Congresso Regionale

SIN SICILIA

Segretario:

Placido Bramanti

LE CURE PALLIATIVE

IN NEUROLOGIA

MR*g*-FUS nel trattamento del Tremore nella Malattia di Parkinson

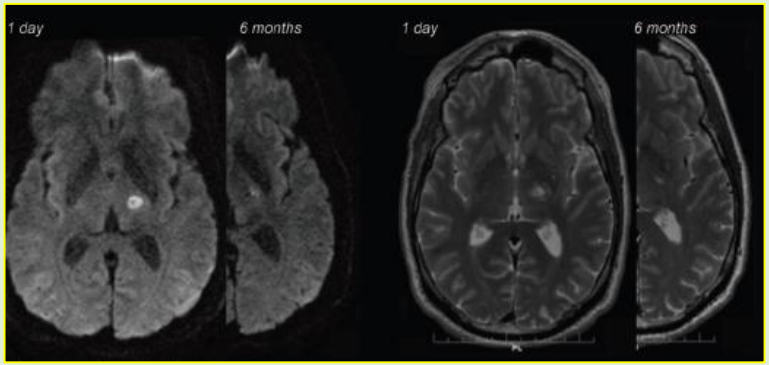
Giuseppe Di Lorenzo

Centro Disordini del Movimento
IRCCS Centro Neurolesi "*Bonino-Pulejo*"
- Messina -

CENTRO NEUROLESI BONINO PULEJO IRCCS MESSINA

the “Sound Therapy”

Gli Ultrasuoni



- *Imaging* diagnostico
- I tessuti attraversati dagli US assorbono energica trasformata in calore
- Trattamenti ripetuti
- Nessun effetto di «accumulo»
- RMN ad alta risoluzione con possibiità di mappe termiche *real-time*

(McDannold NJ, Jolesz FA. **Magnetic resonance image-guided thermal ablations**.Top Magn Reson Imaging 2000)

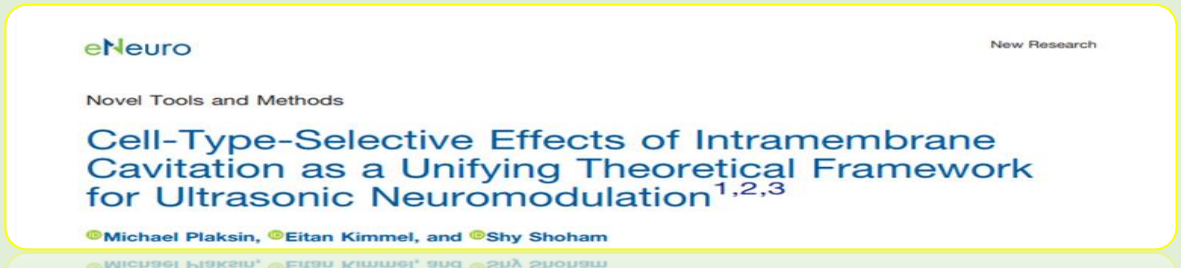
MR*g* – *hi*FUS

- E’ un trattamento **ablativo mini-invasivo** basato sull’uso di ultrasuoni RM guidati
- L’energia degli ultrasuoni **(HI-FU)** viene **focalizzata** su un volume piccolo di tessuto. Questo determina un aumento della temperatura sufficiente a distruggere (**ablare**) le cellule nel volume bersaglio, senza danneggiare i tessuti circostanti
- La procedura si esegue a **paziente sveglio,** collaborante
- TEAM multi-disciplinare

MR*g*-FUS: obiettivi terapeutici

Sono definiti in relazione al livello energetico del fascio US

- BASSO ➔ Neuromodulazione
- MODERATO ➔ Variazioni permeabilità BEE
- ALTO ➔ Lesioni cerebrali focali

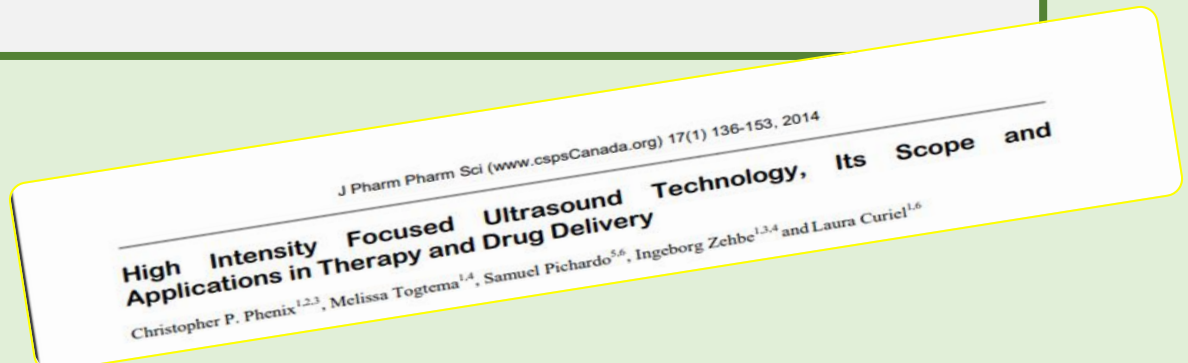

eNeuro

New Research

Novel Tools and Methods

Cell-Type-Selective Effects of Intramembrane Cavitation as a Unifying Theoretical Framework for Ultrasonic Neuromodulation[1,2,3]

Michael Plaksin, Eitan Kimmel, and Shy Shoham


J Pharm Pharm Sci (www.cspsCanada.org) 17(1) 136-153, 2014

High Intensity Focused Ultrasound Technology, Its Scope and Applications in Therapy and Drug Delivery

Christopher P. Phenix[1,2,3], Melissa Togtema[1,4], Samuel Pichardo[5,6], Ingeborg Zehbe[1,3,4] and Laura Curiel[1,6]

MR*g*-FUS: Applicazioni

CASE STUDY

Open Access

MRgFUS for desmoid tumors within the thigh: early clinical experiences

Matthew D. Bucknor* and Viola Rieke

Magn Reson Med Sci 2019; 18; 82–87
doi:10.2463/mrms.tn.2017-0103

Published Online: January 18, 2018

TECHNICAL NOTE

MR-guided Focused Ultrasound for Uterine Fibroids: A Preliminary Study of Relationship between the Treatment Outcomes and Factors of MR Images Including Elastography

Shintaro Ichikawa[1*], Utaroh Motosugi[1], Makiko Omori[2], Katsuhiro Sano[3], Yoshie Omiya[1], Shuji Hirata[2], and Hiroshi Onishi[1]

MR*g*-FUS in Neurologia

Reviews

Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles

Mohammad Rohani[1] & Alfonso Fasano[2,3*]

[1] Department of Neurology, Hazrat Rasool Hospital, Iran University of Medical Sciences, Tehran, Iran, [2] Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and Division of Neurology, University of Toronto, Toronto, Ontario, Canada, [3] Krembil Research Institute, Toronto, Ontario, Canada

CURRENT OPINION

New neurosurgical approaches for tremor and Parkinson's disease

Alfonso Fasano[a,b,c], Andres M. Lozano[c,d,e], and Esther Cubo[f]

MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes

CURRENT OPINION

New neurosurgical approaches for tremor and Parkinson's disease

Alfonso Fasano[a,b,c], Andres M. Lozano[c,d,e], and Esther Cubo[f]

Qualsiasi condizione suscettibile di lesione cerebrale stereotassica o DBS può essere affrontata mediante MR*g*FUS

The NEW ENGLAND JOURNAL of MEDICINE

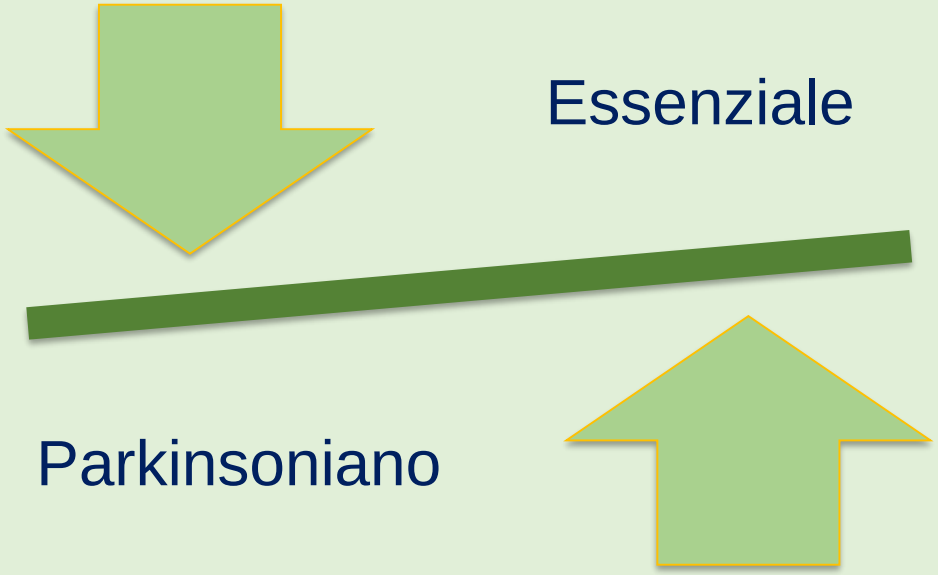
ORIGINAL ARTICLE

A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D., Ryder Gwinn, M.D., Jennifer Witt, M.D., Susie Ro, M.D., Howard M. Eisenberg, M.D., Ph.D., Paul S. Fishman, M.D., Ph.D., Dheeraj Gandhi, M.D., M.B., B.S., Casey H. Halpern, M.D., Rosalind Chuang, M.D., Kim Butts Pauly, Ph.D., Travis S. Tierney, M.D., Ph.D., Michael T. Hayes, M.D., G. Rees Cosgrove, M.D., Toshio Yamaguchi, M.D., Ph.D., Keiichi Abe, M.D., Takaomi Taira, M.D., Ph.D., and Jin W. Chang, M.D., Ph.D.

MR*g*-FUS:
Indicazioni nei Disordini del Movimento

TREMORE



MR*g*-FUS: chi ?

Criteri di inclusione

- Età maggiore di 18 anni
- Tremore clinicamente rilevante ed invalidante le ADL
- Tremore refrattario alla terapia farmacologica
- Il paziente presenti controindicazioni alla DBS
- Il paziente abbia rifiutato di sottoporsi ad altre procedure maggiormente invasive

MR*g*-FUS: chi ?

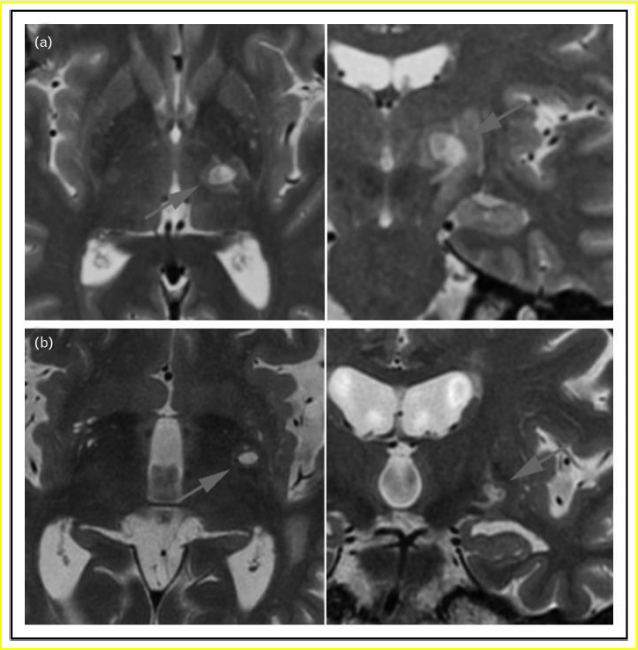
Criteri di esclusione .1

- Fattori di rischio per sanguinamento e terapia anticoagulante
- Stroke multipli o recenti (6 mesi)
- Malattie neurodegenerative, inclusi parkinsonismi atipici
- Deterioramento cognitivo (demenza)
- Patologie psichiatriche gravi o mal controllate dalla terapia (psicosi, depressione severa)
- Crisi epilettiche recenti (12 mesi)

MR*g*-FUS: chi ?

Criteri di esclusione .2

- Gravi patologie internistiche
- Patologia cardiaca ed ipertensione severe o instabili
- Neoplasie cerebrali
- Trombosi venosa profonda AA.II.
- Controindicazioni alla risonanza magnetica (RM)



Protocollo standard di trattamento

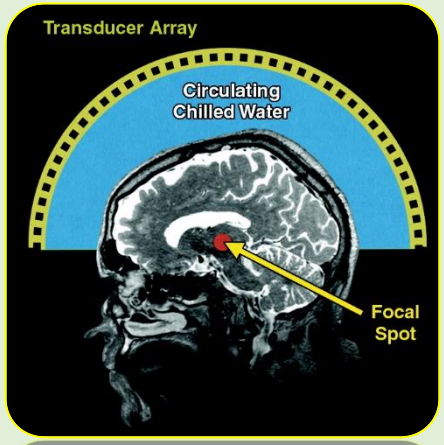
TC ed MR*i* preoperatorie

Pianificazione del trattamento

Preparazione del paziente

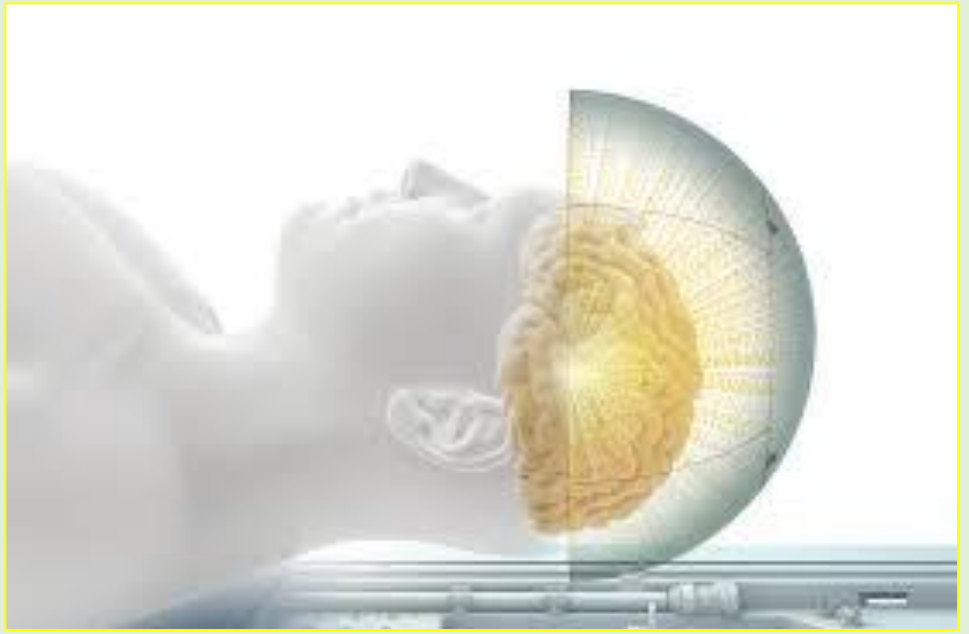
Trattamento

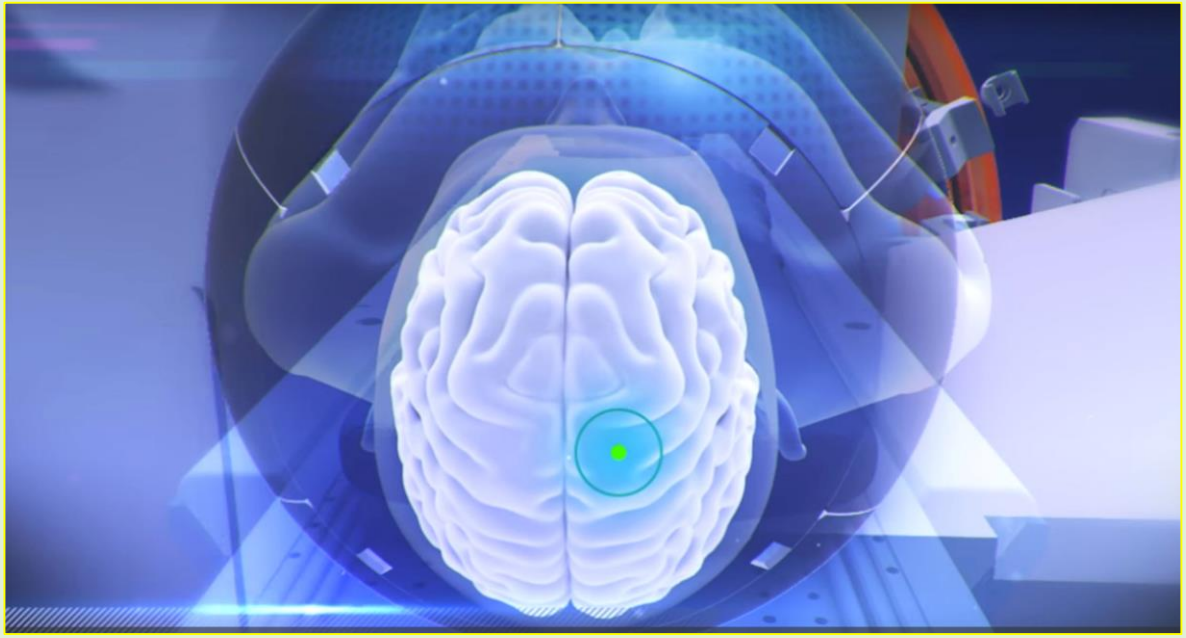
RM post-trattamento



Il paziente sul lettino MR con il capo immobilizzato da un *frame* metallico posto all'interno di un trasduttore di ultrasuoni. Lo spazio tra il capo ed il trasduttore è sigillato da una membrana di silicone ed è riempito di acqua refrigerata

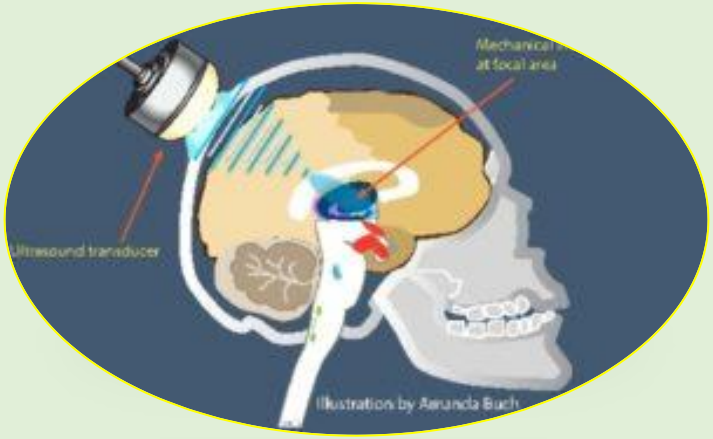
Durante il trattamento il trasduttore genera un punto di energia ultrasonica focalizzata detta ***"sonicazione"***
La temperatura nel focus si incrementerà a causa dell'assorbimento di energia dei tessuti





Complessivamente il trattamento dura 3-4 ore

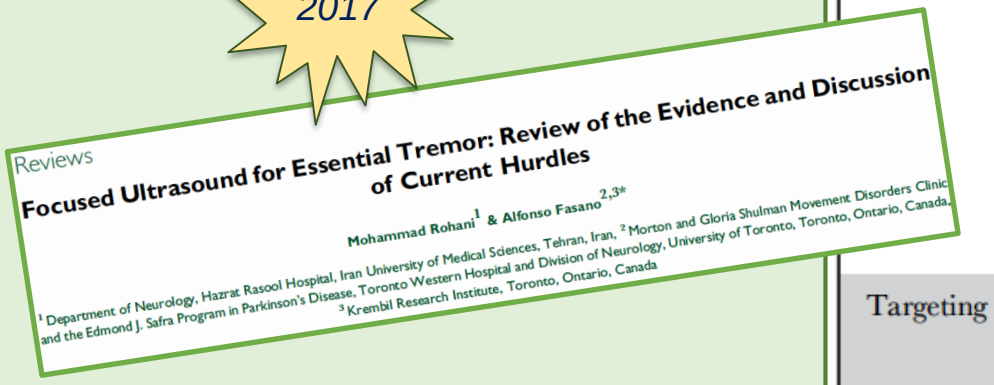
Nella maggior parte dei casi il paziente viene dimesso il giorno successivo



BENEFICI

- Immediato miglioramento del tremore
- Dosi sub-terapeutiche permettono di “rifinire” il target
- Monitoraggio e feed-back “real-time”
- Profilo di alta sicurezza con minime complicazioni

2017



Reviews

Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles

Mohammad Rohani[1] & Alfonso Fasano[2,3*]

[1] Department of Neurology, Hazrat Rasool Hospital, Iran University of Medical Sciences, Tehran, Iran, [2] Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and Division of Neurology, University of Toronto, Toronto, Ontario, Canada, [3] Krembil Research Institute, Toronto, Ontario, Canada

Caratteristiche delle procedure NCH usate nei Disordini del Movimento

	Radiofrequency Lesioning	Deep Brain Stimulation	Gamma Knife Radio Surgery	MR-guided Focused Ultrasound
Technique	A probe inserted into the brain is used to burn neurons in a selected area to create a focal lesion	One or more electrodes are inserted into the brain and are then connected to a implantable pulse generator providing constant electrical stimulation to modulate neuronal activity in the targeted brain region	Ionizing radiations are transmitted through the intact skull to generate a permanent lesion in a specific brain region	Ultrasound waves are transmitted through the intact skull to generate a permanent lesion in a specific brain region
Targeting	Neuroimaging, neuronal recording, intra-operative stimulation, intraoperative test lesions	Neuroimaging, neuronal recording, intra-operative stimulation, (real-time MRI guidance in selected centers)	Neuroimaging	Neuroimaging, thermic maps, real-time MRI guidance, intraoperative test lesions
Worldwide experience	Over 50 years	Over 30 years	Over 15 years	4 years
Ablation (irreversible effects)	Yes	No	Yes	Yes
Use of general anesthesia	No	Yes	No	No
Invasive/incisions	Yes	Yes	No	No
Possibility of bilateral procedure	No	Yes	No	No
Device implantation	No	Yes	No	No
Benefit onset	Immediate	Delayed (when programming is completed, up to 6 months)	Delayed (up to 1 year)	Immediate

Abbreviation: MRI, Magnetic Resonance Imaging.

MR*g*-FUS e TE

2013

MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study

Nir Lipsman, Michael L Schwartz, Yuexi Huang, Liesly Lee, Tejas Sankar, Martin Chapman, Kullervo Hynynen, Andres M Lozano

Summary

Background Essential tremor is the most common movement disorder and is often refractory to medical treatment. Surgical therapies, using lesioning and deep brain stimulation in the thalamus, have been used to treat essential tremor that is disabling and resistant to medication. Although often effective, these treatments have risks associated with an open neurosurgical procedure. MR-guided focused ultrasound has been developed as a non-invasive means of generating precisely placed focal lesions. We examined its application to the management of essential tremor.

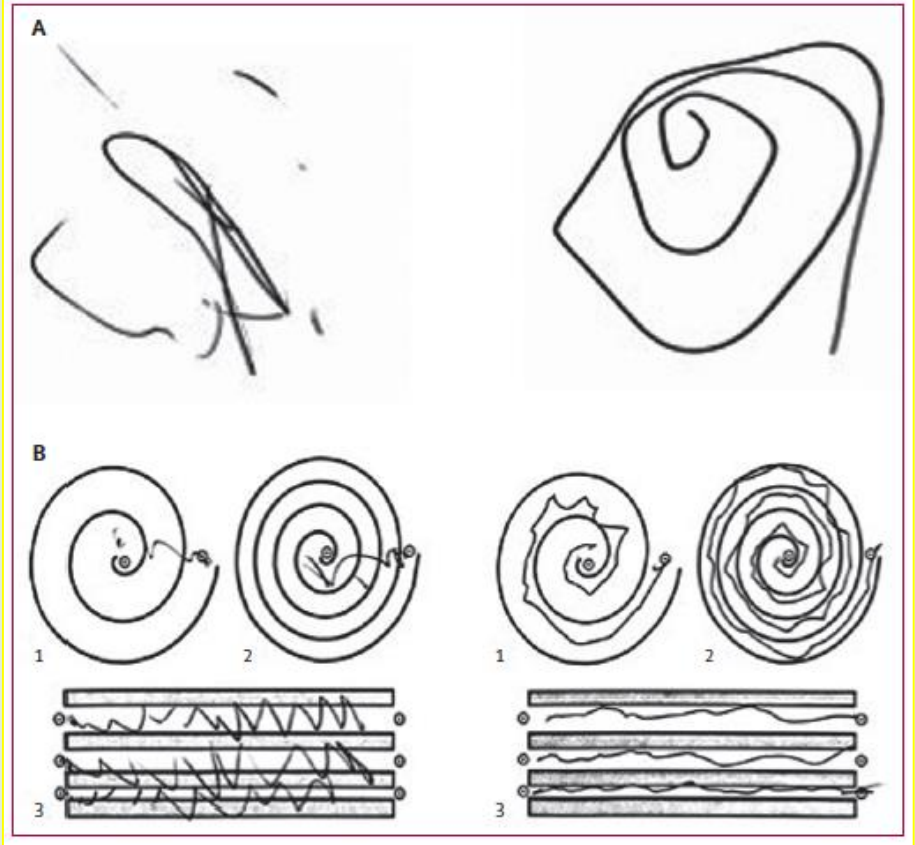
Published Online March 21, 2013 http://dx.doi.org/10.1016/S1474-4422(13)70048-6

See Online/Comment http://dx.doi.org/10.1016/S1474-4422(13)70062-0

	Sex	Treated hand	Age (years)	Illness duration (years)	Medication at surgery	Number of sonications	Maximum temperature achieved (°C)
Patient 1	M	R	71	6	Propranolol Primidone Gabapentin	27	56
Patient 2	M	L	77	25	Primidone Propranolol	22	63
Patient 3	M	R	77	20	Primidone	12	59
Patient 4	M	R	58	20	Propranolol	29	59
Mean			70·8	17·8		22·5	59·3

Table 1: Patient demographics and clinical characteristics

*"MR-g FUS might be a **safe and effective approach** to generation of focal intracranial lesions for the management of disabling, medication-resistant essential tremor. If larger trials validate the safety and ascertain the efficacy and durability of this new approach, it might change the way that patients with essential tremor and potentially other disorders are treated"*



MR*g*-FUS e TE

2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

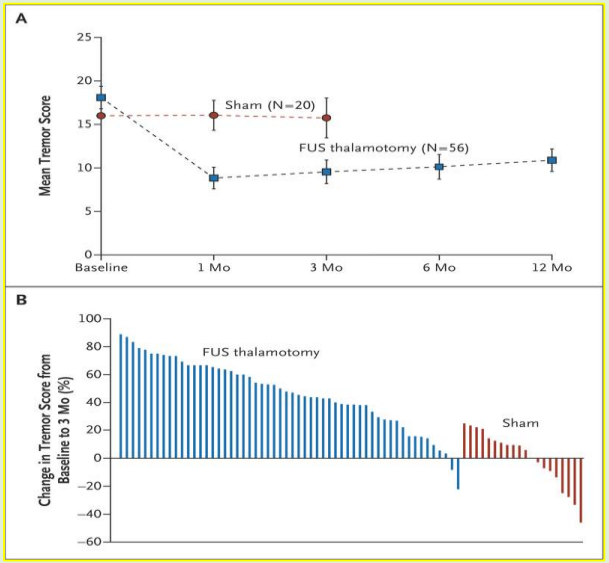
W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D., Ryder Gwinn, M.D., Jennifer Witt, M.D., Susie Ro, M.D., Howard M. Eisenberg, M.D., Ph.D., Paul S. Fishman, M.D., Ph.D., Dheeraj Gandhi, M.D., M.B., B.S., Casey H. Halpern, M.D., Rosalind Chuang, M.D., Kim Butts Pauly, Ph.D., Travis S. Tierney, M.D., Ph.D., Michael T. Hayes, M.D., G. Rees Cosgrove, M.D., Toshio Yamaguchi, M.D., Ph.D., Keiichi Abe, M.D., Takaomi Taira, M.D., Ph.D., and Jin W. Chang, M.D., Ph.D.

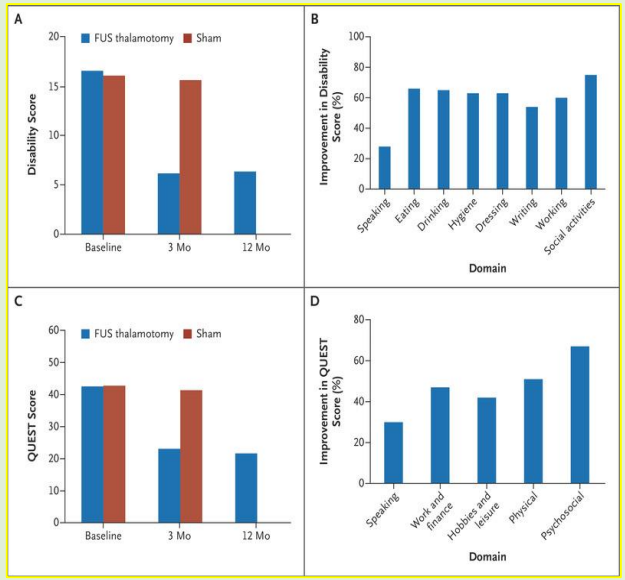
ABSTRACT

Arruolati 76 pz. con TE moderato-severo

A breve termine:

la riduzione media del tremore è di circa il **60%** nel lato trattato nei 12 mesi successivi alla procedura



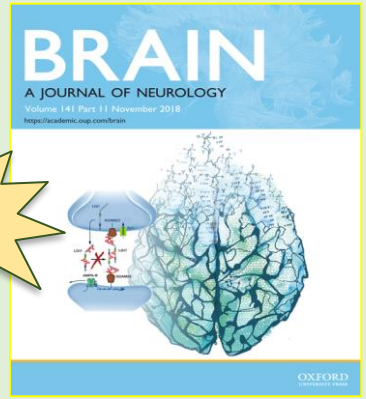


A lungo termine:

recrudescenza del tremore?

MR*g*-FUS e TE

2018



doi:10.1093/brain/awy278 BRAIN 2018: 141: 3405–3414 | 3405

BRAIN
A JOURNAL OF NEUROLOGY

Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor

Alexandre Boutet,[1,*] Manish Ranjan,[2,*] Jidan Zhong,[2] Jurgen Germann,[3] David Xu,[2] Michael L. Schwartz,[4] Nir Lipsman,[4,5] Kullervo Hynynen,[6,7,8] Gabriel A. Devenyi,[3,9] Mallar Chakravarty,[3,9] Eugen Hlasny,[1] Maheleth Llinas,[1] Christopher S. Lozano,[2] Gavin J. B. Elias,[2] Jason Chan,[1] Ailish Coblentz,[1] Alfonso Fasano,[2,10] Walter Kucharczyk,[1,11] Mojgan Hodaie[1,2] and Andres M. Lozano[1,2]

- 66 pazienti con TE
- Sottoposti a trattamento MR*g*-FUS dal 2012 al 2017
- Valutate a 3 mesi le scale per il tremore (CRST)
- Rilevati gli eventi avversi *(sensitivi, motori, linguaggio, marcia e dismetria)* dopo 1 giorno (acuti) e 3 mesi
- L'area di **ottimale** risposta al tremore dopo 3 mesi è stata individuata nella **parte posteriore del VIM**

*"...clinical outcomes of this procedure are highly dependent on the **location** and **size** of lesions. These findings could refine current procedural methods, thereby improving clinical outcomes..."*

MR*g*-FUS e PD

VIM

Schlesinger I, Eran A, Sinai A, et al.
MRI guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease.
Parkinsons Dis 2015

- 7 pz. con PD severo con tremore farmaco-resistente
- Tremore è scomparso immediatamente in tutti i pz
- In 3 pz ricomparsa di lieve tremore a distanza
- Nessuna efficacia su rigidità e bradicinesia
- Eventi avversi di modesta entità e reversibili
- Limiti dello studio: esiguo n° di casi e breve follow-up

Effetti persistenti per almeno 3 mesi successivi al trattamento

"…Thalamotomy using MRgFUS is safe and effective in PD patients. Large randomized studies are needed to assess prolonged efficacy and safety…"

UPDRS (*item 20*)

Pre	Post (7 gg)
2,7 ± 1,1	0,0 ± 0,0

MR*g*-FUS e PD

PTT

Magara A, Buhler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D.

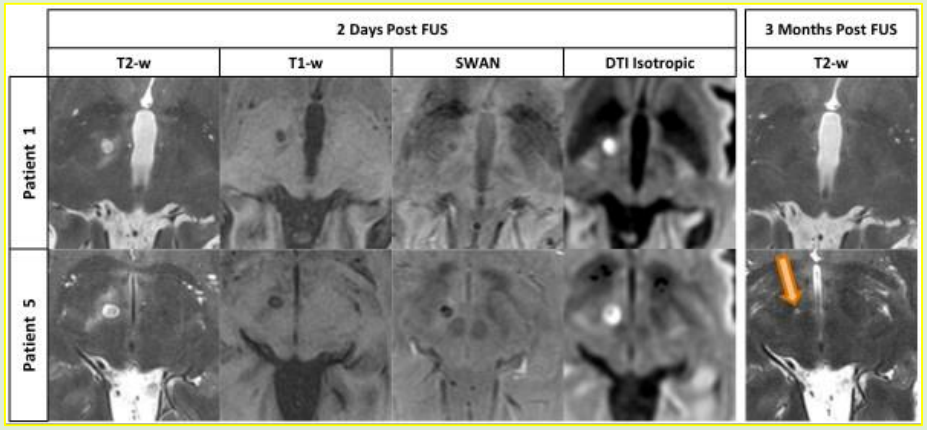
First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease

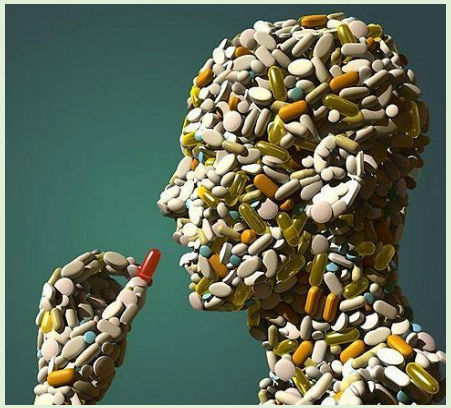
J Ther Ultrasound 2014

↑ UPDRS e QoL

↓ Disartria

"…The MRgFUS PTT provided similar clinical improvements to parkinsonian patients as the ones obtained by RF PTT. There were no post-operative neurological side effects…"





MR*g*-FUS e PD GP*i*

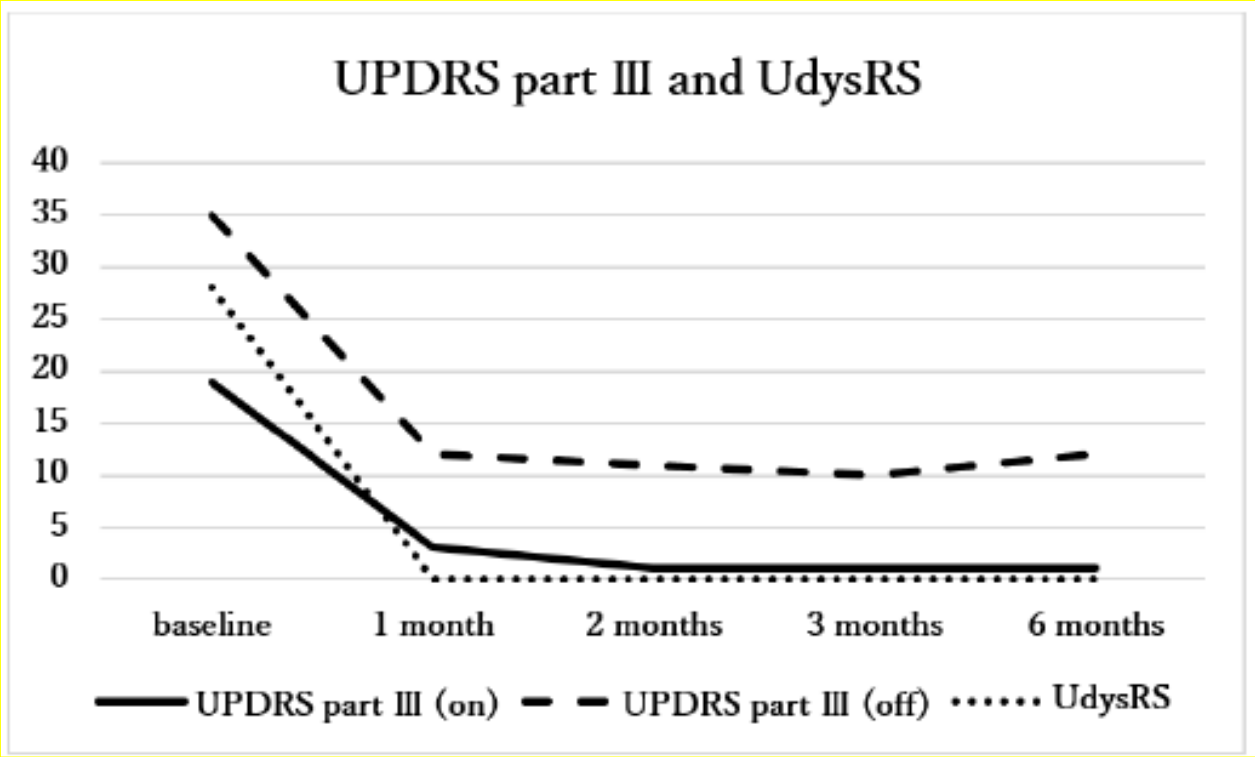
Mini Review ISSN: 2631-4010

Unilateral magnetic resonance imaging-guided focused ultrasound pallidotomy: A novel treatment of Parkinson's disease

Hisashi Ito[1]*, Shigeru Fukutake[1], Kazuaki Yamamoto[2] and Tetsumasa Kamei[1]

[1]Department of Neurology, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Japan
[2]Department of Neurosurgery, Shonan Kamakura General Hospital, Kamakura, Japan

2018



"… Although the efficacy and safety of MRgFUS Gpi pallidotomy for PD remains to be elucidated, it might become one of therapeutic options for PD patients with intractable motor fluctuation. Further investigations with more patients and longer follow-up periods should be necessary…"

MR*g*-FUS e PD

STN

2018

Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study

Raul Martínez-Fernández, Rafael Rodríguez-Rojas, Marta del Álamo, Frida Hernández-Fernández, Jose A Pineda-Pardo, Michele Dileone, Fernando Alonso-Frech, Guglielmo Foffani, Ignacio Obeso, Carmen Gasca-Salas, Esther de Luis-Pastor, Lydia Vela, José A Obeso

Neurol 2018; 17: 54-63
Published Online December 1, 2017
http://dx.doi.org/10.1016/

Summary

Background Ablative neurosurgery has been used to treat Parkinson's disease for many decades. MRI-guided focused ultrasound allows focal lesions to be made in deep brain structures without skull incision. We investigated the safety and preliminary efficacy of unilateral subthalamotomy by focused ultrasound in Parkinson's disease.

- Razionale: investigare la **sicurezza** e l'**efficacia** della sub-talamotomia **unilaterale** con Hi-FUS
- Sono stati arruolati **10 pazienti** con PD marcatamente **asimmetrico** scarsamente controllati dalla terapia farmacologica
- Il più frequente evento avverso è stata l'**atassia della marcia** transitoria
- I punteggi MDS-UPDRS III sono mediamente **migliorati** nel lato trattato del 53% in *off-med* e del 47% in *on-med* (6 mesi)
- La procedura è ben tollerata e sembra migliorare la performances motorie nei pazienti trattati

MR*g*-FUS

Review

Stereotactic and Functional Neurosurgery

Stereotact Funct Neurosurg 2004;82:115–126
DOI: 10.1159/000079843
Published online: July 15, 2004

Center Median-Parafascicular Complex and Pain Control

Review from a Neurosurgical Perspective

Ralf Weigel Joachim K. Krauss

Department of Neurosurgery, University Hospital, Mannheim, Germany

Miglioramento del **dolore neuropatico cronico** successivamente a MRgFUS del talamo centrale

JNS

LITERATURE REVIEW

Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: a systematic review of observational studies

Lauren T. Brown, BA,[1] Charles B. Mikell, MD,[1] Brett E. Youngerman, MD,[1] Yuan Zhang, MS, MA,[2] Guy M. McKhann II, MD,[1] and Sameer A. Sheth, MD, PhD[1]

Efficacia della cingulotomia e capsulotomia mediante MRgFUS nel trattamento del **DOC grave** refrattario.

MR*g*-FUS: Rischi ed Eventi Avversi

Edema cerebrale:
può essere precoce o tardivo
(fino a 3 mesi)

Eventi Avversi

- Dolore indotto dalle sonicazioni
- Cefalea, anche intensa
- Possibili ustioni cutanee
- Nausea e/o vomito
- Comparsa di brividi

- Disturbi dell'andatura (9%)
- Parestesie (14%)

Elias WJ, Lipsman N, Ondo WG, et al. ***A randomized trial of focused ultrasound thalamotomy for essential tremor.*** N Engl J Med 2016; 375:730–739.

Problems

Variable effects on symptoms control
Decay of tremor control in the short term
Relatively high number of persistent side effects
Unpredictable hyper-response of brain tissue
Not suitable to target both hemispheres
Not possible in patients with MRI contraindications
Not possible in patients with high skull thickness
Not possible in patients with previous brain surgery
Limited experience
Patients' misperception of being non-surgical

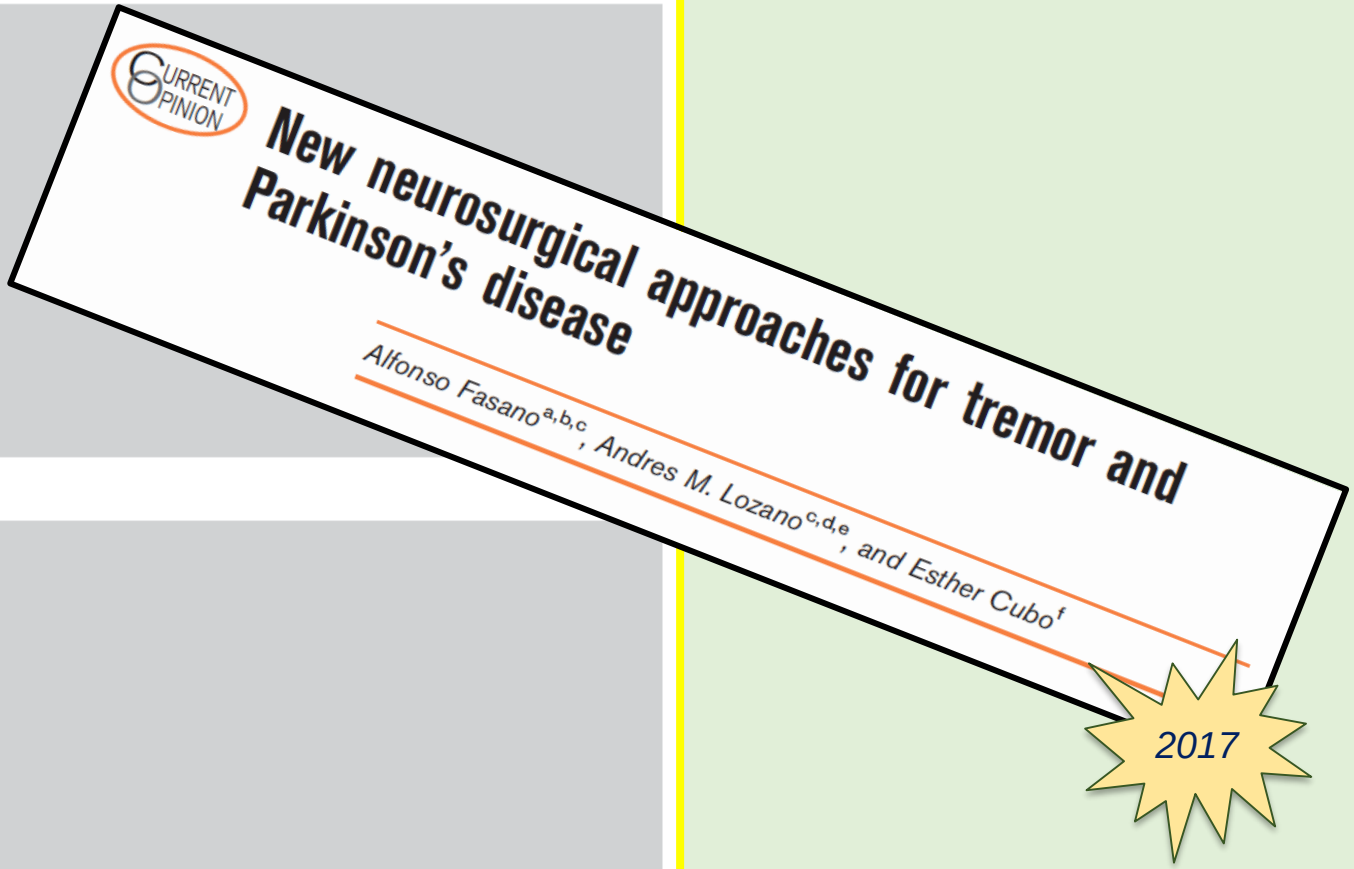
Unknowns

Long-term effects
Re-operation of the same brain area (e.g., in case of tremor recurrence)
Efficacy of lesioning less centered brain targets (e.g., GPi)
Safety of bilateral procedures
Efficacy of DTI MRI to better target brain nuclei/fibers
Safety of STN lesioning (risk of hemiballismus)
Bleeding risk in selected populations (e.g., patients on anticoagulants)
Impact of placebo effect in previous and future RCTs

Possible future applications

Opening the BBB using moderate-intensity pFUS to improve the delivery of therapeutic agents (growth factors and genes)[60–68]
Improving the spread of nanoparticles combined with CED for the delivery of protein and gene therapy to the brain[69]
Neuromodulation with a high degree of spatial resolution (either activation[60,70] or suppression of neuronal activity[71]) using low-intensity pFUS
"Enhanced sonication" through inertial cavitation by microbubbles compressed and expanded by FUS[72]
Sonothrombolysis of clotted blood in ICH, thereby facilitating minimally invasive evacuation of the clot via craniostomy and aspiration tube[73]

Abbreviations: BBB, Blood–Brain Barrier; CED, Convection Enhanced Delivery; DTI, Diffusion Tensor Imaging; FUS, Focused Ultrasound; GPi: Globus Pallidus Pars Interna; ICH, Intracerebral Hemorrhage; pFUS, Pulsed-mode Focused Ultrasound; RTC, Randomized Controlled Trial; STN, Subthalamic Nucleus.



Conclusioni

- MR*g*-FUS è un **interessante e promettente** approccio, di grande potenziale, per il trattamento di diverse patologie cerebrali
- MR*g*-FUS una **tecnica mini-invasiva** che può essere usata per «ablare» *target* cerebrali senza danno ai tessuti circostanti
- Ad oggi la Talamotomia MR*g*-FUS è una **tecnica approvata** per il trattamento del TE e del Tremore nella MP
- Sebbene per l'opinone publica ed il paziente venga percepita come un intervento «non chirurgico», **MR*g*-FUS non è esente da rischi**
- MR*g*-FUS rappresenta una valida opzione per pazienti che **rifiutano o non siano candidabili** per altre procedure, DBS in particolare


Grazie per l’attenzione