

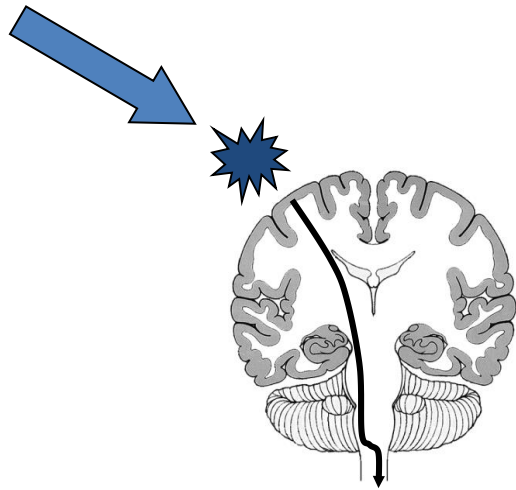
# rTMS et douleurs neuropathiques

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Toulouse

# **COMMENT ÇA MARCHE LA RTMS ET LES AUTRES NIBS?**

# TMS: Transcranial Magnetic Stimulation

## Principe



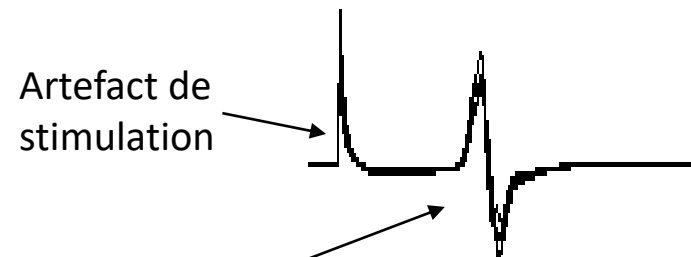
stimulateur

Recueil du PEM à l'aide  
d'électrode  
(EMG: électromyographie)



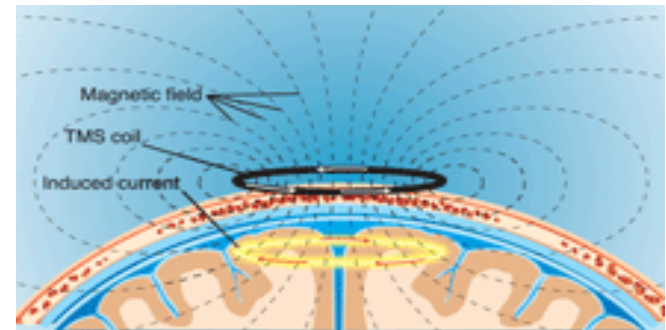
Bobine de  
stimulation

### Activation Voie cortico- spinale



PEM: potentiel évoqué moteur  
reflète l'activité musculaire induite  
par la stimulation corticale

TMS active sélectivement les  
neurones à orientation horizontale

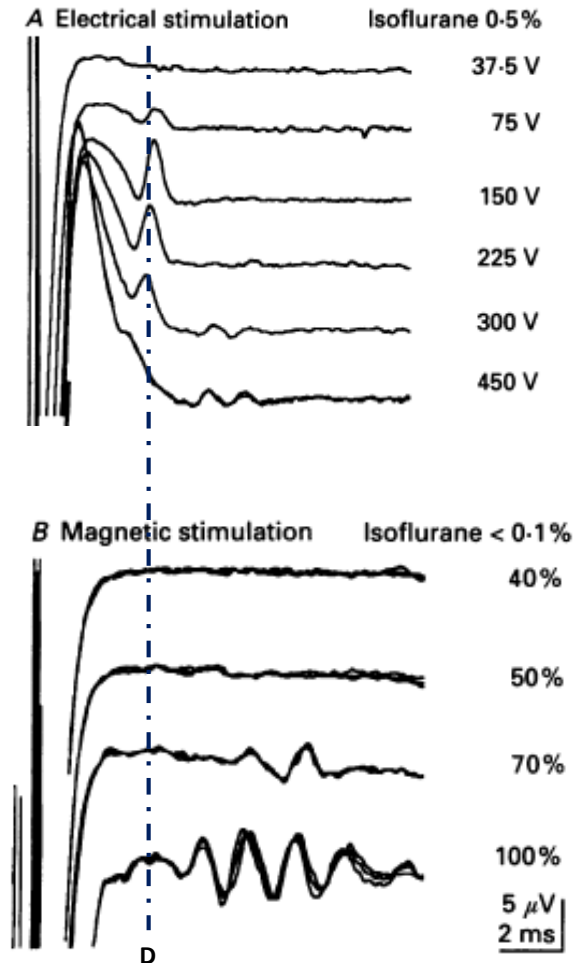


TMS permet de stimuler à travers  
(« trans ») le crâne  
et « mime » les stimulations  
corticales (ICMS) chez l'animal

# Volées corticospinales induites par TMS

## Volées corticospinales induites

### Enregistrements épiduraux



# Différentes formes de sonde TMS

*Sonde circulaire 50 mm*



*Sonde circulaire 70 mm*



*Sonde circulaire 90 mm*



*Sonde papillon 25 mm*

*Sonde papillon 70 mm*



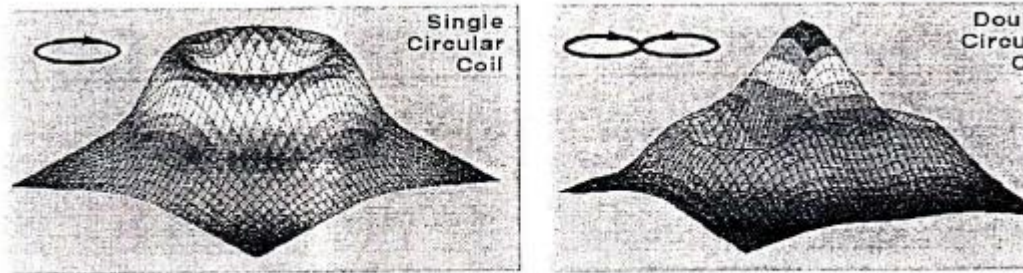
*Sonde double cône*



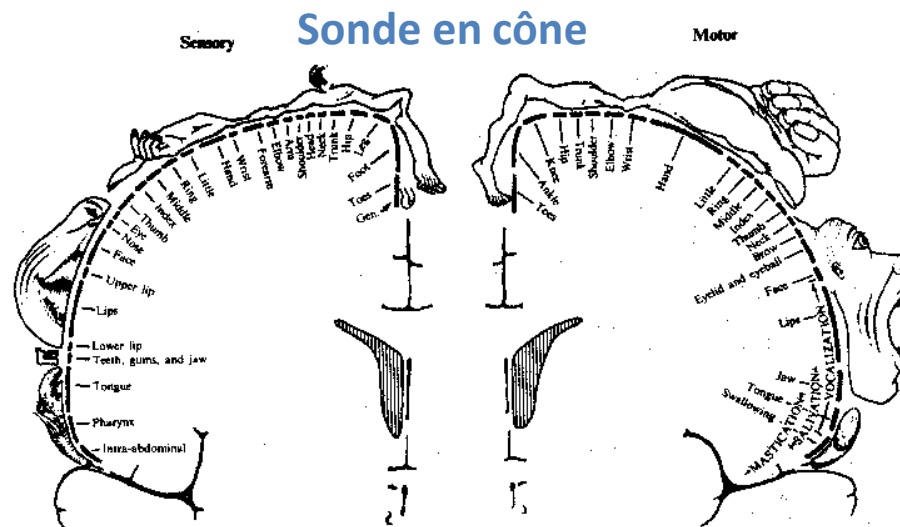
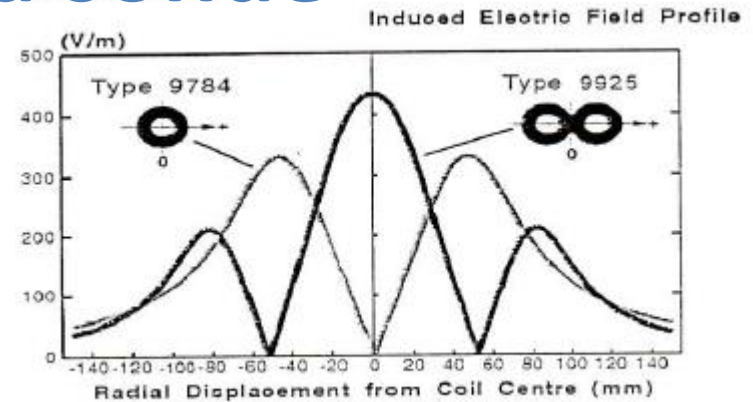
*Sonde double cône  
70 mm réfrigérée*



# Champ électrique induit en fonction de la forme de la sonde



Induced Electric Field Profile

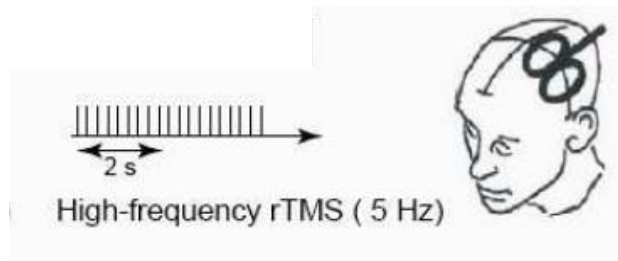


Sonde en papillon  
Sonde circulaire

# rTMS

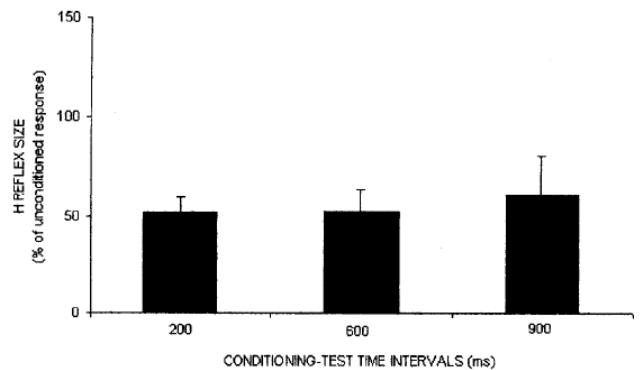
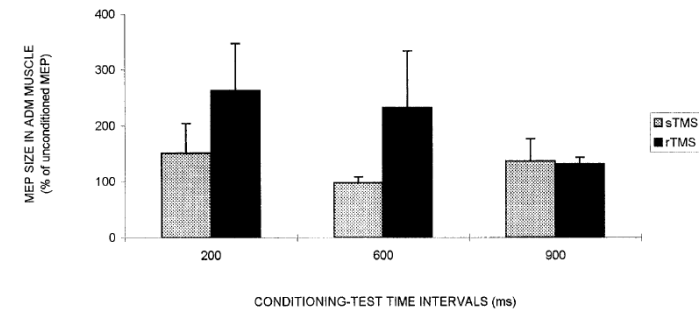
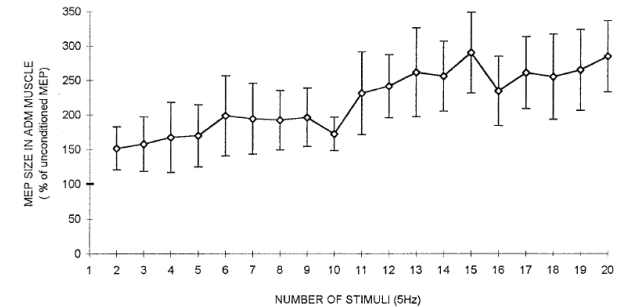
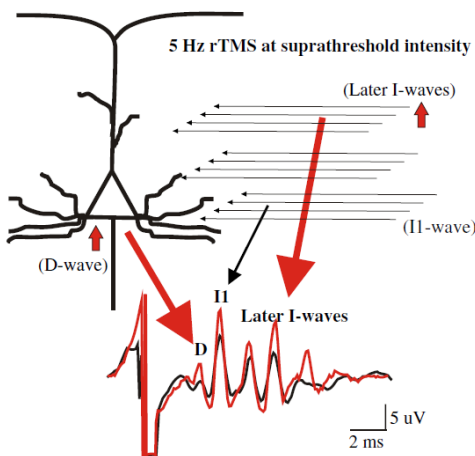
## rTMS haute fréquence 5Hz

Le PEM ↑ avec le nb de stimuli



ISI 200 et 600

Pas d'effet sur le H  
aux ISI 200 et 600



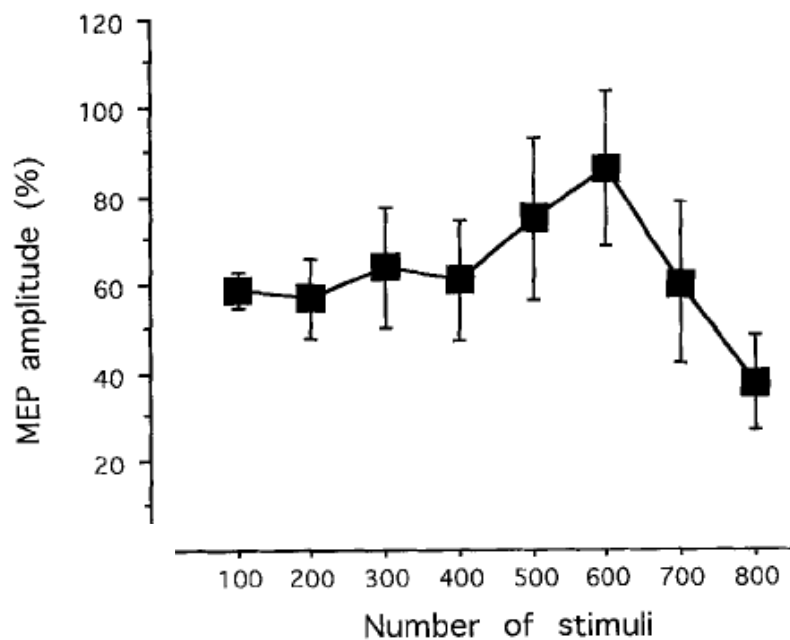
# rTMS

## *rTMS basse fréquence 1Hz*

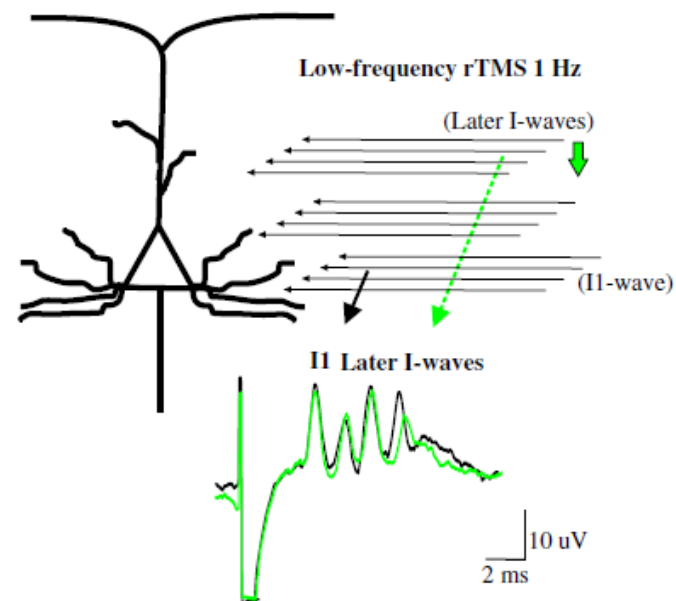
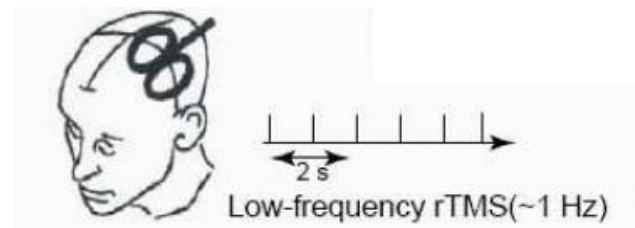
15 min de stimulation

TMS =115% RMT

0.9 Hz stimulation (Intervention)

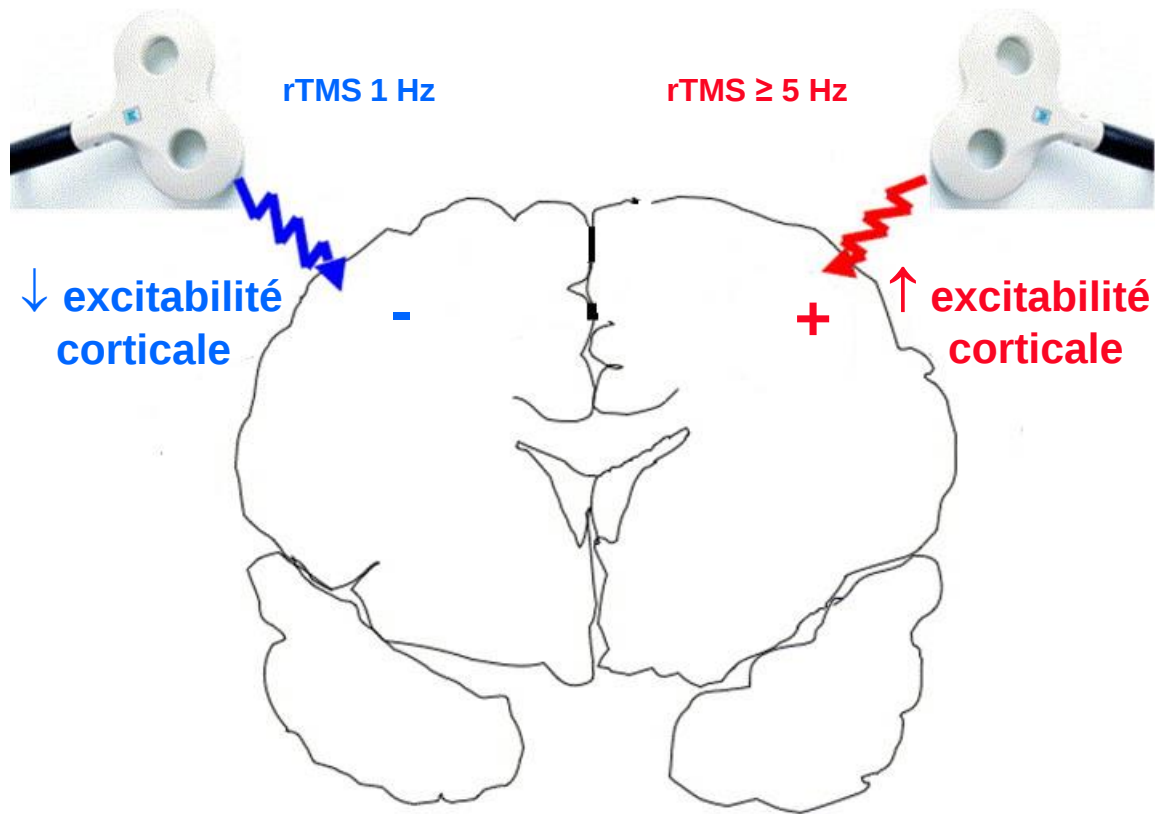


Chen et al. Neurology (1997) 48:1398 -1403c



Di Lazzaro et al. Clinical Neurophysiology (2010) 121:464-573c

# rTMS et Cortex moteur : rôle de la fréquence



*Pascual-Leone et al. 1994*  
*Maeda et al. 2000*  
*Romeo et al. 2000*

*Chen et al. 1997*  
*Maeda et al. 2000*  
*Muellbacher et al. 2000*

↑ de l'amplitude du PEM

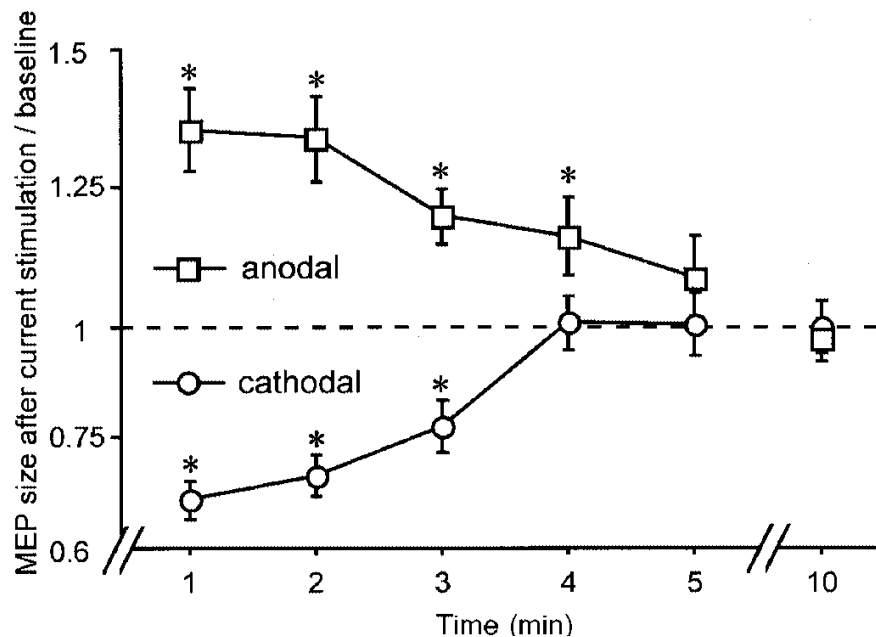
↓ de l'amplitude du PEM



# Courants galvaniques :

## tDCS (transcranial Direct Current Stimulation)

- Stimulation anodale: excitation
- Stimulation cathodale : Inhibition

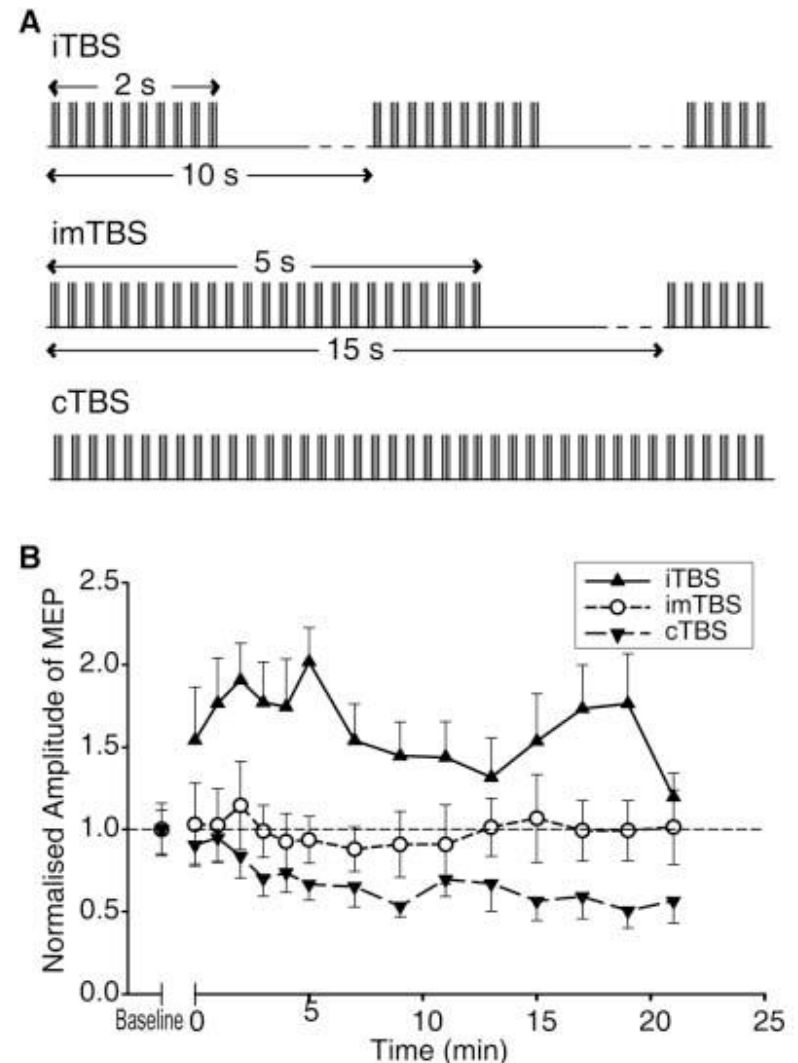


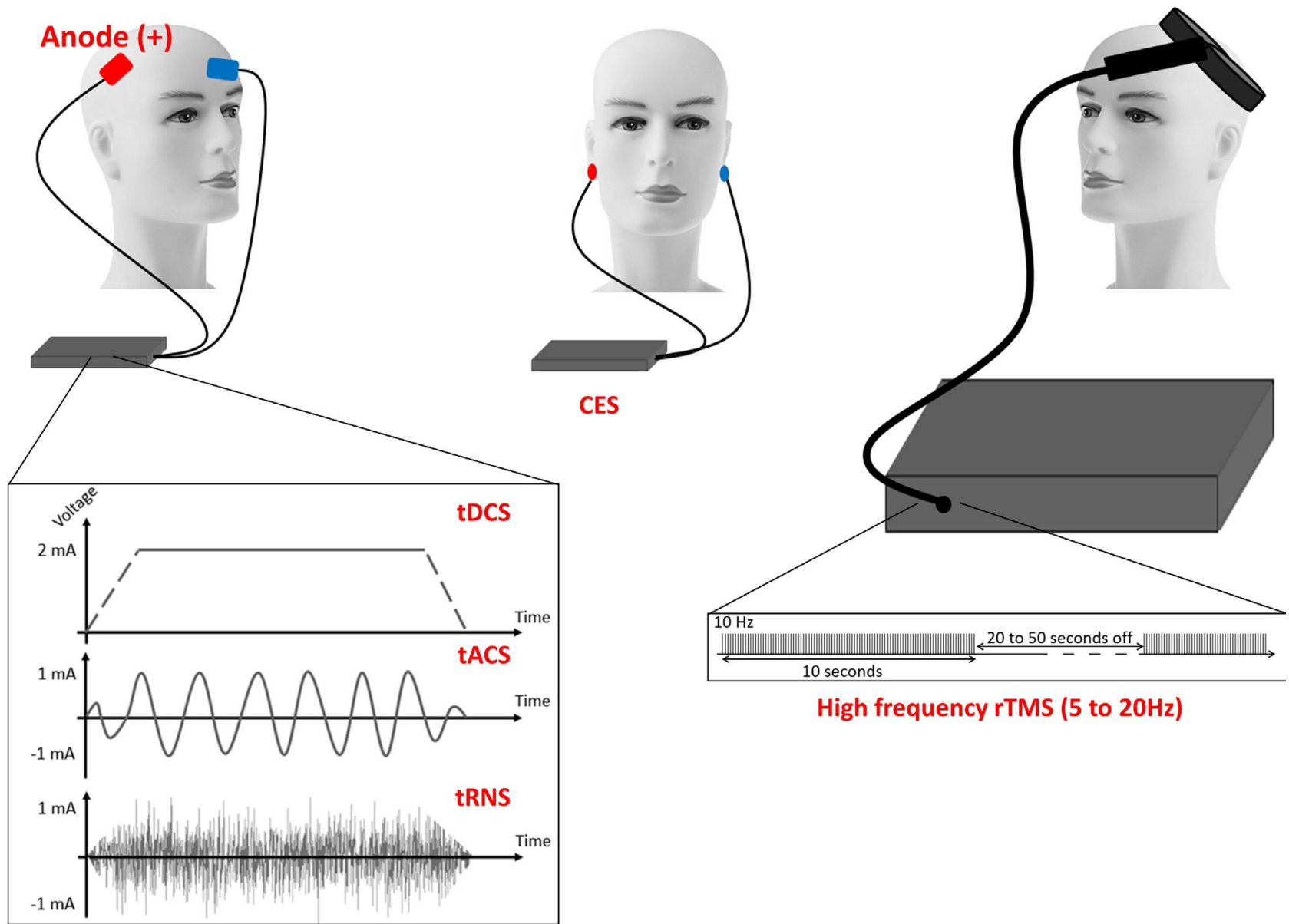
✧ Stimulation placebo

# Theta burst Stimulation (TBS)

- Train de 3 coups
- fréquence 50Hz
- toutes les 200 ms (5Hz)
- 80% seuil moteur
- Post-effets + longs pour durée stim très courte < 60 sec (600 pulses (sur M1))

Huang et al. 2005





D'après Moisset et Lefaucheur

REVUE NEUROLOGIQUE 175 (2019) 51-58

**EST-CE EFFICACE SUR LES  
DOULEURS NEUROPATHIQUES?**

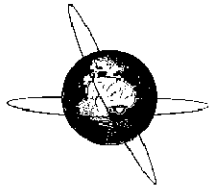


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### Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)



Jean-Pascal Lefaucheur<sup>ab,□</sup>, Nathalie André-Obadia<sup>cd</sup>, Andrea Antal<sup>e</sup>, Samar S. Ayache<sup>ab</sup>, Chris Baeken<sup>fg</sup>, David H. Benninger<sup>h</sup>, Roberto M. Cantello<sup>i</sup>, Massimo Cincotta<sup>j</sup>, Mamede de Carvalho<sup>k</sup>, Dirk De Ridder<sup>l,m</sup>, Hervé Devanne<sup>n,o</sup>, Vincenzo Di Lazzaro<sup>p</sup>, Saša R. Filipović<sup>q</sup>, Friedhelm C. Hummel<sup>r</sup>, Satu K. Jääskeläinen<sup>s</sup>, Vasilios K. Kimiskidis<sup>t</sup>, Giacomo Koch<sup>u</sup>, Berthold Langguth<sup>v</sup>, Thomas Nyffeler<sup>w</sup>, Antonio Oliviero<sup>x</sup>, Frank Padberg<sup>y</sup>, Emmanuel Poulet<sup>z,aa</sup>, Simone Rossi<sup>ab</sup>, Paolo Maria Rossini<sup>ac,ad</sup>, John C. Rothwell<sup>ae</sup>, Carlos Schönfeldt-Lecuona<sup>af</sup>, Hartwig R. Siebner<sup>ag,ah</sup>, Christina W. Slotema<sup>ai</sup>, Charlotte J. Stagg<sup>aj</sup>, Josep Valls-Sole<sup>ak</sup>, Ulf Ziemann<sup>al</sup>, Walter Paulus<sup>ae,1</sup>, Luis Garcia-Larrea<sup>d,am,1</sup>

**Table 1**  
rTMS studies in chronic neuropathic pain (target: primary motor cortex).

[illegible]

**Table 2**  
rTMS studies in complex regional pain syndrome type I (target: primary motor cortex).

[illegible]

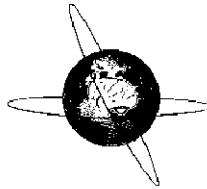


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## Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)



Jean-Pascal Lefaucheur<sup>a,b,□</sup>, André Aleman<sup>c</sup>, Chris Baeken<sup>d,e,f</sup>, David H. Benninger<sup>g</sup>, Jérôme Brunelin<sup>h</sup>, Vincenzo Di Lazzaro<sup>i</sup>, Saša R. Filipović<sup>j</sup>, Christian Grefkes<sup>k,l</sup>, Alkomiet Hasan<sup>m</sup>, Friedhelm C. Hummel<sup>n,o,p</sup>, Satu K. Jääskeläinen<sup>q</sup>, Berthold Langguth<sup>r</sup>, Letizia Leocani<sup>s</sup>, Alain Londero<sup>t</sup>, Raffaele Nardone<sup>u,v,w</sup>, Jean-Paul Nguyen<sup>x,y</sup>, Thomas Nyffeler<sup>z,aa,ab</sup>, Albino J. Oliveira-Maia<sup>ac,ad,ae</sup>, Antonio Oliviero<sup>af</sup>, Frank Padberg<sup>m</sup>, Ulrich Palm<sup>ma,ag</sup>, Walter Paulus<sup>ah</sup>, Emmanuel Poulet<sup>h,ai</sup>, Angelo Quartarone<sup>aj</sup>, Fady Rachid<sup>ak</sup>, Irena Rektorová<sup>al,am</sup>, Simone Rossi<sup>an</sup>, Hanna Sahlsten<sup>ao</sup>, Martin Schecklmann<sup>r</sup>, David Szekely<sup>ap</sup>, Ulf Ziemann<sup>aq</sup>

**Table 1**

HF-rTMS of M1 contralateral to pain region in neuropathic pain.

| Articles                               | Number of patients                                                      | Target, coil type                                                                                            | Control condition     | Stimulation frequency and intensity | Number of pulses/session and number of sessions | Significant clinical effects of real versus sham condition                                                                                                                              | Class of the study |
|----------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| <a href="#">Khedr et al. (2015)</a>    | 30 patients with malignant neuropathic pain (real: 15; sham: 15)        | Hand M1 contralateral to pain, F8c (anteroposterior orientation)                                             | Tilted coil           | 20 Hz, 80% RMT                      | 2000 pulses, 10 sessions                        | Reduction of pain score at the end of rTMS protocol (49% on VRS and 37% on VAS), up to 2 weeks after the last session (46% on VRS and 36% on VAS); 87–80% responders (>30% pain relief) | II                 |
| <a href="#">Ma et al. (2015)</a>       | 40 patients with postherpetic neuralgia (real: 20; sham: 20)            | Homotopic M1 contralateral to pain region, F8c (anteroposterior orientation)                                 | Tilted coil           | 10 Hz, 80% RMT                      | 1500 pulses, 10 sessions                        | Reduction of pain score (17% on VAS), up to 3 months after the last session; 50% responders (>50% pain relief)                                                                          | II                 |
| <a href="#">Attal et al., 2016</a>     | 32 patients with neuropathic lumbar radicular pain (real: 21; sham: 11) | Hand M1 contralateral to pain, F8c (anteroposterior orientation)                                             | Sham coil             | 10 Hz, 80% RMT                      | 3000 pulses, 3 sessions                         | Reduction of pain score at the end of rTMS protocol (#60% on VAS), up to 5 days after the last session (#25% on VAS); 43% responders (>30% pain relief)                                 | II                 |
| <a href="#">Nurmikko et al. (2016)</a> | 27 patients with neuropathic pain of various origins (crossover)        | Homotopic M1 contralateral to pain region or an adjacent motor region, F8c (perpendicular to central sulcus) | Occipital stimulation | 10 Hz, 90% RMT                      | 2000 pulses, 5 sessions                         | Reduction of pain score compared to control condition one week after the last session (9–11% on VAS); 30% responders (>30% pain relief)                                                 | II                 |



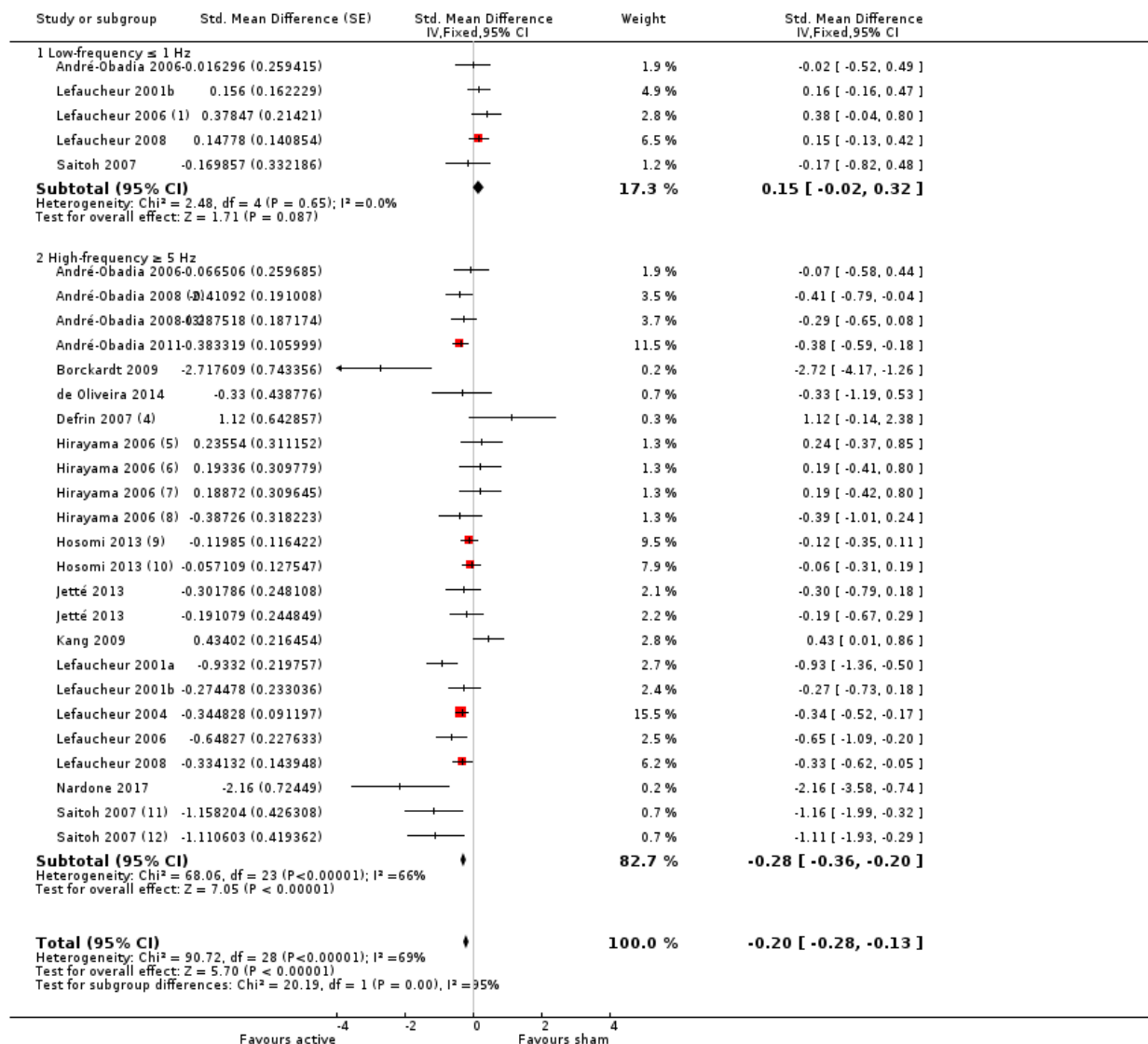
**Cochrane**  
**Library**

**Cochrane** Database of Systematic Reviews

## **Non-invasive brain stimulation techniques for chronic pain (Review)**

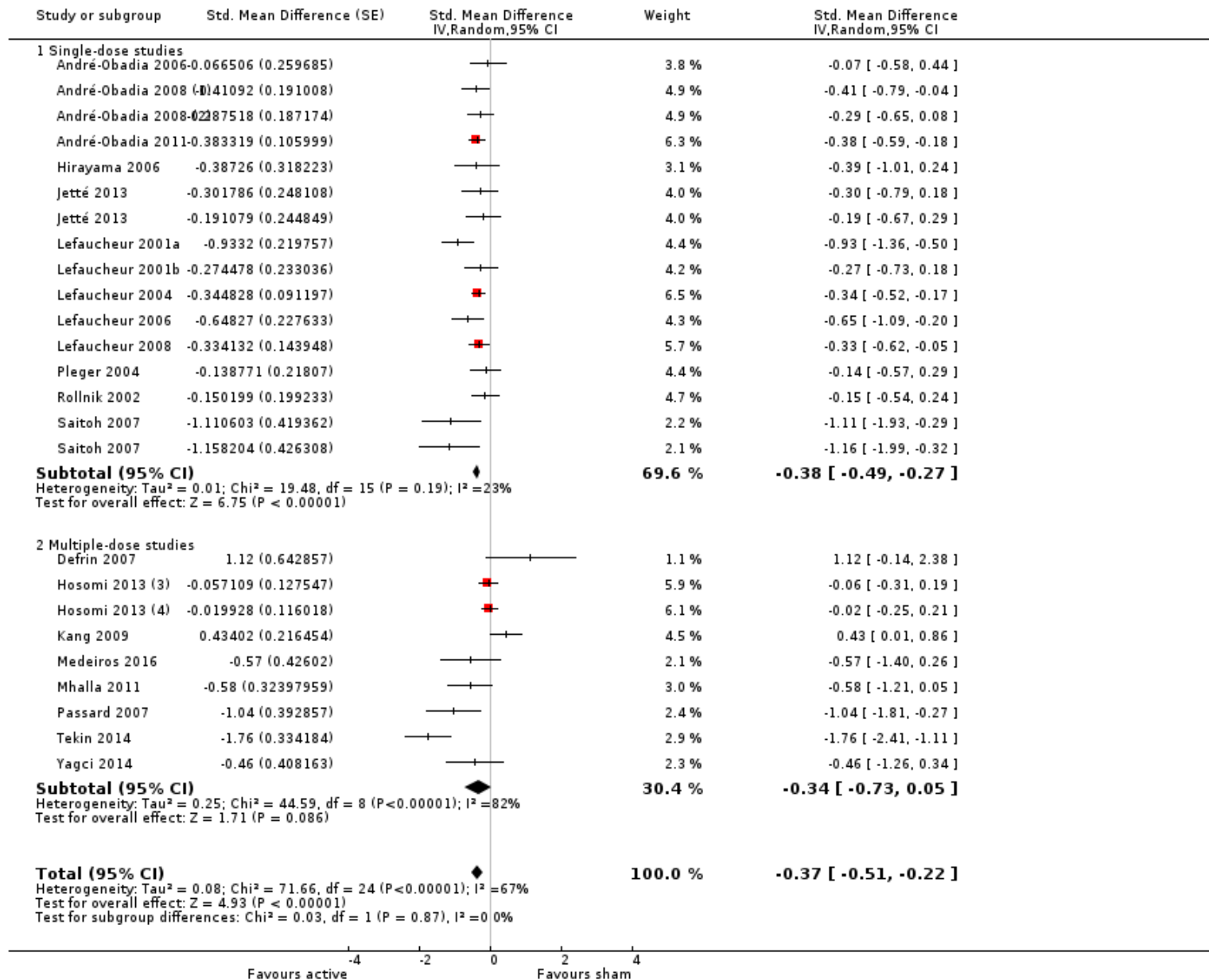
O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM

Review: Non-invasive brain stimulation techniques for chronic pain  
 Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)  
 Outcome: 3 Pain: short-term follow-up, subgroup analysis, neuropathic pain participants only



- (1) 1Hz
- (2) antero-posterior coil orientation
- (3) medial-lateral coil orientation
- (4) Pain score higher at baseline in active stim group
- (5) S1
- (6) PMA
- (7) SMA
- (8) M1
- (9) M1 Group B (sham followed by real)
- (10) M1 Group A (real followed by sham)
- (11) 5Hz
- (12) 10 Hz

Review: Non-invasive brain stimulation techniques for chronic pain  
 Comparison: 1 Repetitive transcranial magnetic stimulation (rTMS)  
 Outcome: 5 Pain: short-term follow-up, subgroup analysis: motor cortex studies only, low-frequency studies excluded



- (1) antero-posterior coil orientation  
 (2) medial-lateral coil orientation  
 (3) Group B sham followed by real  
 (4) Group A real followed by sham

## Summary of findings for the main comparison. Repetitive transcranial magnetic stimulation (rTMS) compared with sham for chronic pain

### rTMS compared with sham for chronic pain

**Patient or population:** adults with chronic pain

**Settings:** laboratory/ clinic

**Intervention:** active rTMS

**Comparison:** sham rTMS

| Outcomes                                                                                                                       | Effect size                       | Relative and absolute effect<br>(average % improvement (reduction) in pain (95% CIs) in relation to post-treatment score from sham group)*<br><br>*Where 95%CIs do not cross the line of no effect. | No of participants (studies) | Quality of the evidence (GRADE)      |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------|
| <b>Pain intensity</b> (0 to < 1 week postintervention)<br><br>measured using visual analogue scales or numerical rating scales | SMD -0.22 (-0.29 to -0.16)        | This equates to a 7% (95% CI 5% to 9%) reduction in pain intensity, or a 0.40 (95% CI 0.53 to 0.32) point reduction on a 0 to 10 pain intensity scale.                                              | 655 (27)                     | ⊕⊕⊕⊕ <b>low</b> <sup>1</sup>         |
| <b>Disability</b> (0 to < 1 week postintervention)<br><br>measured using self-reported disability/pain interference scales     | SMD -0.29, 95% CI -0.87 to 0.29   | -                                                                                                                                                                                                   | 119 (5)                      | ⊕⊕⊕⊕<br><b>very low</b> <sup>2</sup> |
| <b>Quality of life</b> (0 to < 1 week postintervention)<br><br>measured using Fibromyalgia Impact Questionnaire                | MD -10.80, 95% CI -15.04 to -6.55 | -                                                                                                                                                                                                   | 105 (4)                      | ⊕⊕⊕⊕ <b>low</b> <sup>3</sup>         |

**CI:** confidence interval; **MD:** mean difference; **rTMS:** repetitive transcranial magnetic stimulation; **SMD:** standardised mean difference

### Summary of findings 3. Transcranial direct current stimulation (tDCS) compared with sham for chronic pain

#### tDCS compared with sham for chronic pain

**Patient or population:** adults with chronic pain

**Settings:** laboratory/ clinic

**Intervention:** active tDCS

**Comparison:** sham tDCS

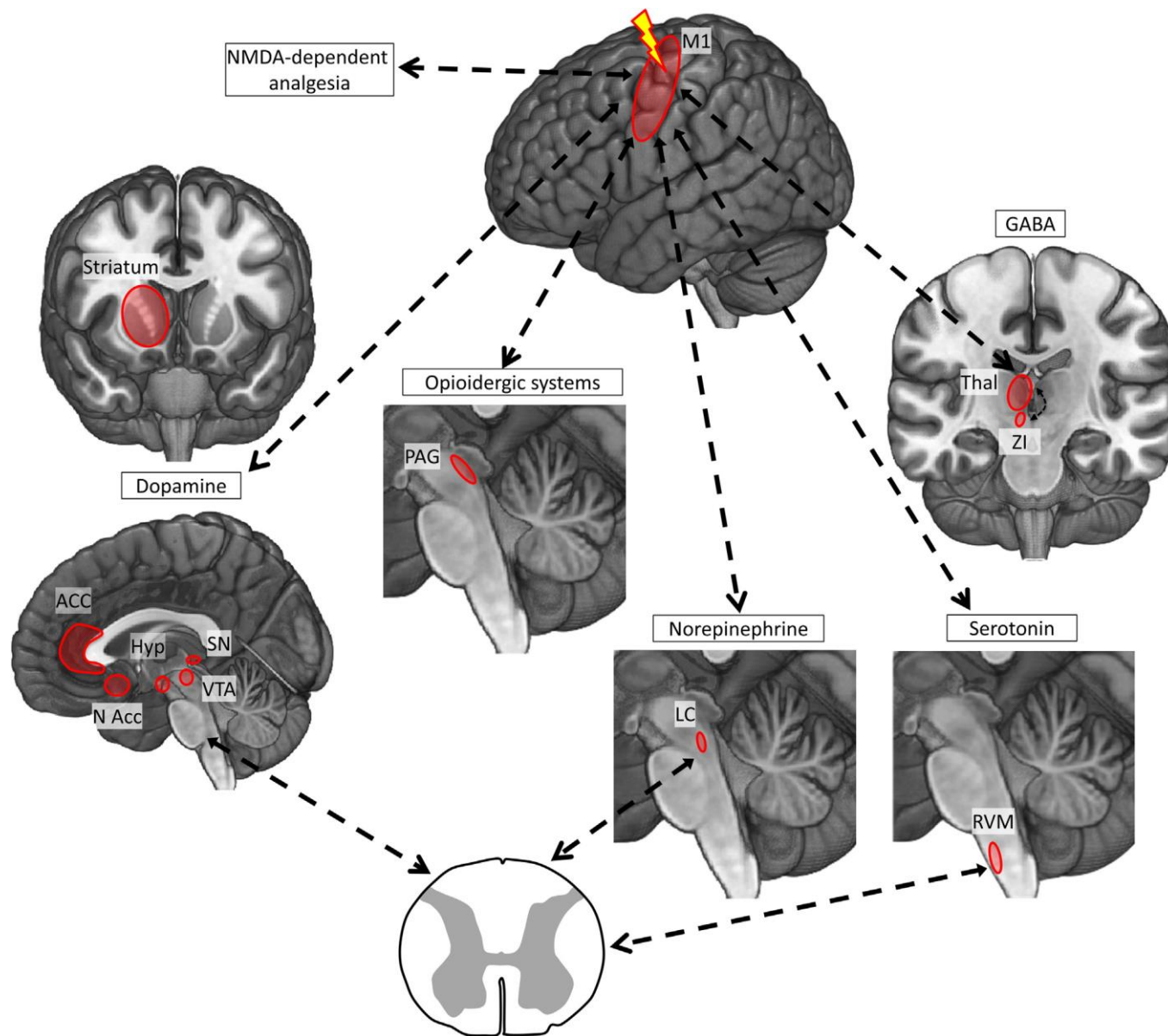
| Outcomes                                                                                                                       | Effect size                       | Relative effect<br>(average % improvement (reduction) in pain (95% CIs) in relation to post-treatment score from sham group)*<br><br>*Where 95%CIs do not cross the line of no effect. | No of participants (studies) | Quality of the evidence (GRADE)   |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------|
| <b>Pain intensity</b> (0 to < 1 week postintervention)<br><br>measured using visual analogue scales or numerical rating scales | SMD -0.43 (-0.63 to -0.22)        | This equates to a 17% (95% CI 9% to 25%) reduction in pain intensity or a 0.82 (95% CI 0.42 to 1.2) point reduction on a 0 to 10 pain intensity scale.                                 | 747 (27)                     | ⊕⊕⊕⊕ <b>very low</b> <sup>1</sup> |
| <b>Disability</b> (0 to < 1 week postintervention)<br><br>measured using self-reported disability/pain interference scales     | SMD -0.01, (95% CI -0.28 to 0.26) | -                                                                                                                                                                                      | 212 (4)                      | ⊕⊕⊕⊕ <b>low</b> <sup>2</sup>      |
| <b>Quality of life</b> (0 to < 1 week postintervention)<br><br>measured using different scales across studies                  | SMD 0.66, 95% CI 0.21 to 1.11     | -                                                                                                                                                                                      | 82 (4)                       | ⊕⊕⊕⊕ <b>low</b> <sup>2</sup>      |

**CI:** confidence interval; **MD:** mean difference; **SMD:** standardised mean difference; **tDCS:** transcranial direct current stimulation

# Est-ce efficace?

- Recommandation de grade A pour la rTMS dans les douleurs neuropathiques
- Niveau C pour le tDCS et le thetaburst
- Pas de recommandations pour les autres techniques

# MÉCANISMES D'ACTION

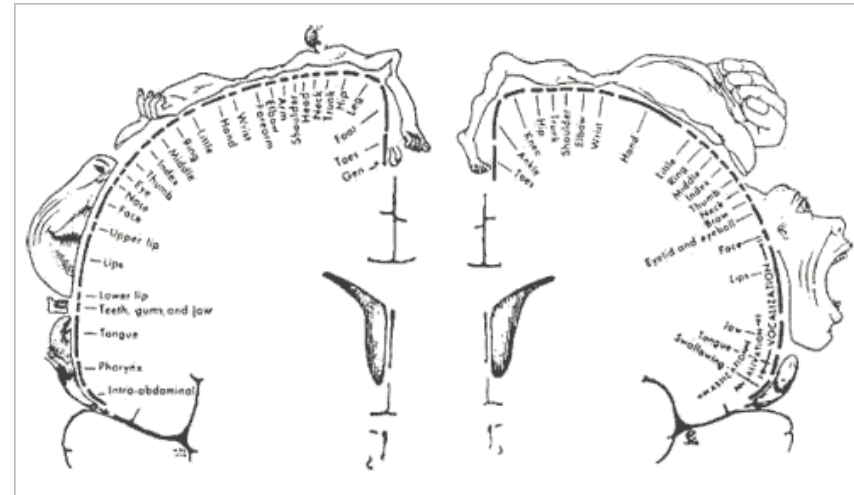


D'après Moisset et Lefaucheur

# MODALITÉS PRATIQUES

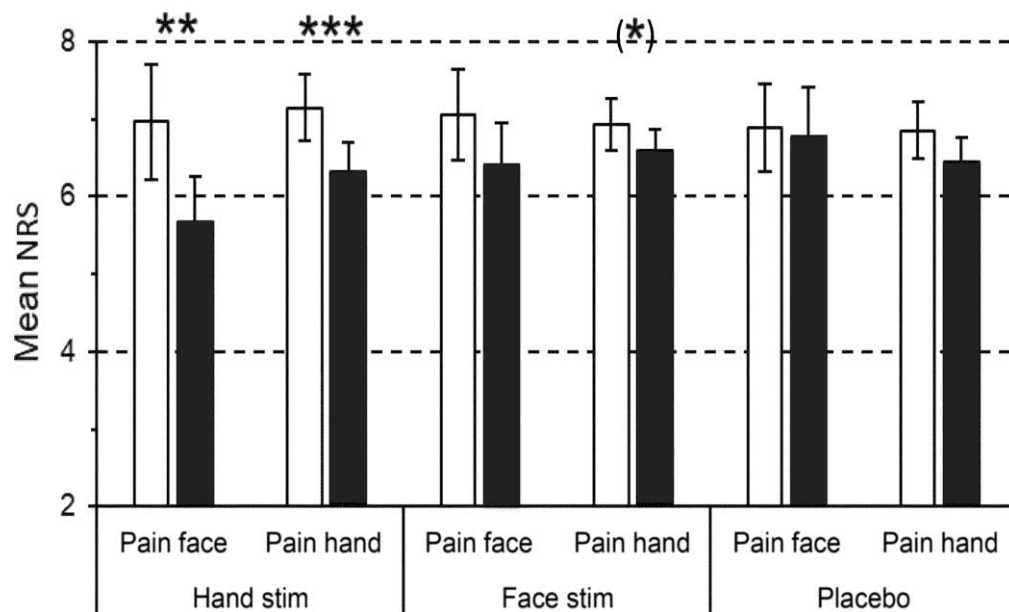
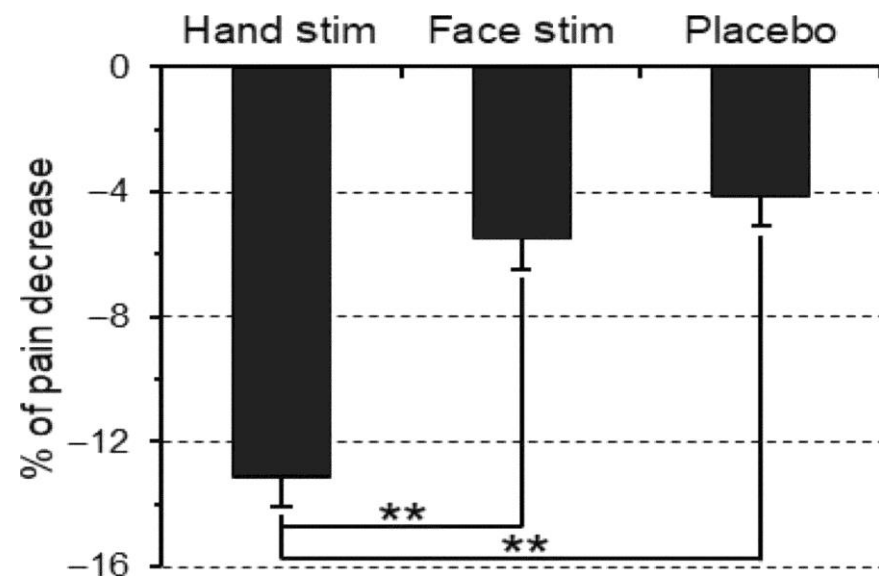
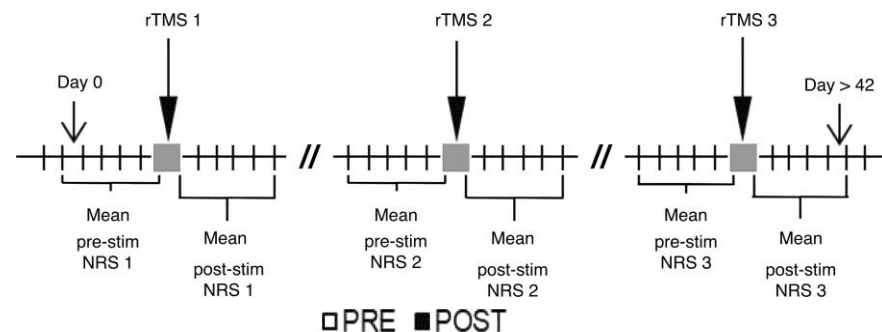
# Où stimuler?

- Cortex moteur primaire :
  - recommandations grade A
- Autres sites :
  - Préfrontal
  - S1 et S2
  - Trop peu d'études pas de recommandations



# Où stimuler?

- Pas de somatotopie
- Recommandation : l'aire de la main



# Quel programme?

- Haute fréquence  $>5$  Hz : 10Hz, 20 Hz
- Nombre de coups : 1200 à 2000 pulses par session
- 80% du seuil moteur
- Des trains de 5 à 10s
- Des repos de 20 à 60 s
- 1 à 5 sessions
- Tous les 1 à 6 mois

# Combien de temps ça marche?

- 1 session :
  - Début d'effet 1 à 3 jours
  - Durée 5 à 7 jours
- 5 sessions :
  - Jusqu'à 1 mois d'efficacité

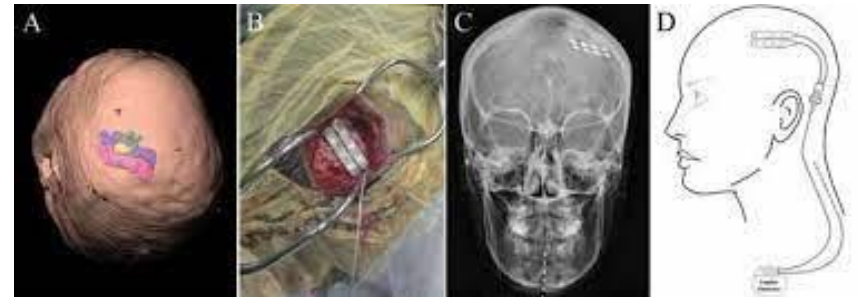
# Les effets indésirables

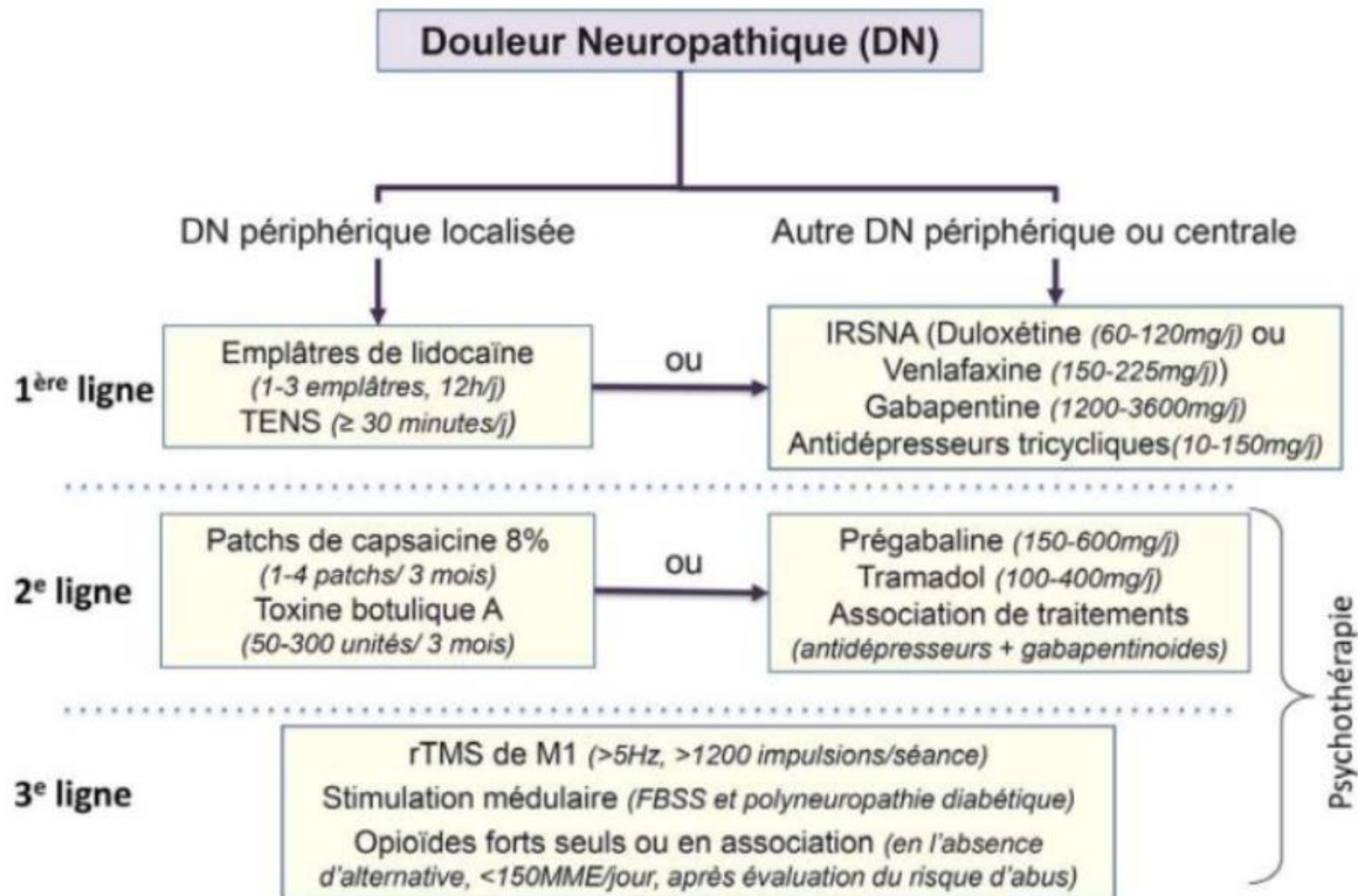
- Crise d'épilepsie :
  - Cf recommandations européenne
- Migraine
- maux de tête
- Trouble de l'attention
- Acouphènes, phosphènes
- Tous transitoires

# **QUELLE PLACE DANS LE TRAITEMENT DES DOULEURS NEUROPATHIQUES?**

# Test pré-implantatoire?

- Essai d'une session
- Si efficace :
  - Diminution 50%  
douleurs dans les 1 à 3 j
- Implantation électrodes  
épidurales sur le cortex  
moteur





**Fig. 1** Algorithme thérapeutique proposé pour la prise en charge de la douleur neuropathique de l'adulte. TENS : *transcutaneous electrical nerve stimulation* ; IRSNA : antidépresseur inhibiteur de recapture de la sérotonine et de la noradrénaline ; rTMS : *repetitive transcranial magnetic stimulation*

**NOTRE EXPERIENCE**



# Methods

71 patients were included (December 2014-2017)

**Adults**

**DN4 > 4**

**No contra indication to rTMS**

rTMS +  
motor imagery and mirror  
therapy

**1 Day**

rTMS +  
motor imagery and mirror  
therapy

**5 Days**



**rTMS**  
10 Hz 20 min  
Contralateral motor cortex to  
pain

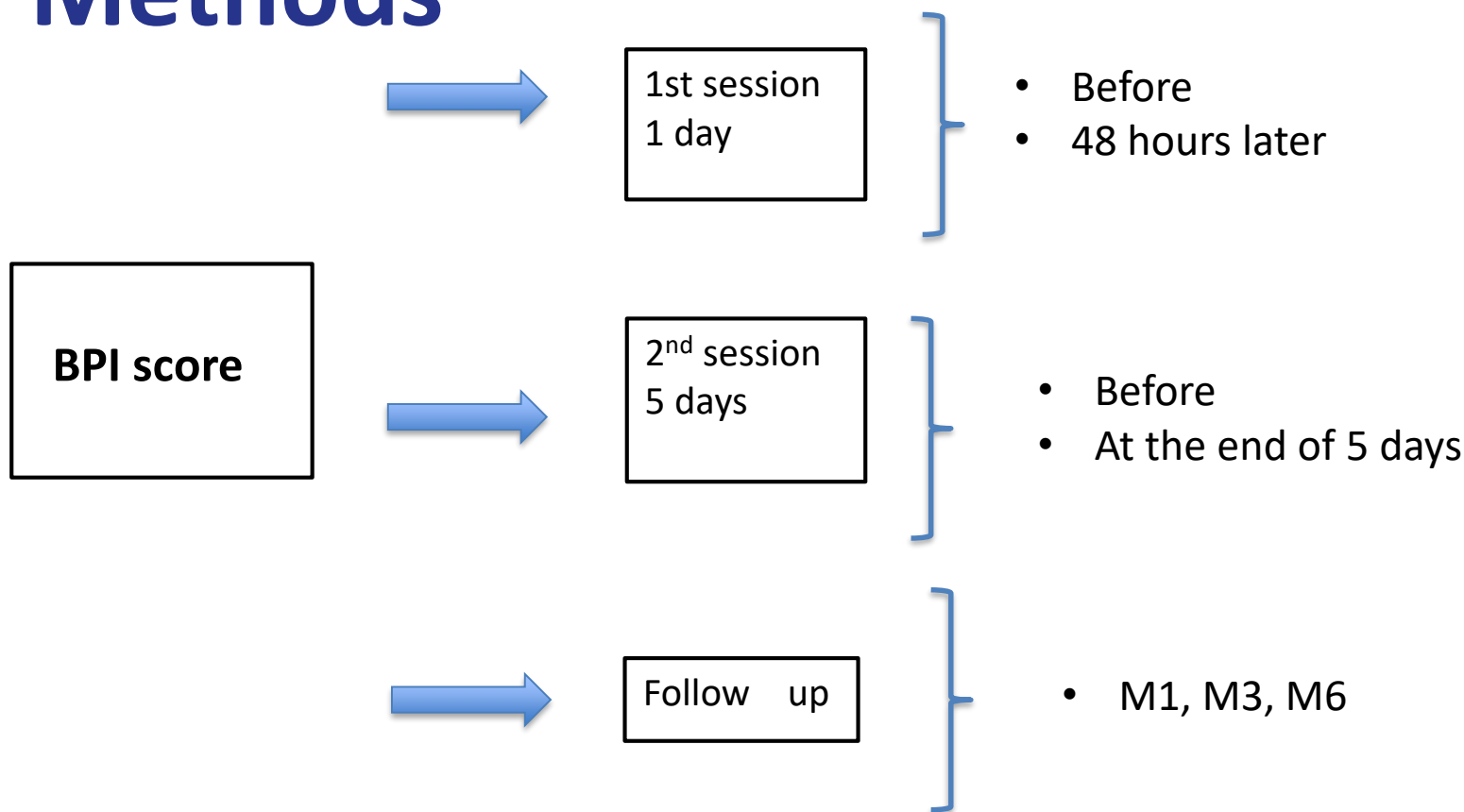
➤ (Jin Y, Pain Physician. 2015)

**motor imagery and mirror  
therapy**

By a physiotherapist 2/ day



# Methods



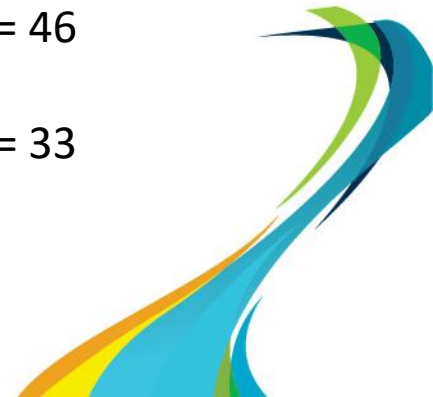


## Patient characteristics

|                                          |       |
|------------------------------------------|-------|
| No. of patients                          | 71    |
| Sex (male/female)                        | 43/28 |
| Mean age                                 | 56,3  |
|                                          |       |
| <b><u>Pain duration</u></b> mean (years) | 6,5   |
| < 2 years                                | 38    |
| > 2 years                                | 33    |
| <b><u>Pathology</u></b>                  |       |
| Stroke                                   | 32    |
| Multiple sclerosis                       | 6     |
| Spinal cord injuries                     | 31    |
| Head trauma                              | 2     |
| <b><u>Pain Location</u></b>              |       |
| Arm (unilateral / both side)             | 16/2  |
| Leg (unilateral / both side)             | 19/8  |
| Hemibody                                 | 18    |
| 4 members                                | 7     |

## Results

- Day 0 : n= 71
- 48 H: n= 39
- D1: n=
- D5: n=
- M1: n= 47
- M3: n= 46
- M6: n= 33





# (Results)

- Primary outcome = decreasing of the most intense pain of two points
- Responders
  - 30,5% at 48 hours (n= 39)
  - 25,5% at M1 (n= 47)
  - 28,2% at M3 (n= 46)
  - 33,3% at M6 (n= 33)



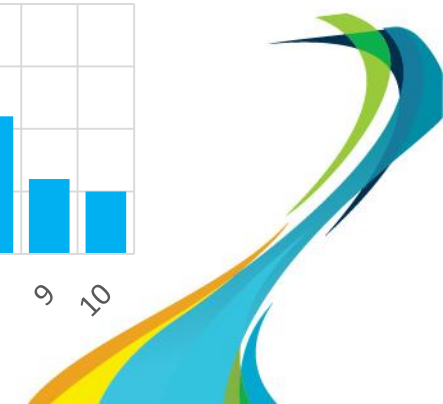
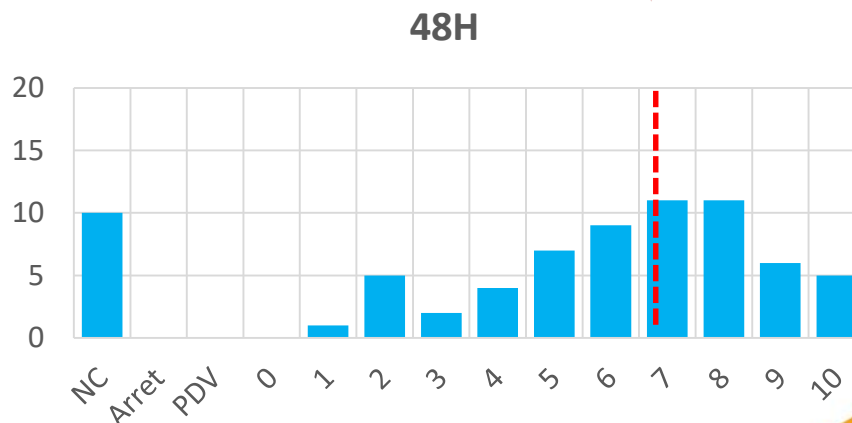
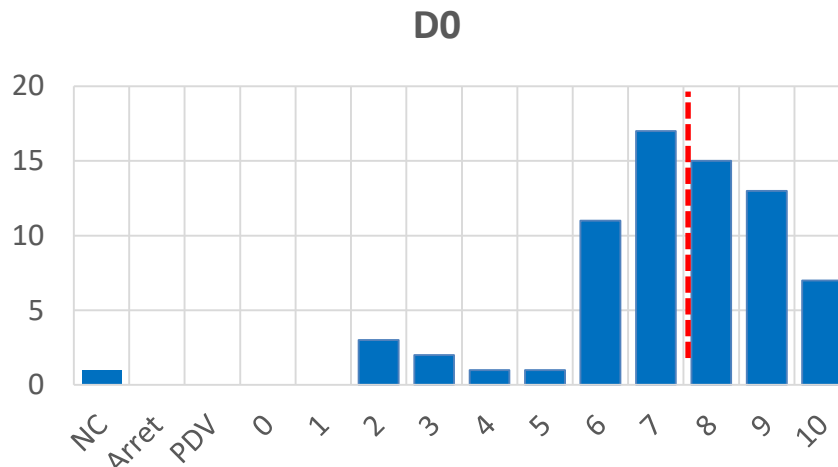


# Results

## Most intense pain evolution

Significant  
improvement  
 $p < 0,05$

----- median



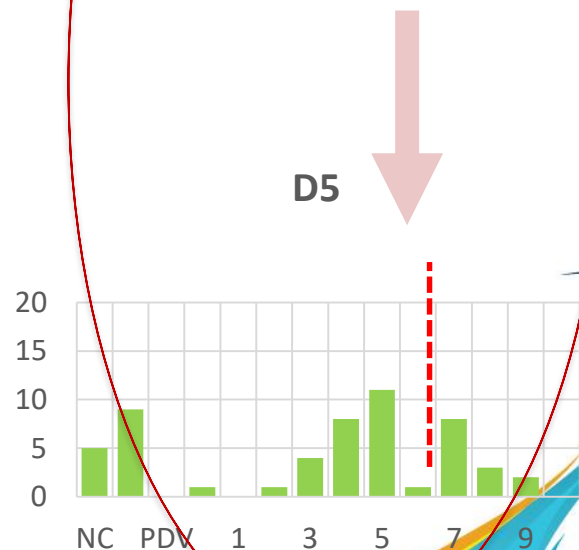
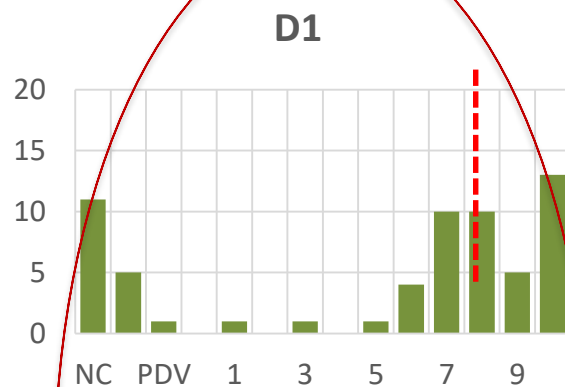
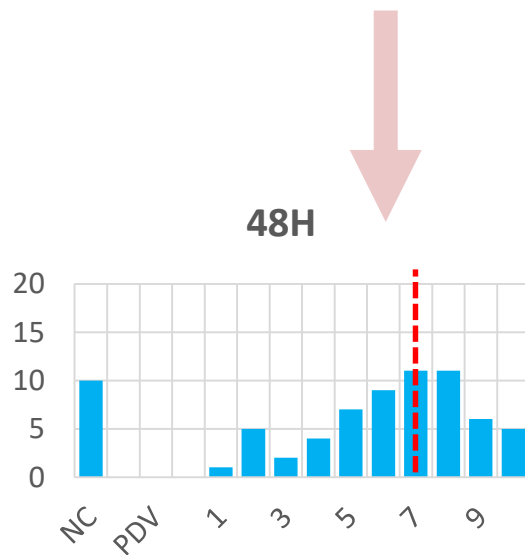
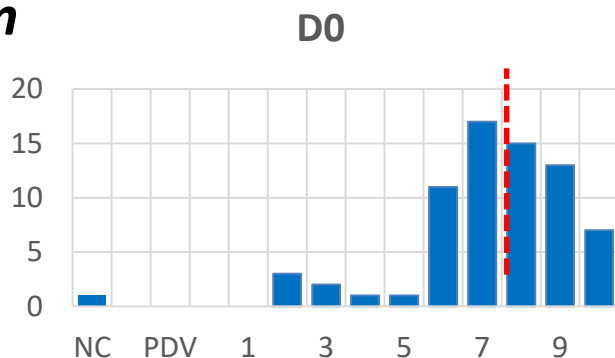


# Results

## Most intense pain evolution

Significant  
improvement  
 $p < 0,05$

----- median



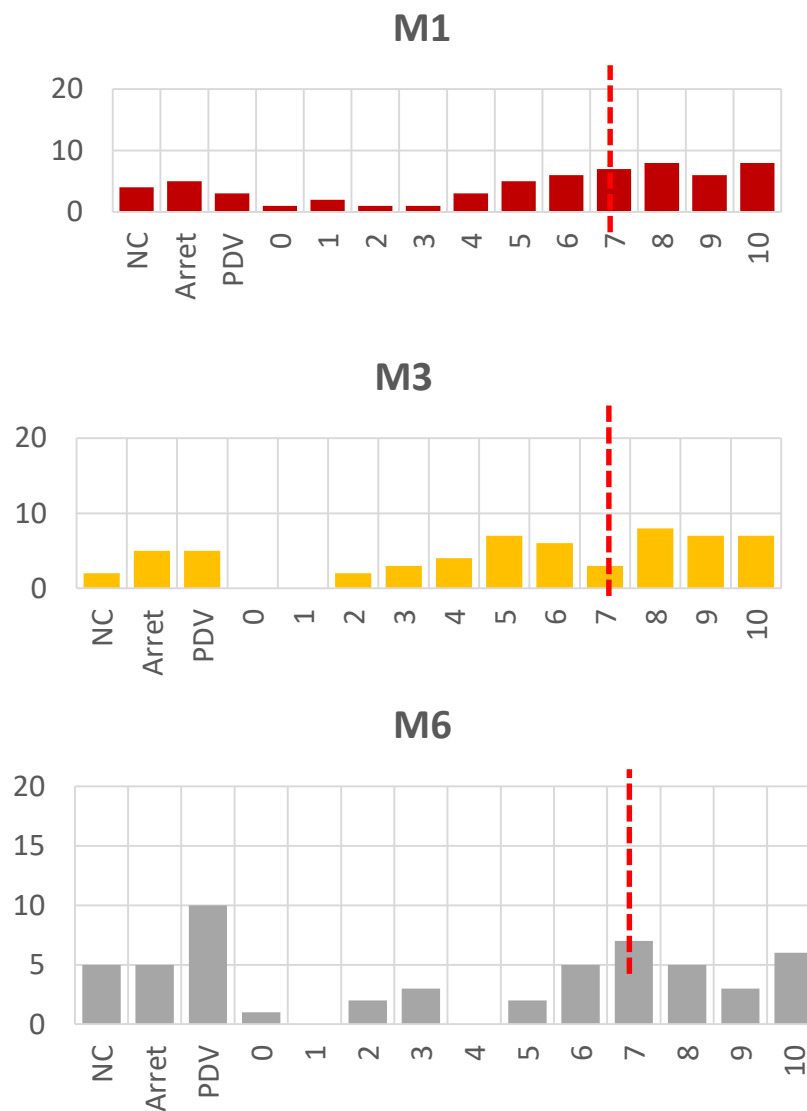


# Results

## Most intense pain evolution

Significant  
improvement  
 $p < 0,05$

----- median

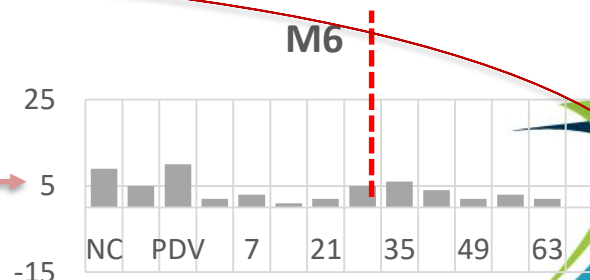
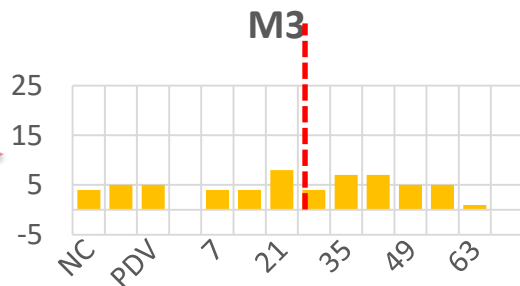
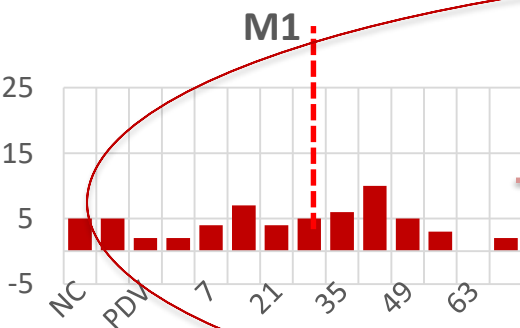
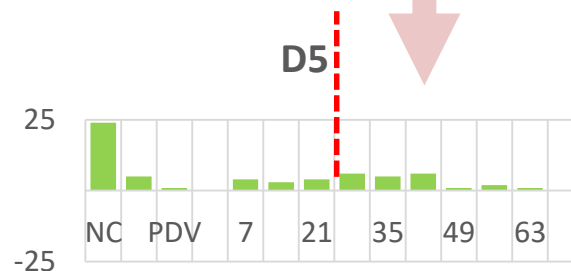
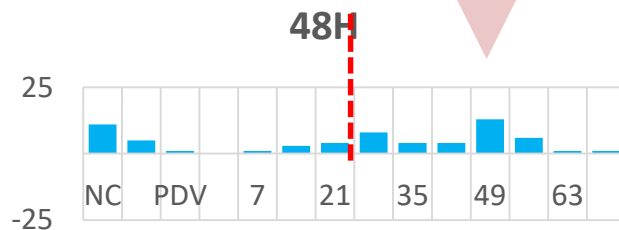
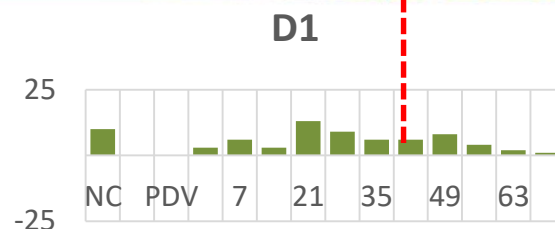
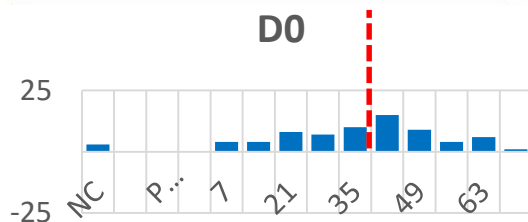




# Results

## Pain impact evolution

Significant  
improvement  
 $p < 0,05$



# Conclusion

- rTMS et douleurs neuropathiques : grade A , effet temporaire
- Répétitions de sessions de rTMS et/ou techniques complémentaires (imagerie en miroir ou imagination du mouvement) augmentent la durée d'efficacité
- Il existe de bons répondeurs : 30% dans notre série
- Si bonne réponse mais courte (<1mois) = test préimplantatoire d'une stimulation épidurale du cortex moteur
- Traitement de 3<sup>ième</sup> ligne des douleurs neuropathiques