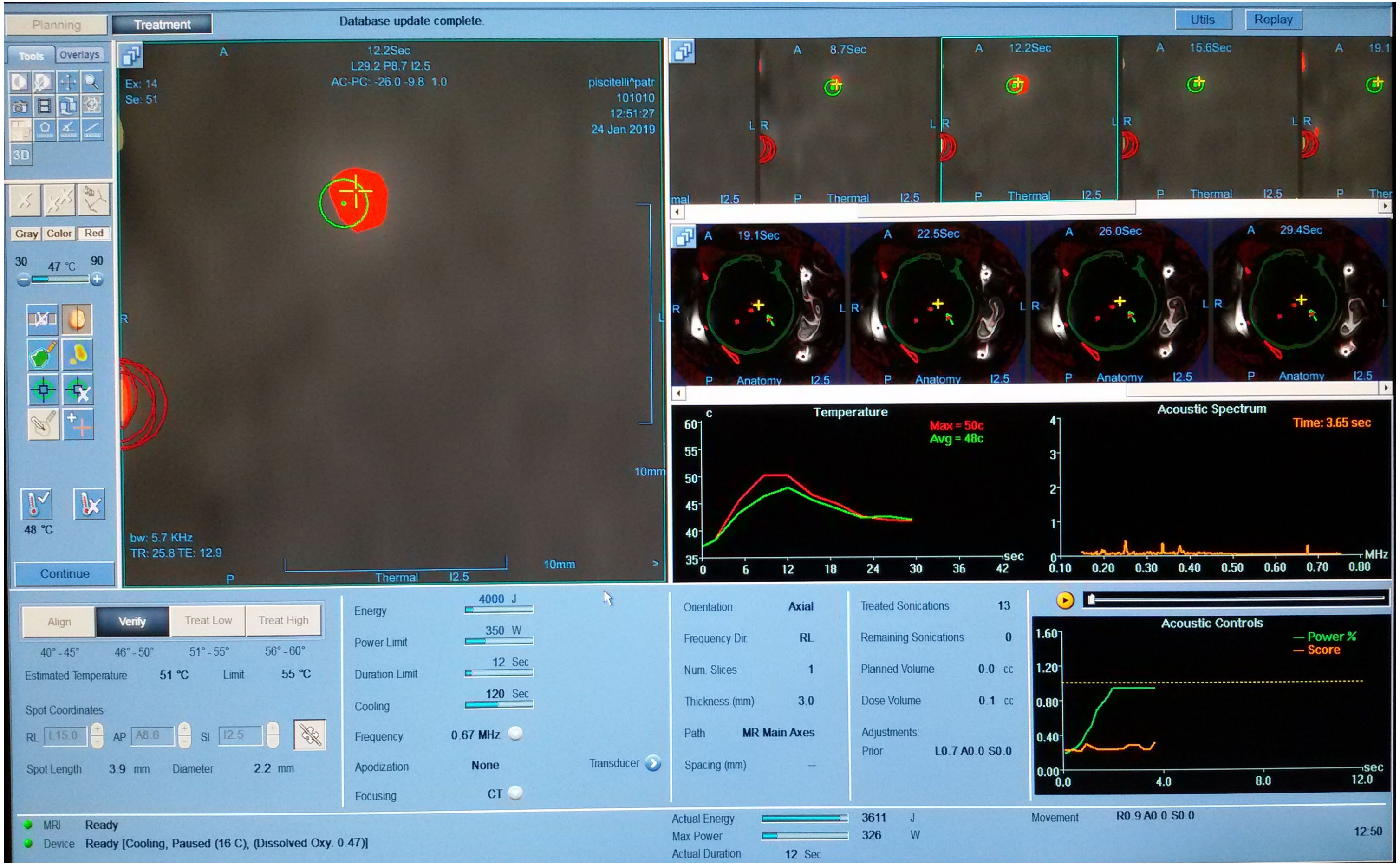
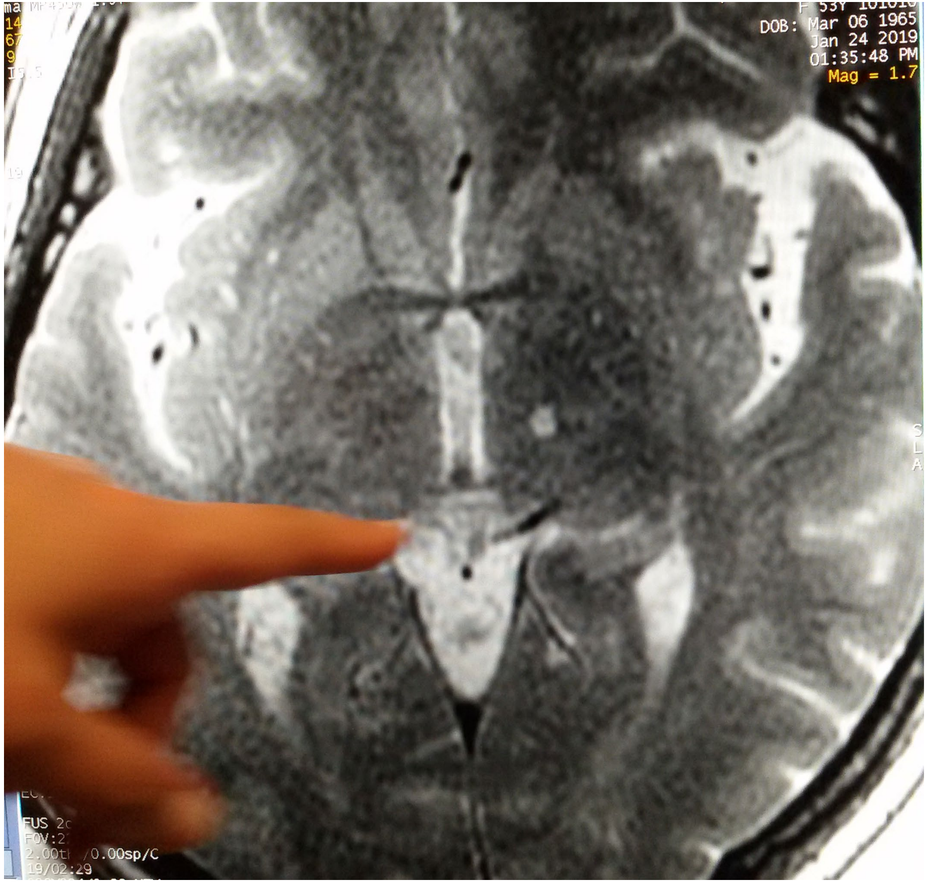
CT Filter GE BONEPLUS
Calculate


Planning
Treatment
Database update complete.
Utils
Replay
12.2Sec
L29.2 P8.7 I2.5
AC-PC: -26.0 -9.8 1.0
Ex: 14
Se: 51
12:51:27
24 Jan 2019
bw: 5.7 KHz
TR: 25.8 TE: 12.9
Thermal
Temperature
Max = 50c
Avg = 48c
Acoustic Spectrum
Time: 3.65 sec
Acoustic Controls
Power %
Score
Align
Verify
Treat Low
Treat High
Estimated Temperature 51 °C Limit 55 °C
Spot Coordinates
Spot Length 3.9 mm Diameter 2.2 mm
Energy 4000 J
Power Limit 350 W
Duration Limit 12 Sec
Cooling 120 Sec
Frequency 0.67 MHz
Apodization None
Focusing CT
Transducer
Orientation Axial
Frequency Dir. RL
Num. Slices 1
Thickness (mm) 3.0
Path MR Main Axes
Spacing (mm)
Treated Sonications 13
Remaining Sonications 0
Planned Volume 0.0 cc
Dose Volume 0.1 cc
Adjustments:
Prior L0.7 A0.0 S0.0
MRI Ready
Device Ready [Cooling, Paused (16 C), (Dissolved Oxy. 0.47)]
Actual Energy 3611 J
Max Power 326 W
Actual Duration 12 Sec
Movement R0.9 A0.0 S0.0
12:50
Continue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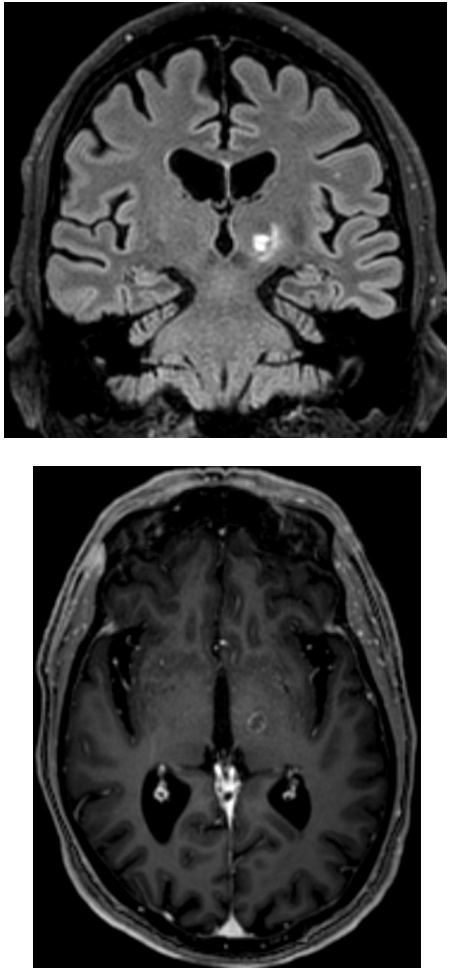
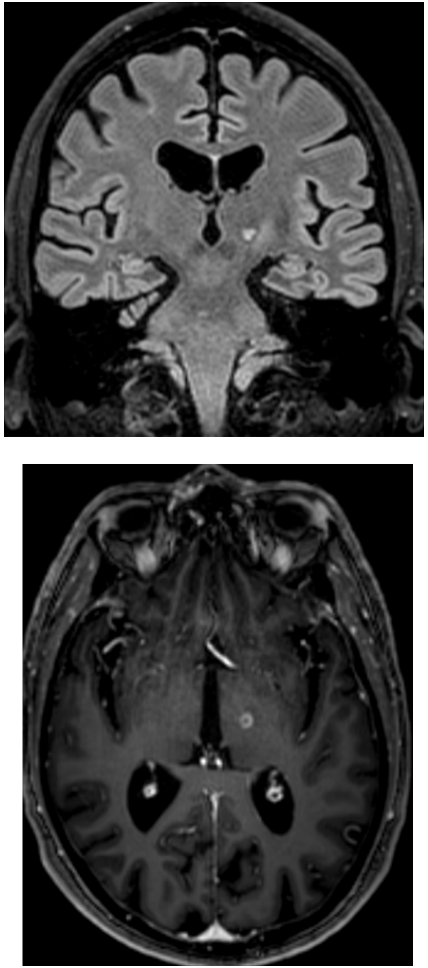


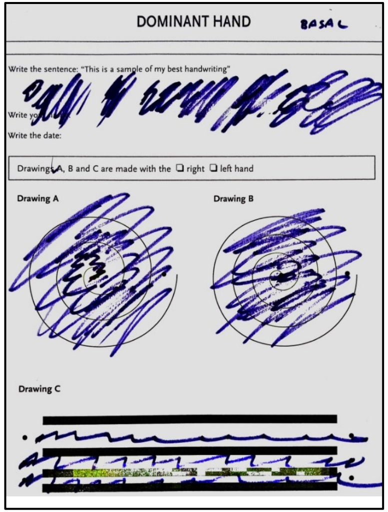
dopo 24 ore



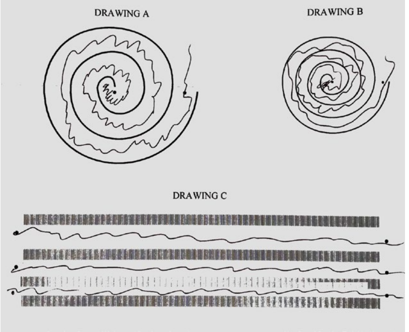
Dopo 30 giorni

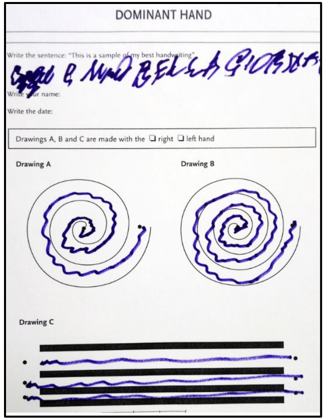
Scrittura

Pre Trattamento

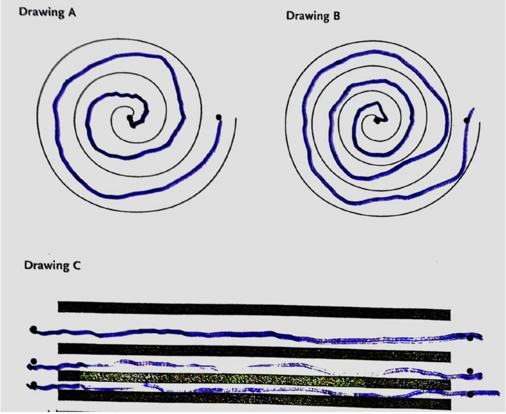


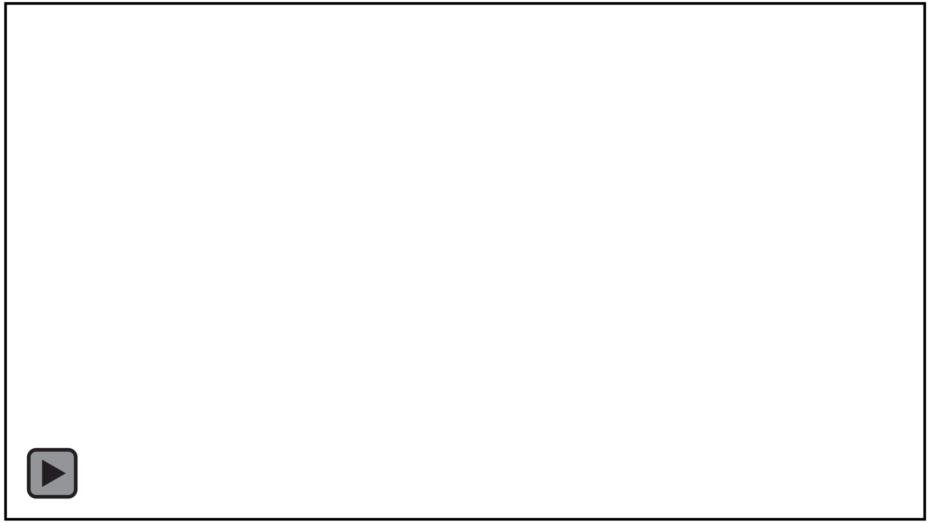
durante MRgFUS



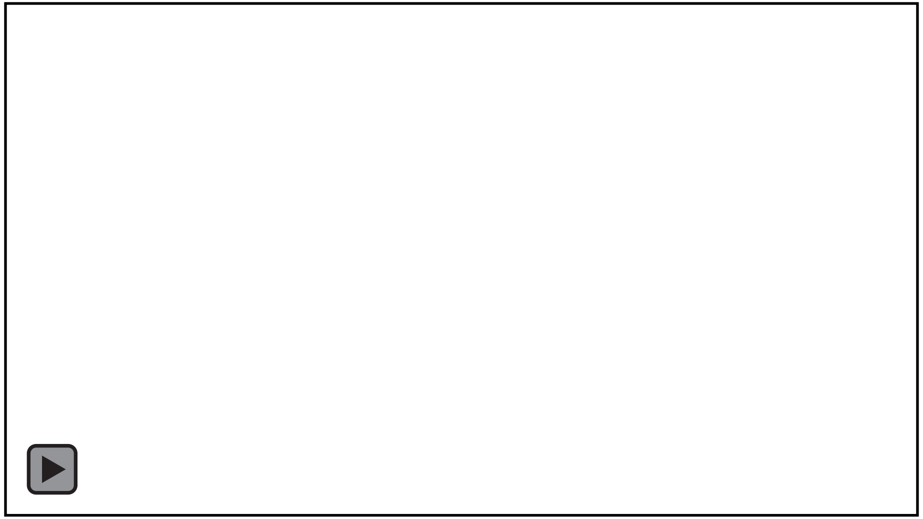


Termine Trattamento





pre MRgFUS



post MRgFUS

Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments

Marc N. Gallay, MD, David Moser, BSc, and Daniel Jeanmonod, MD

Sonimodul Center for Ultrasound Functional Neurosurgery, Solothurn, Switzerland

OBJECTIVE Since the first clinical application of the incisionless magnetic resonance–guided focused ultrasound (MRgFUS) technology only small series of patients have been reported, and thus only extrapolations of the procedure-related risks could be offered. In this study, the authors analyze side-effects and targeting accuracy in 180 consecutive treatments with MRgFUS for chronic therapy-resistant idiopathic Parkinson's disease (PD), essential tremor (ET), cerebellar tremor (CT), and neuropathic pain (NP), all performed in their dedicated center.

METHODS A total of 180 treatments with MRgFUS for chronic therapy-resistant idiopathic PD, ET, CT, and NP were prospectively assessed for side-effects and targeting accuracy. Monitoring for later side-effects was continued for at least 3 months after the procedure in all but 1 case (0.6%); in that single case, the patient was lost to follow-up after an uneventful early postoperative cours J Neurosurg May 25, 2018 ets were the pallidothalamic tract (pallidothalamic tractotomy, n = 105), the cerebellothalamic tract (cerebellothalamic tractotomy, n = 50), the central lateral nucleus (central lateral thalamotomy, n = 84), the centrum medianum (centrum medianum thalamotomy, n = 12), and the globus pallidus (pallidotomy, n = 2). Cognitive testing was performed before, 1–2 days after, and 1 year after the procedure. The Mini–Mental State Examination (MMSE) was used for the first 29 cases and was then replaced by the Montreal Cognitive Assessment (MoCA). Lesion reconstruction and measurement of targeting accuracy were done on 2-day posttreatment MR images for each performed target. To determine targeting accuracy measurement, 234 out of the 253 lesions depicted in the 2-day postoperative MR examination could be 3D-reconstructed.

RESULTS The mean MoCA score was slightly improved 2 days postoperatively ($p = 0.002$) and remained stable at 1-year follow-up ($p = 0.03$). The mean MMSE score was also slightly improved 2 days postoperatively and at 1-year follow-up, but the improvement was not statistically significant ($p = 0.06$ and $p = 0.2$, respectively). The mean (± SD) accuracy was 0.32 ± 0.29 mm, 0.29 ± 0.28 mm, and 0.44 ± 0.39 mm for the mediolateral, anteroposterior, and dorsoventral dimensions, respectively. The mean 3D accuracy was 0.73 ± 0.39 mm. As to side-effects, 14 events over 180 treatments were documented. They were classified into procedure-related (n = 4, 2.2%), effect on neighboring structures (n = 3, 1.7%), and disease-related (n = 7, 3.9%). There was no bleeding.

CONCLUSIONS The incisionless transcranial MRgFUS technology demonstrates a higher targeting accuracy and a lower side-effect profile than techniques requiring cerebral penetration. In the absence of penetration brain shift, this technique avoids the placement of a thermolesion away from the chosen target, thus suppressing the need for reversible therapeutic energy application. With the use of proper physiopathology-based targets, definitive therapeutic effects can be coupled with sparing of sensory, motor, and paralimbic/multimodal thalamocortical functions. Clinical efficacy, not analyzed in this investigation, will ultimately rest in proper target selection and optimized thermolesional coverage of the target.

https://thejns.org/doi/abs/10.3171/2017.12.JNS172054

J Neurosurg May 25, 2018

MRgFUS: AEs in E.T.

1. **Frame related (pin site numbness, infection, or pain)**
2. **Sonication related (headache, scalp burn, nausea, vomiting)**
3. **Thalamotomy related, divided into four subgroups:**

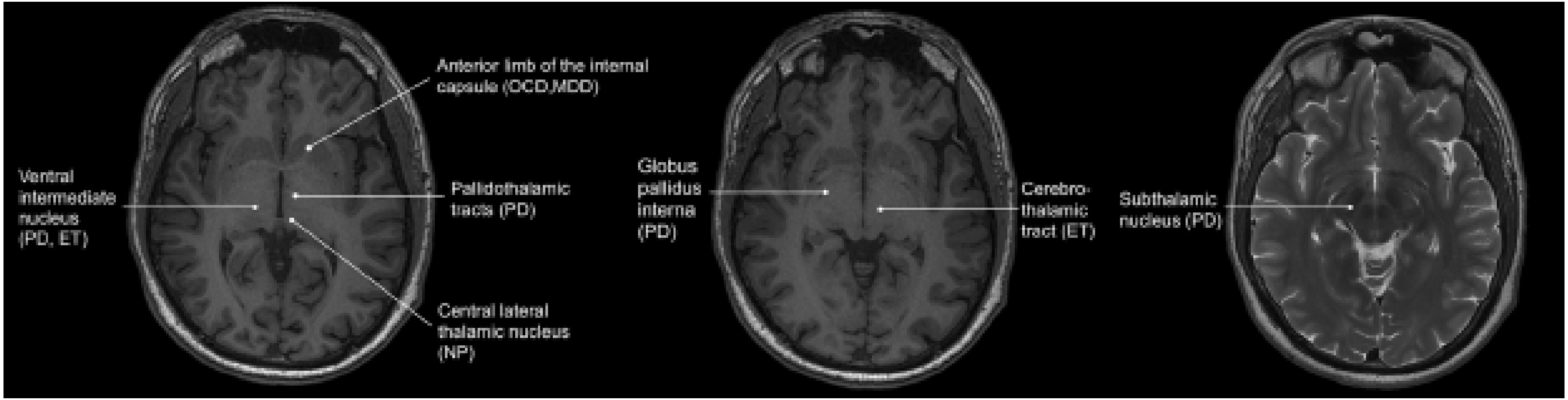
- **Sensory disturbances including numbness, paresthesia, dysesthesias, and dysgeusia.**
- **Speech and swallowing disturbances (dysarthria, dysphagia).**
- **Balance and gait disturbances (ataxia).**
- **Weakness or decreased limb coordination**

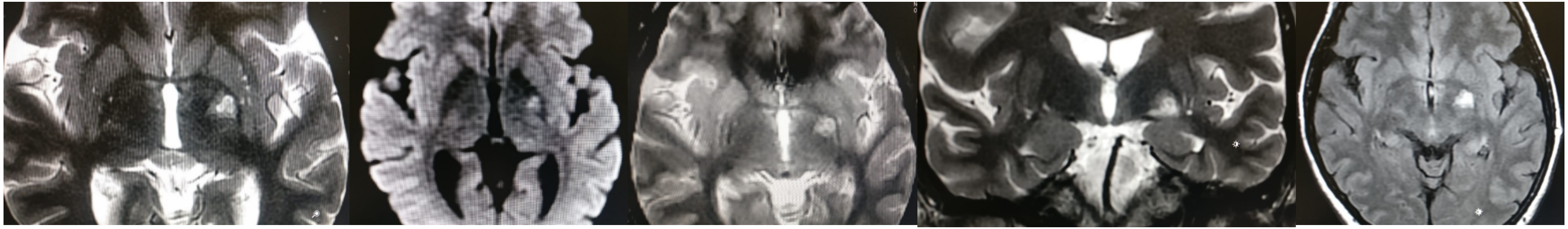
Fishmann et al, Mov Dis 2018

TABLE 2. Summary of AEs after MRgFUS thalamotomy by type and level of severity (N = 186 subjects/443 events)

	Mild	Moderate	Severe
Frame-related	39 (9%)	3 (0.7%)	0
Sonication-related	132 (30%)	55 (12.4%)	2 (0.4%)
Thalamotomy-related			
Sensory	84 (19%)	8 (2%)	
Speech	15 (3%)	2 (0.4%)	
Balance	59 (13%)	14 (3.2%)	3 (0.7%)
Strength	23 (5%)	4 (1%)	
Totals	352 (79%)	86 (20%)	5 (1%)

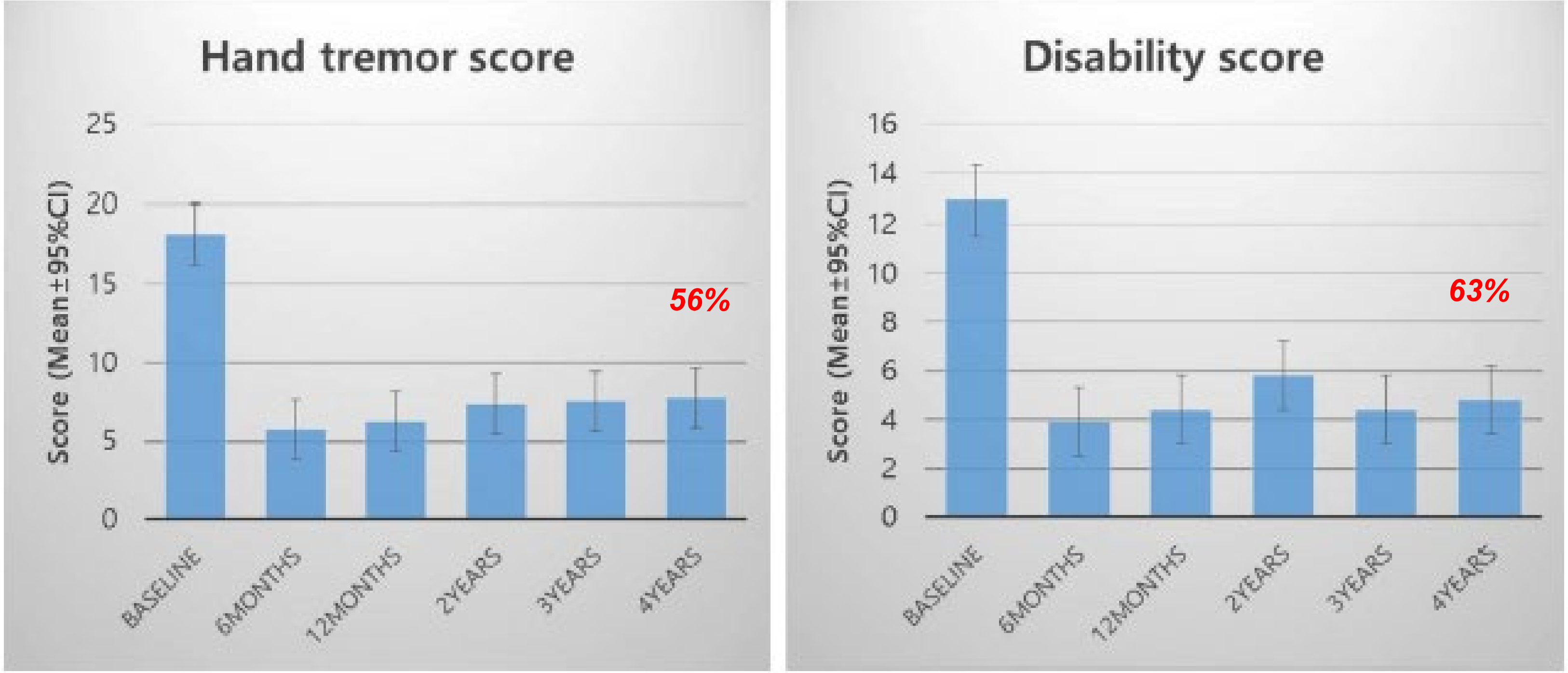
MRgFUS: Prospettive Cliniche



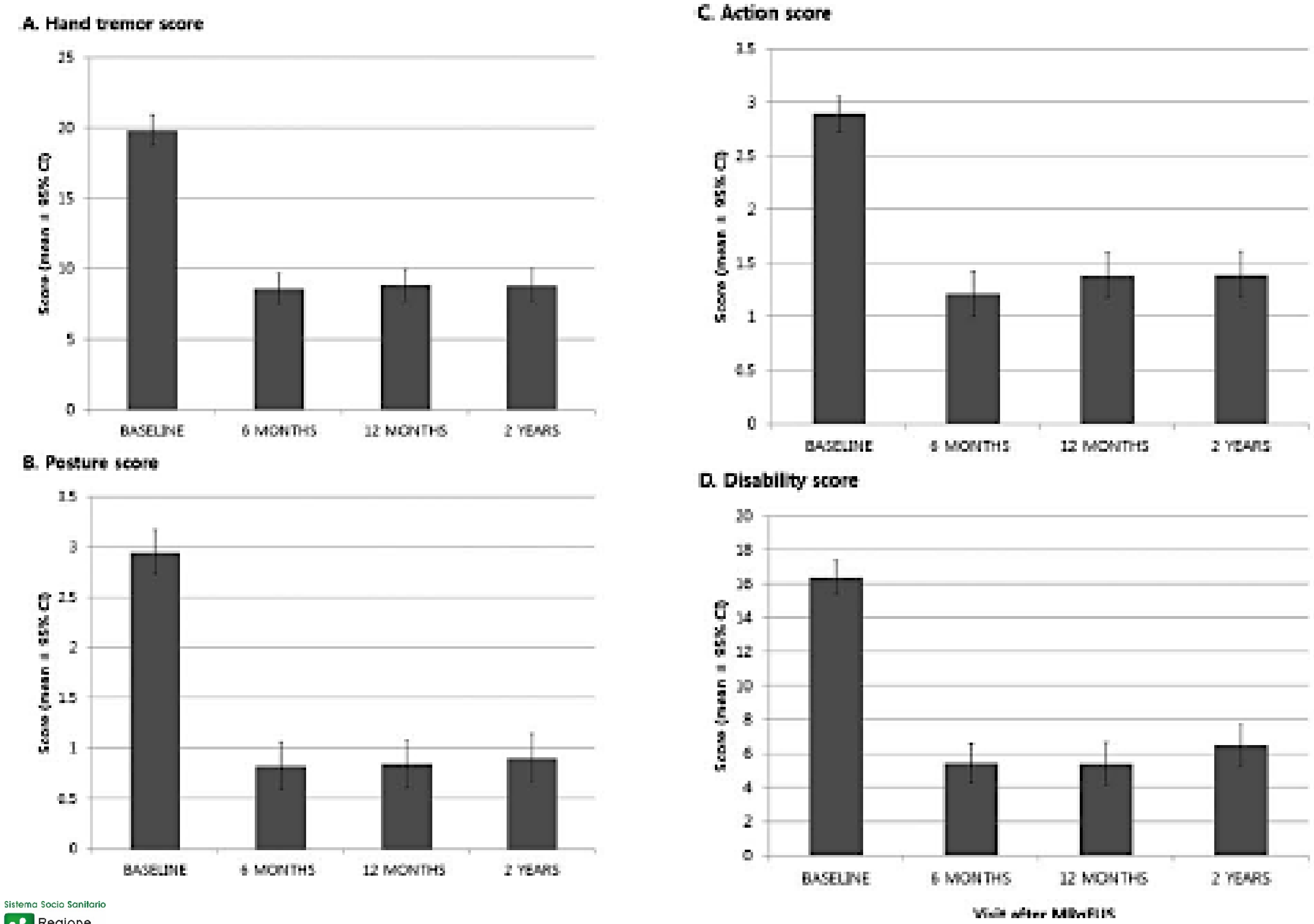


PD006 Trial

MRgFUS in ET



Yong-Sook Park et al., Mov Dis 2019



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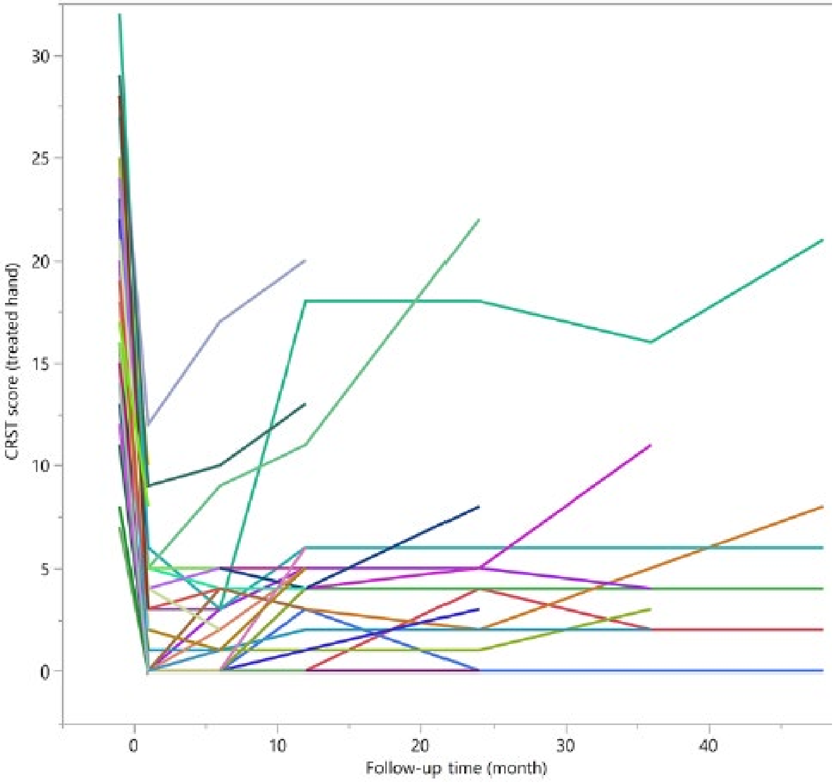
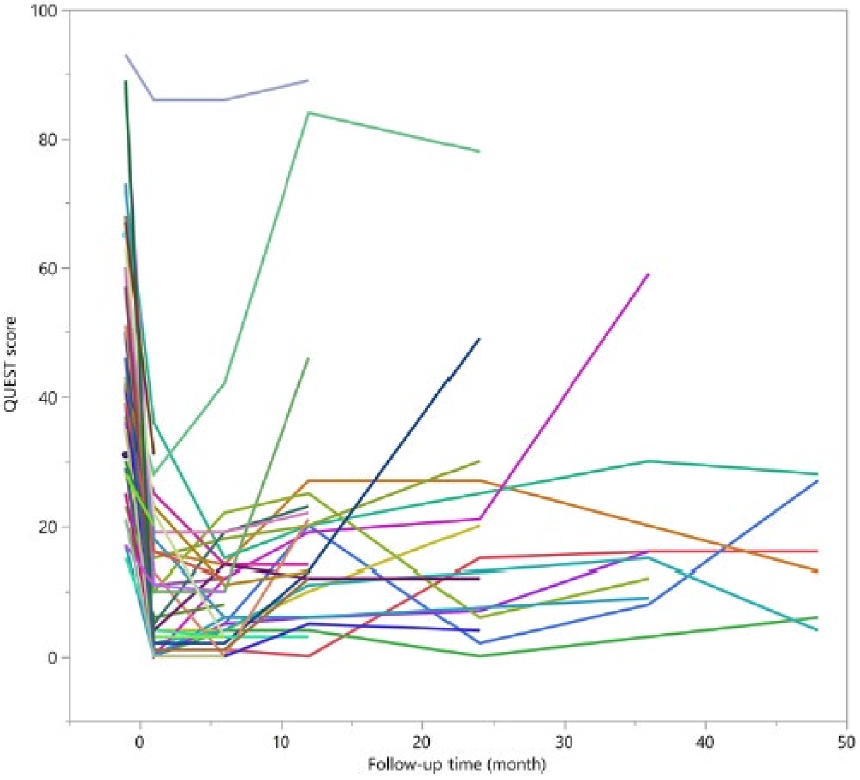
Chang et al, Ann Neurol 2018

MRgFUS in ET



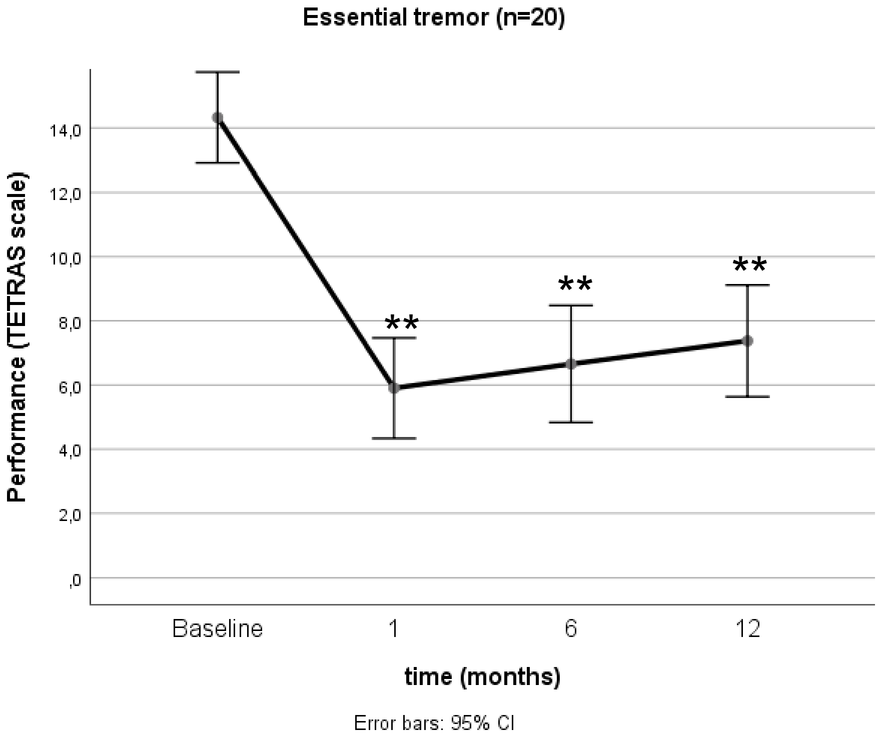


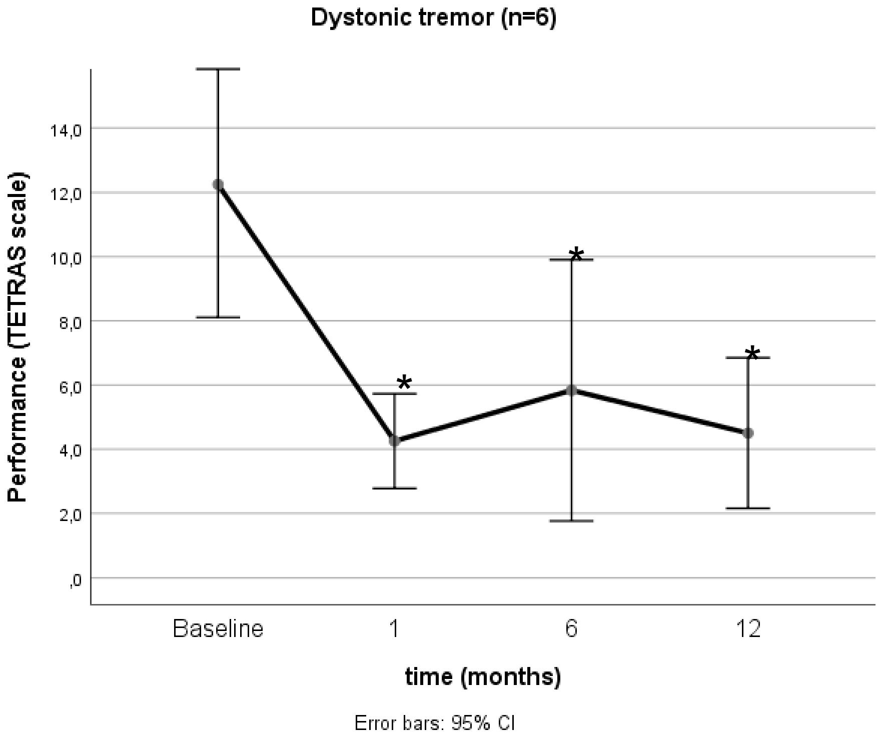
Sinai et al., JNS 2019

MRgFUS VIM thalamotomy: Besta experience

	Parkinson's Disease (n=43)	Essential tremor (n=54)	Dystonic tremor (n=9)
Sex (M/F)	35/8	38/16	7/2
Age at onset (years)	57,2 (10,5)	41,1 (21,2)	19,7 (13,9)
Age at surgery (years)	64,4 (8,7)	72,2 (9,6)	51,7 (14,1)
Disease duration (years)	6,8 (4,3)	30,3 (21,1)	32,2 (11,6)
Target (left/right)	24/19	49/5	8/1

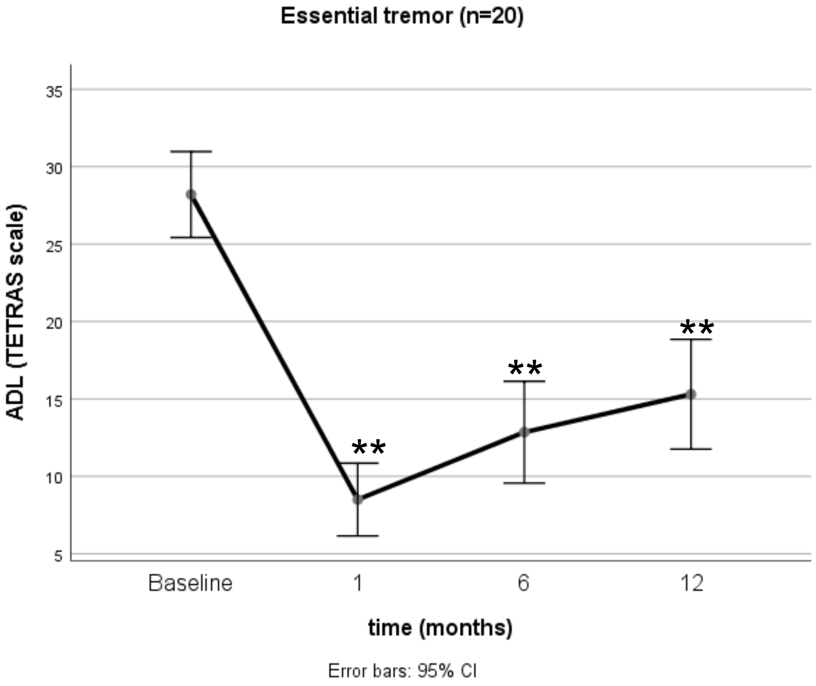
Performance (ET and DT with 12 months FU)

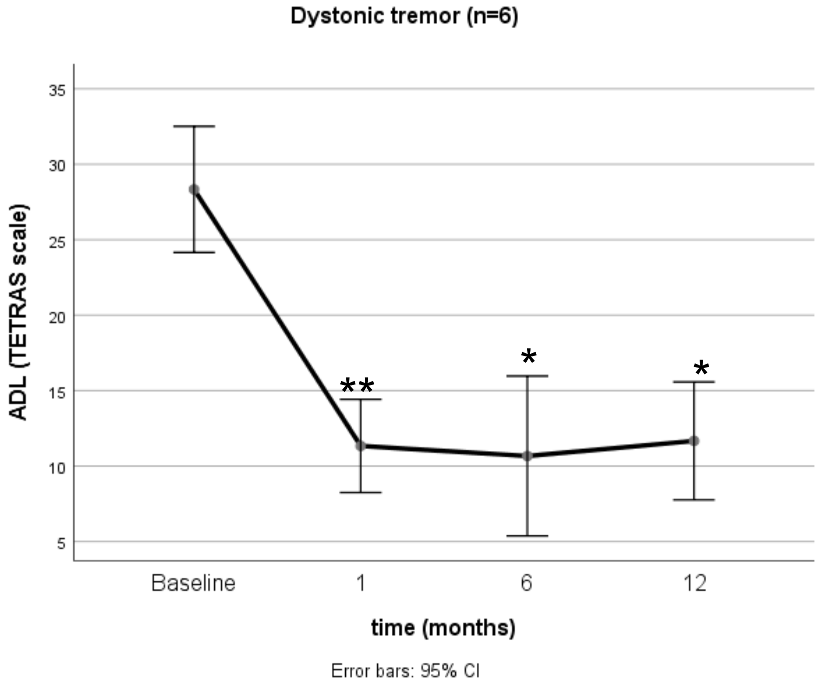




rmANOVA, Bonferroni correction
*, $p<0.05$ compared to baseline values
**, $p<0.01$ compared to baseline values

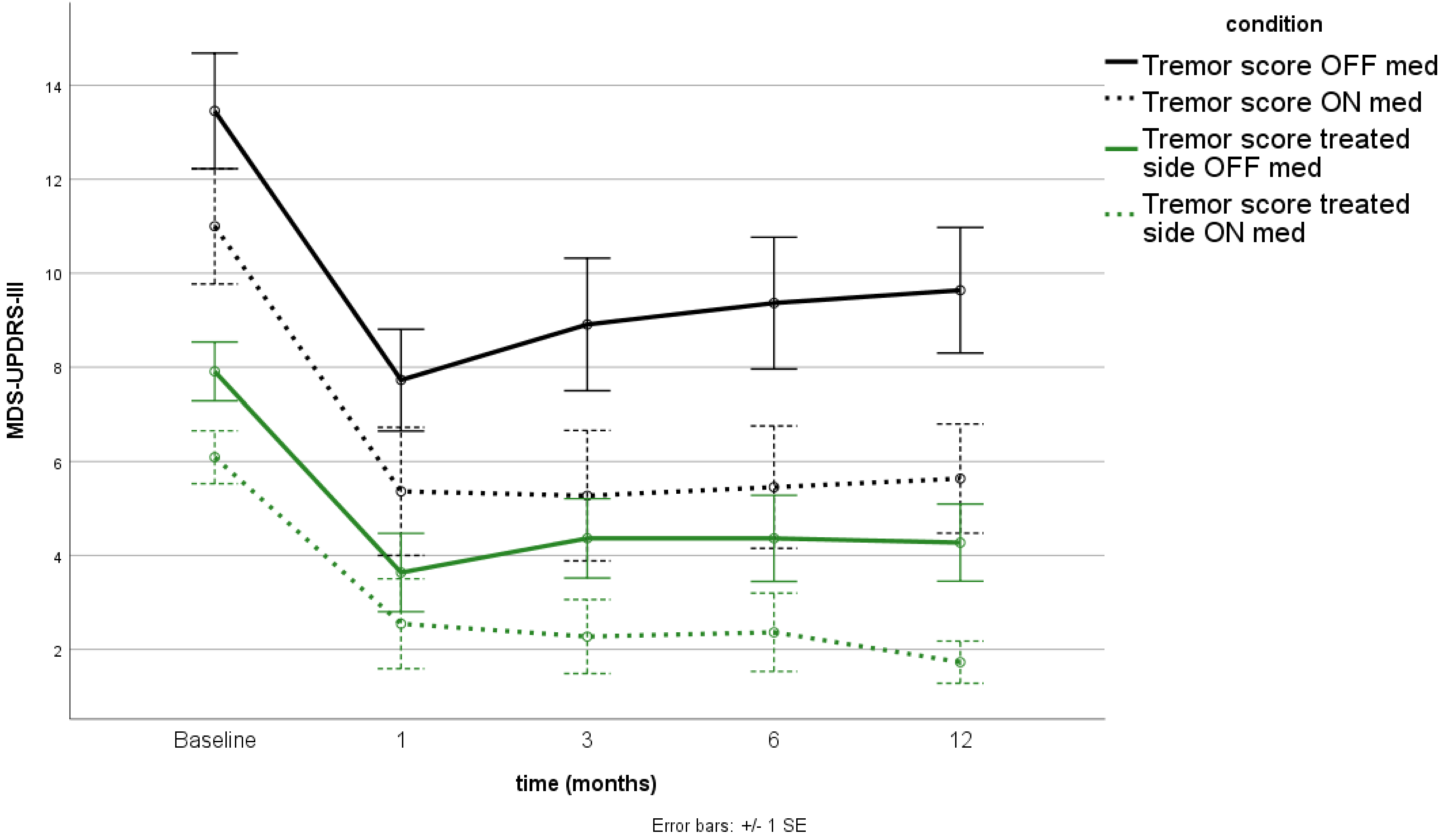
Activities of Daily Living (ET and DT with 12 months FU)



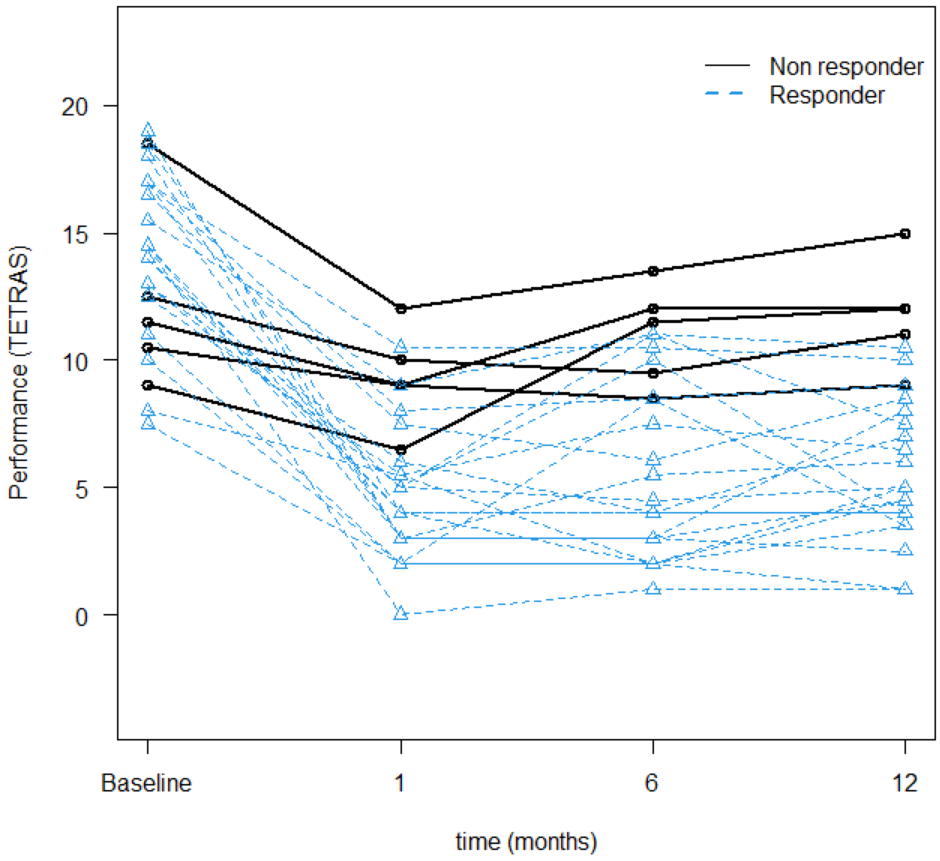


rmANOVA, Bonferroni correction
**, p<0.05 compared to baseline values*
***, p<0.01 compared to baseline values*

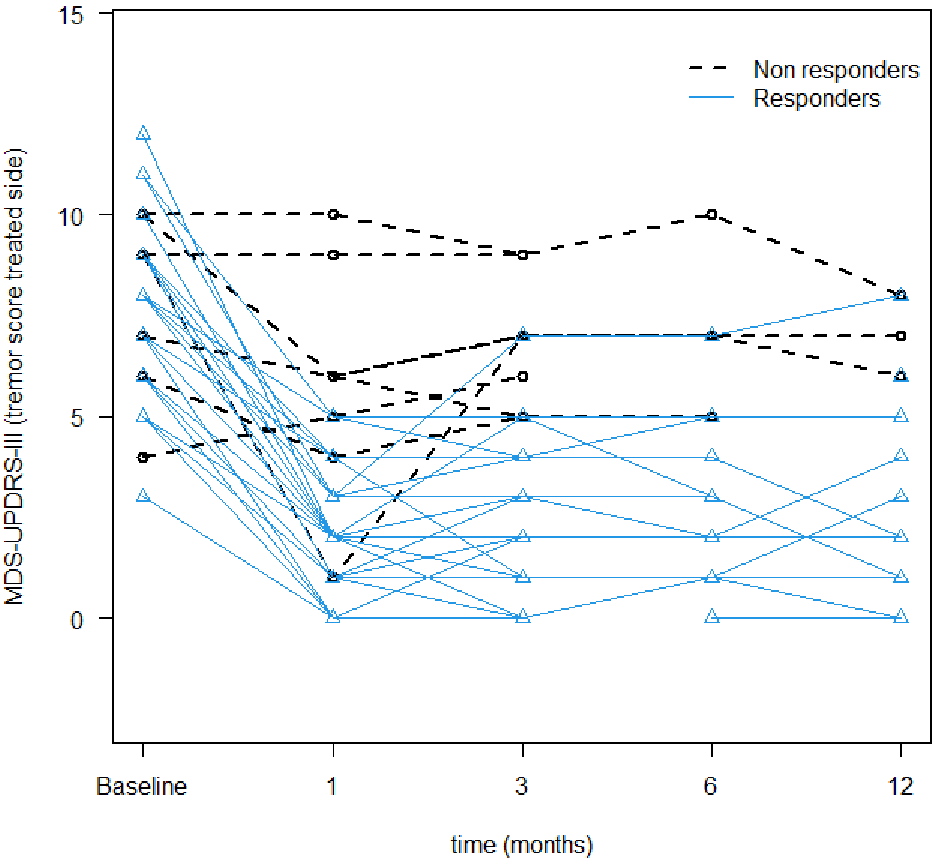
PD patients with 1 year complete FU (n=22)



ET: responders vs non responders
n=54/5

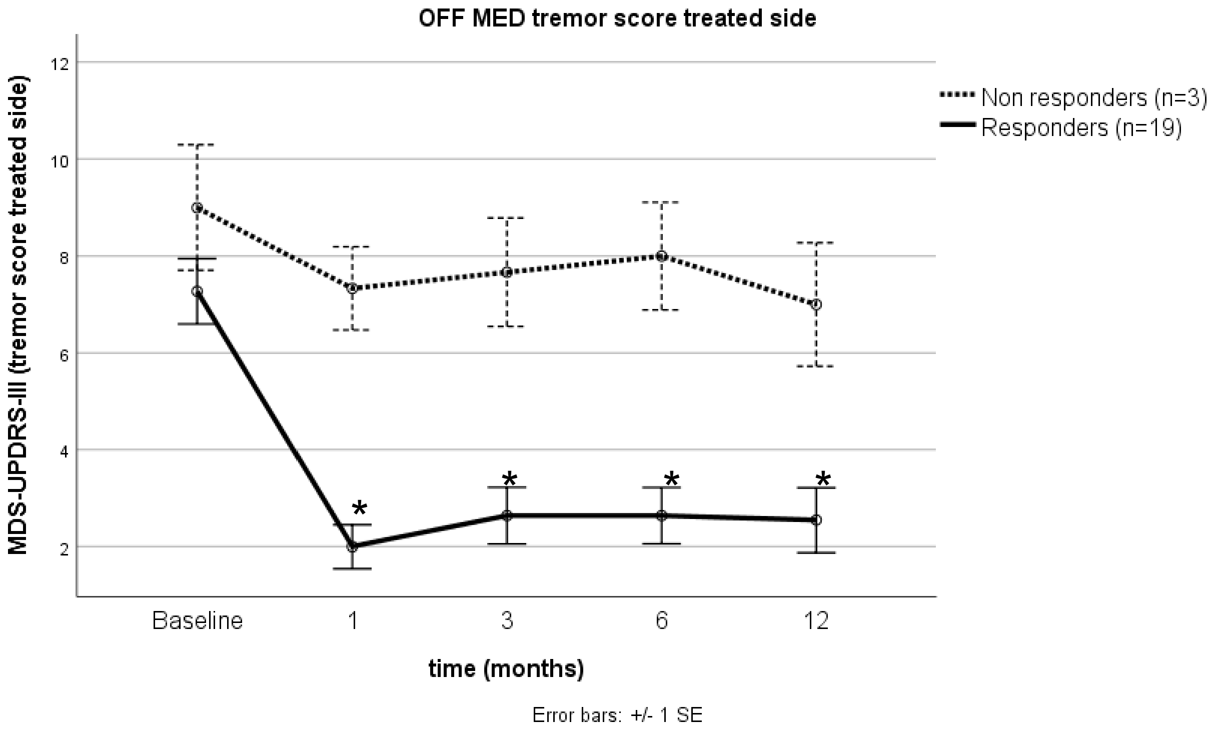


PD: responders vs non responders
n=43/7



OFF Medication

PD patients with 1 year complete FU (n=22)



rmANOVA, Bonferroni correction
*, p<0.01 compared to baseline values

POST-MRgFUS increase in FC:

- within bilateral primary motor (M1) cortices
- between bilateral M1 and crossed primary somatosensory cortices
- between pallidum and the dentate nucleus of the untreated hemisphere.

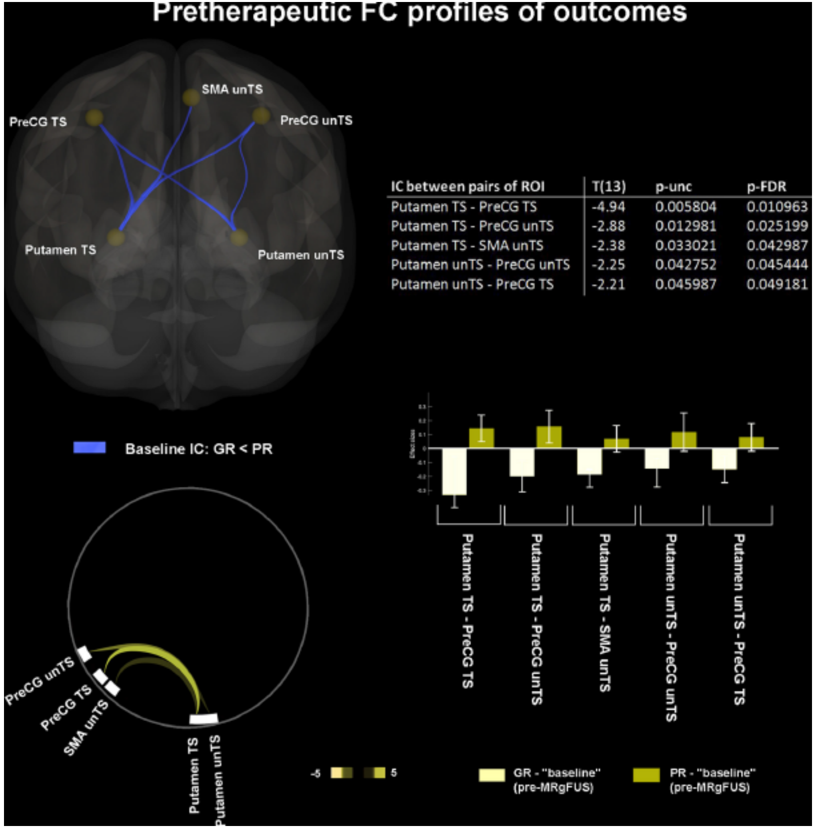
CHANGE (drop-points value) in MDS-UPDRS at 3 months correlated with post-treatment decrease in FC:

- between the anterior cingulate cortex and bilateral SMA
- between the Lobe VI of treated cerebellar hemisphere and the interpositus nucleus of untreated cerebellum.

GOOD RESPONDERS were characterized at baseline:

- crossed hypoconnectivity between bilateral putamen and M1
- as well as between the putamen of the treated hemisphere and the contralateral SMA

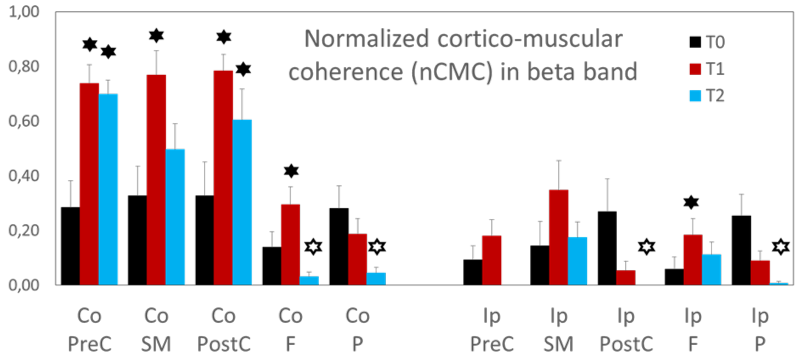
MRgFUS MODULATE BRAIN FC within the tremor network. Such changes are associated with clinical outcome.

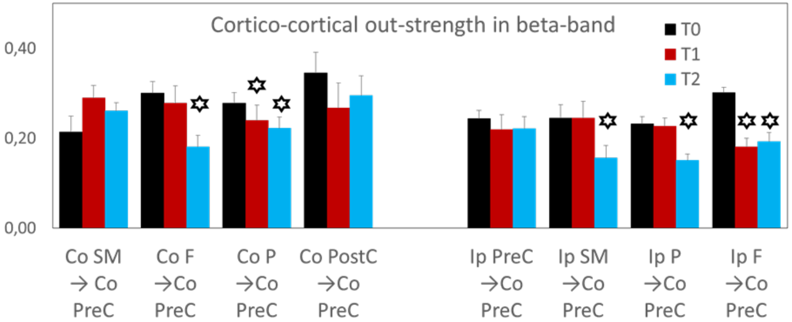


Stanziano M. et al. Front Neurol 2021

MRgFUS THALAMOTOMY IN ESSENTIAL TREMOR: CORTICO-MUSCULAR COHERENCE AND CORTICO-CORTICAL OUT-STRENGTH ASSESSED ON MEG SIGNALS

- MEG-EMG signals in 16 ET patients the day before MRgFUS (T0) treatment, 24-hours (T1), and 3-months (T2) after.
- Beta band normalized CMC (nCMC) and cortico-cortical out-strength among cortical areas were assessed during isometric extension of the hand contralateral to ViM target.





In ET patients positively responding to MRgFUS, the CMC increased in the contralateral motor-area immediately after the intervention. During the follow-up the decline of nCMC in cortical areas other than contralateral primary motor ones suggest a delayed circuitry rearrangement.

The overall reorganization consisted in a recovery of the leadership of the primary motor cortex with respect to the other areas during a sustained movement.

The effective treatment with MRgFUS corresponds with a readjustment of the CMC and of the communication between cortical areas

Co: contralateral, Ip: ipsilateral, PreC: precentral, SM: supplementary motor, PostC: postcentral, F=frontal, P=parietal.

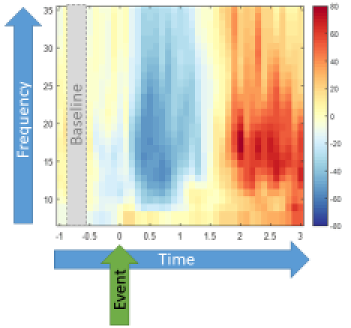
Visani et al., Clinical Neurophysiology (under review)

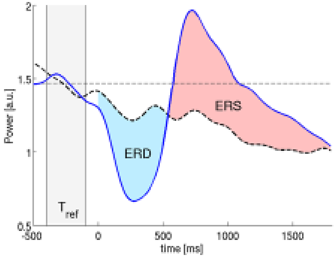
MRgFUS THALAMOTOMY IN patients with tremor: an event-relatedMEG study

- MEG-EMG signals in 20 patients the day before MRgFUS (T0) treatment, 24-hours (T1), and 3-months (T2) after.
- Beta band event-related desynchronization/synchronization were evaluated during voluntary self-paced movements.

Time-Frequency Representation (TFR) analysis

→ Event-related modulation of MEG rhythm referred to a baseline

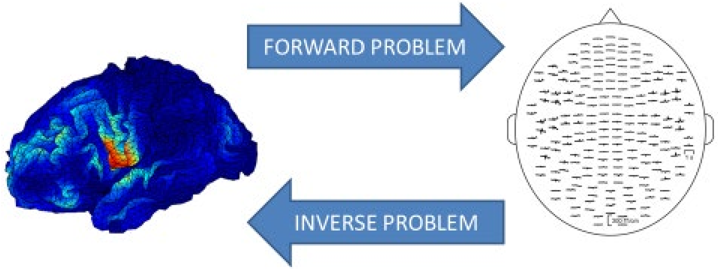




ERD=desynchronization (power decrease)
ERS=synchronization (power increase)

Magnetic Source Imaging (MSI)

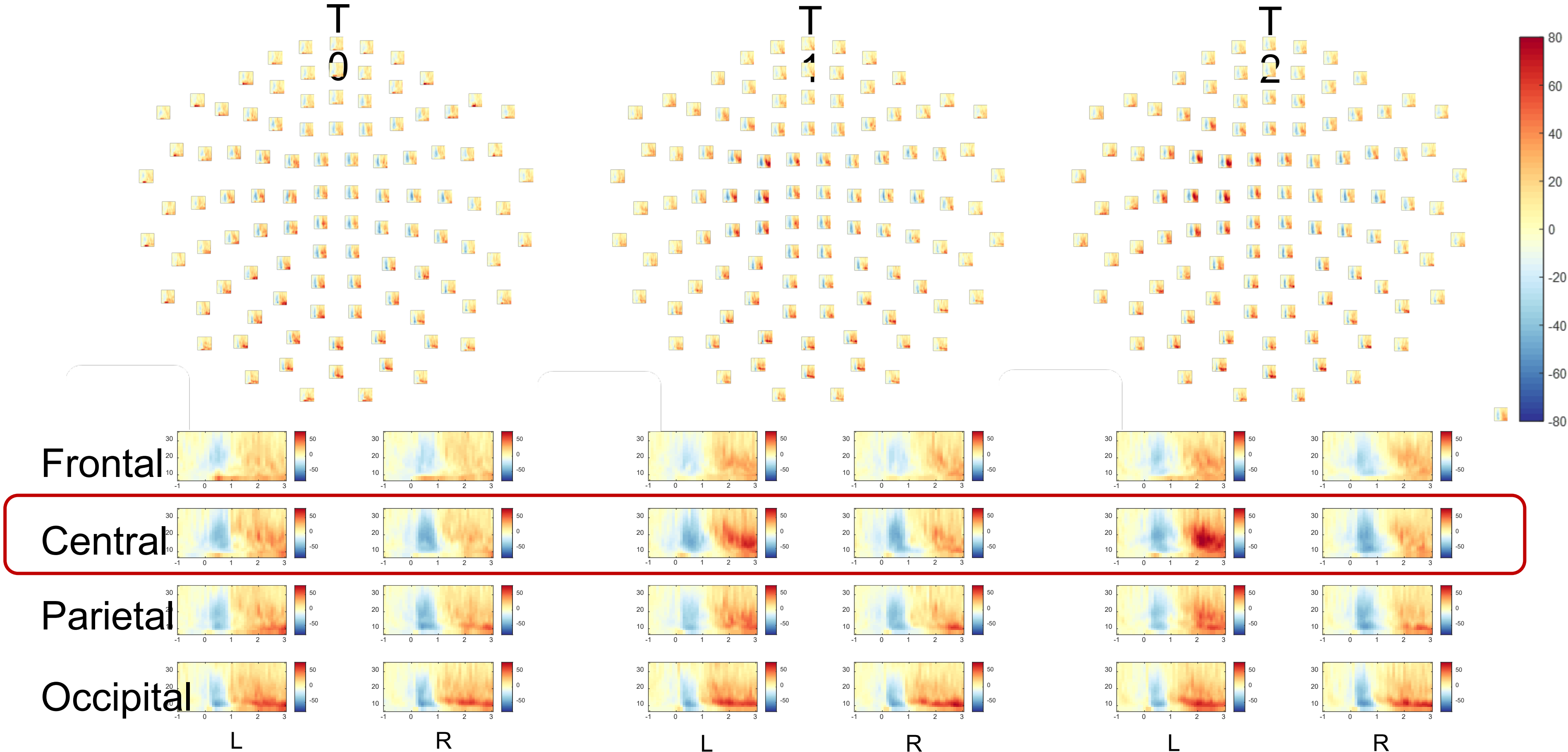
Forward and inverse problem



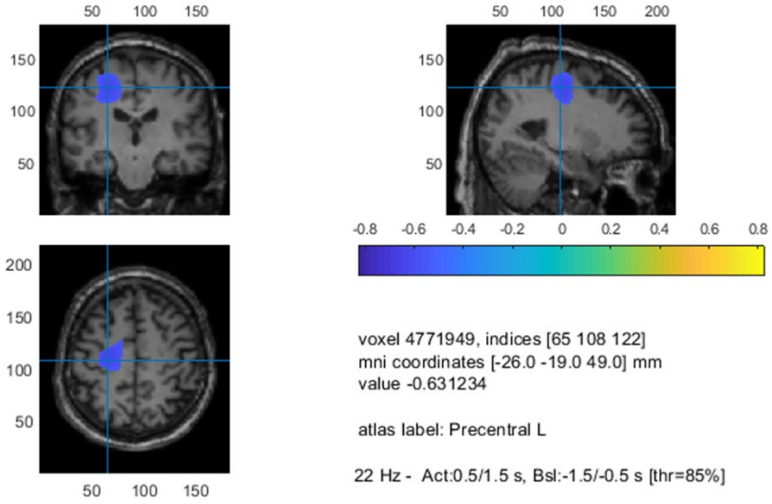
The inverse problem attempts to locate the sources from recorded measurements, whereas the forward problem assumes a source definition in order to calculate a potential distribution map.

Visani et al. (in preparation)

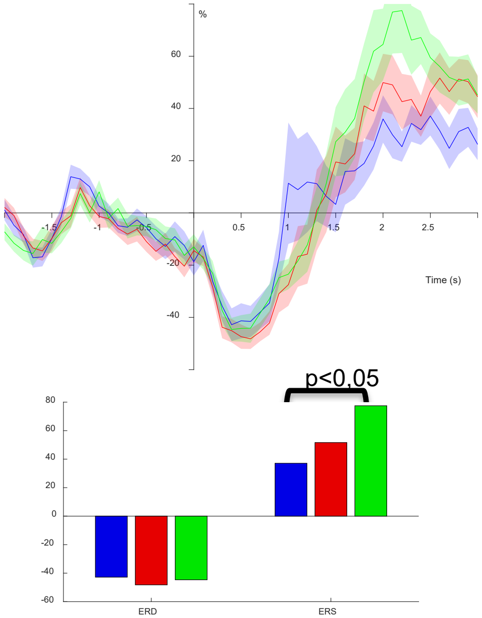
TFR analysis on MEG sensors



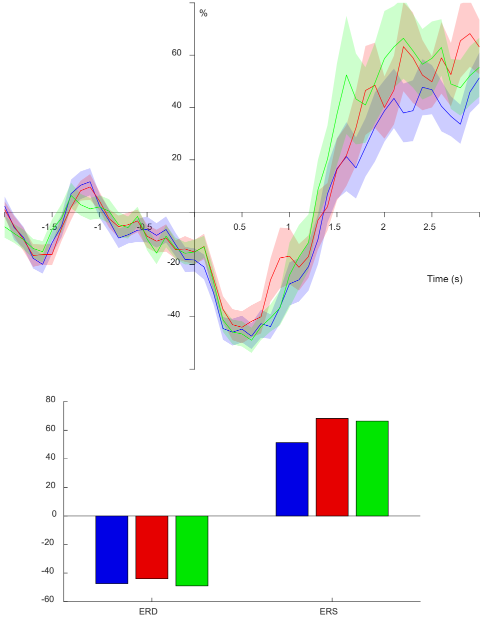
TFR analysis on MEG virtual sensors

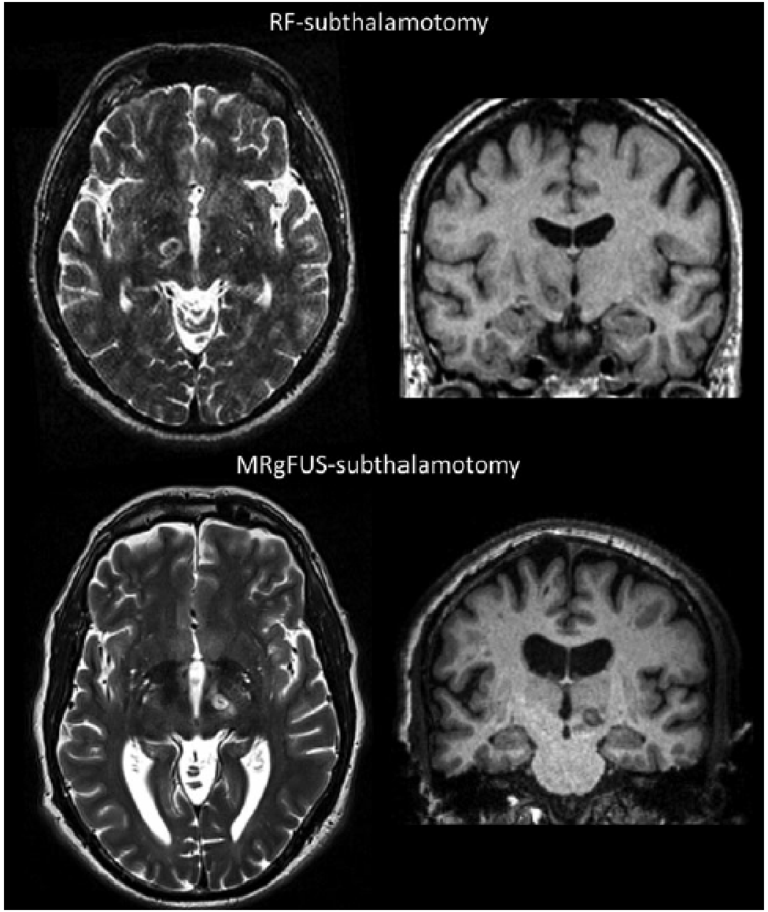


Treated side movement

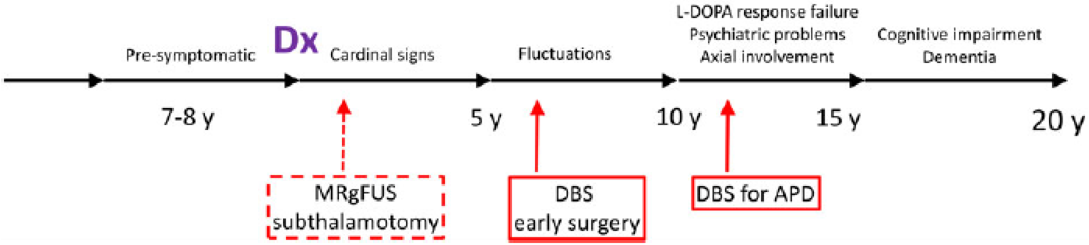


Un-treated side movement

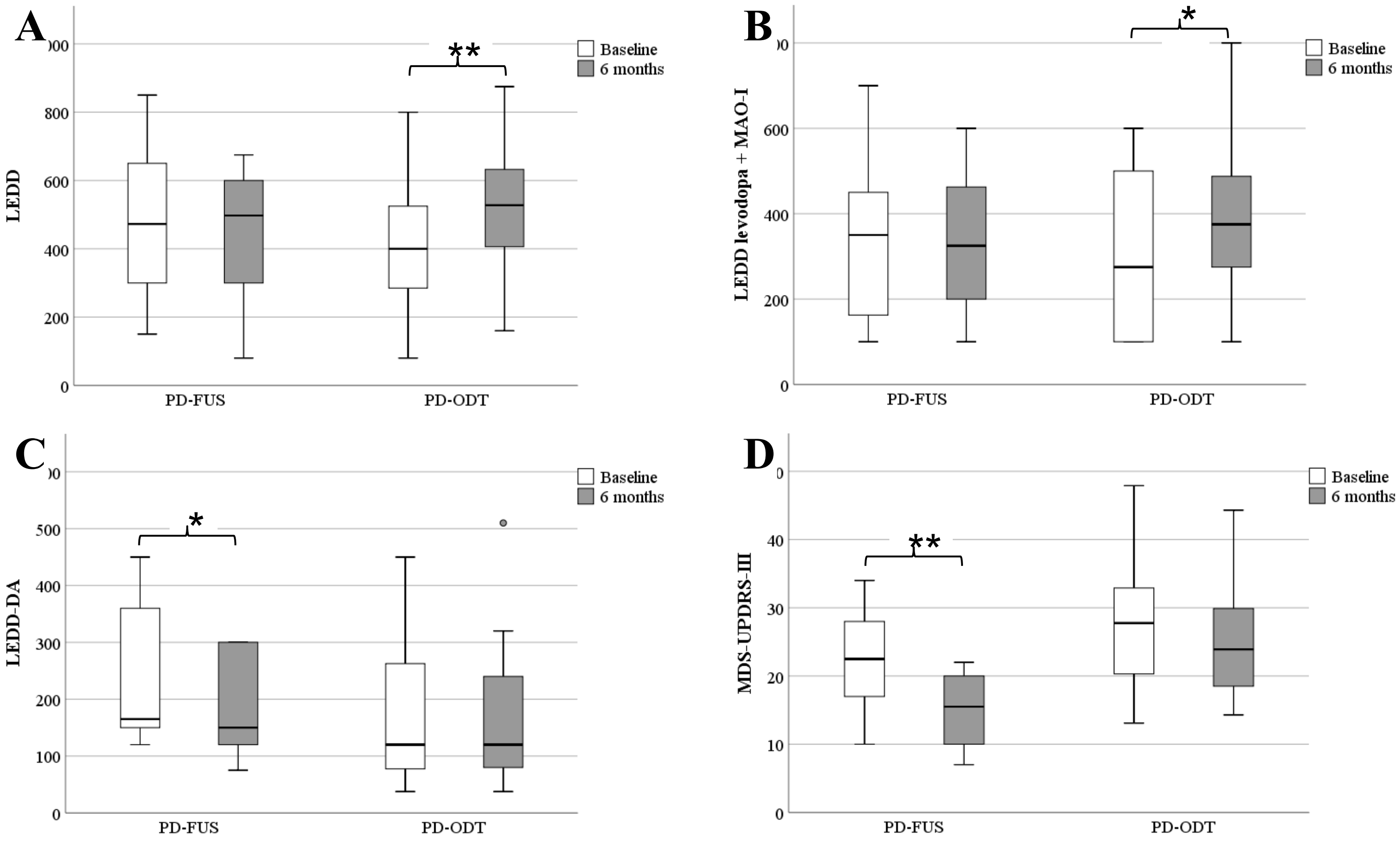




Progression of PD and timing of surgical therapeutic options



Guridi et al, Mov Dis 2018

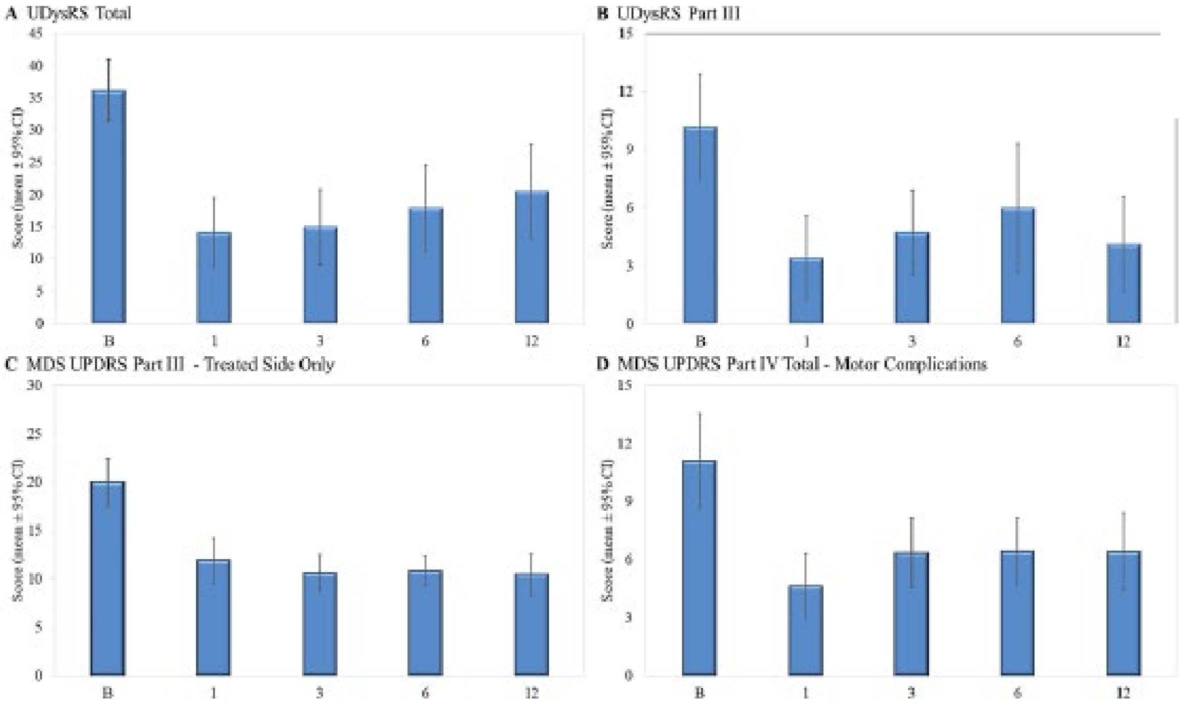


Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

Sistema Socio Sanitario
Regione
Lombardia

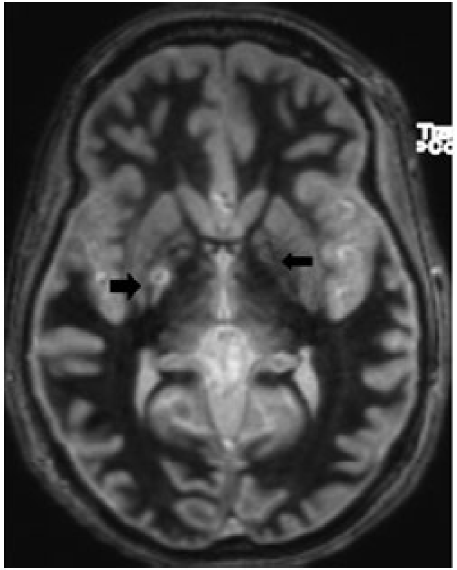
Golfrè Andreasi et al., Mov Dis (in revision)

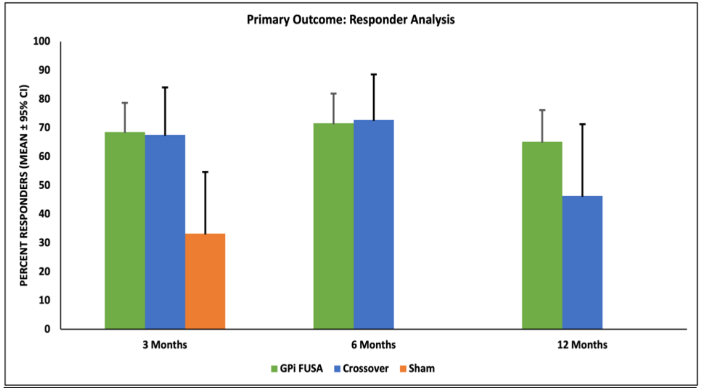
JNS
CLINICAL ARTICLE
J Neurosurg 135:792–798, 2021



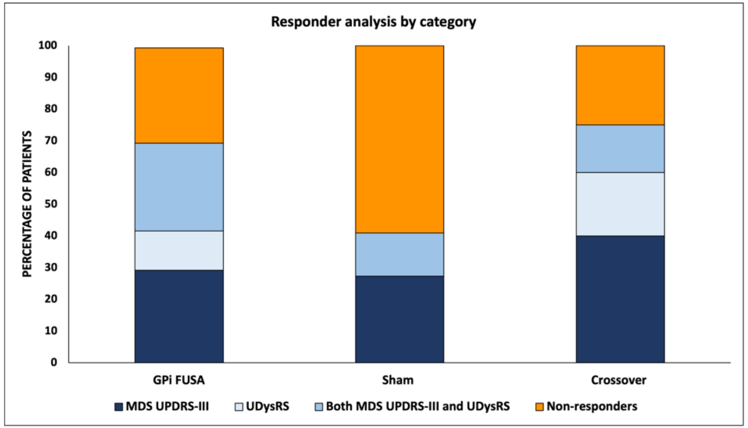
MR-guided focused ultrasound pallidotomy for Parkinson's disease: safety and feasibility

Howard M. Eisenberg, MD,[1] Vibhor Krishna, MD, SM,[2] W. Jeffrey Elias, MD,[3] G. Rees Cosgrove, MD,[4] Dheeraj Gandhi, MD,[5] Charlene E. Aldrich, RN, MSN,[1] and Paul S. Fishman, MD, PhD[6]

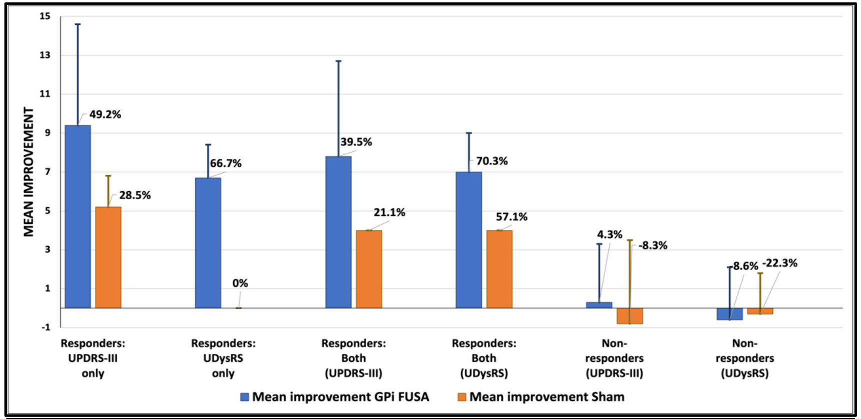




Comparison of percent of subjects rated as responders in GPi FUSA and sham group at 3 months. The open label follow-up in the GPi FUSA (6 and 12 months) and crossover groups (3, 6, and 12 months) are also shown.



Percentage of responders with improvements in MDS UPDRS-III, UDysRS, both MDS UPDRS-III & UDysRS and non-responders.



Score improvements (mean and SD) in the GPi FUSA and sham groups at 3 months. The corresponding percentage improvement are shown as well.

PD006 results

Krishna et al. NEJM 2022 (in revision)

Magnetic Resonance guided Focused UltraSound
MRgFUS

Conclusioni

Trattamento sicuro ed efficace per il tremore essenziale unilaterale (in corso di validazione il trattamento bilaterale)

Trattamento sicuro ed efficace per il tremore unilaterale nella malattia di Parkinson (in corso di validazione per gli altri sintomi)

MRgFUS non deve essere considerate alternativa a DBS

Utilità neurofisiologia per caratterizzazione ”miglior candidato”

Grazie per l’attenzione….
Domande ???