LES NOUVELLES TECHNIQUES DE STIMULATIONS CÉRÉBRALES

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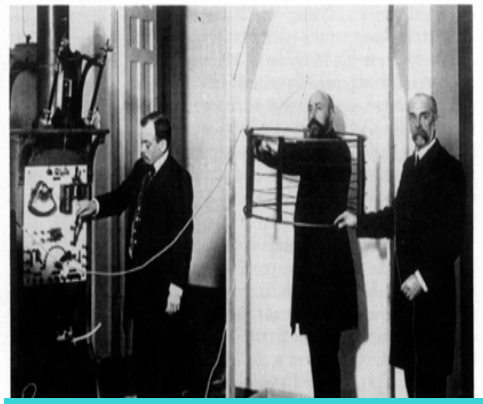
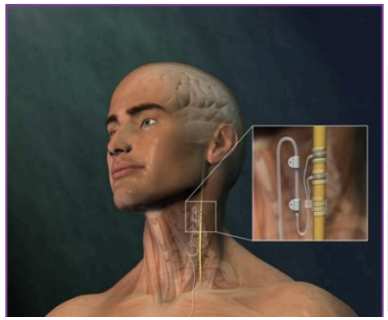
Les techniques de stimulation



d'Arsonval (1896/1911)

- Reprise ou actualisation de techniques anciennes ECT, tDCS
- Apparition de nouvelles techniques : stimulation magnétique transcrânienne répétée (rTMS) et ses variantes, magnétoconvulsivothérapie (MST), stimulation du nerf vague (VNS) et stimulation profonde (DBS).

VNS en images



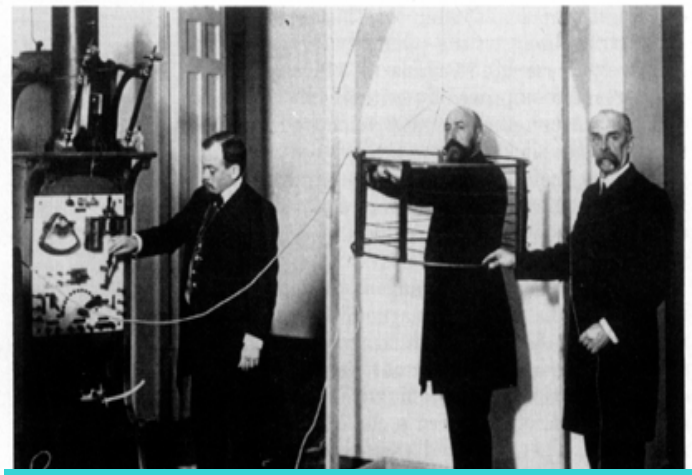
- ECT : gold standard, âge prédictif de meilleure réponse et rémission…
- magnétoconvulsivothérapie (MST), stimulation du nerf vague (VNS) et stimulation profonde (DBS) : rapports de cas…

- rTMS et tDCS

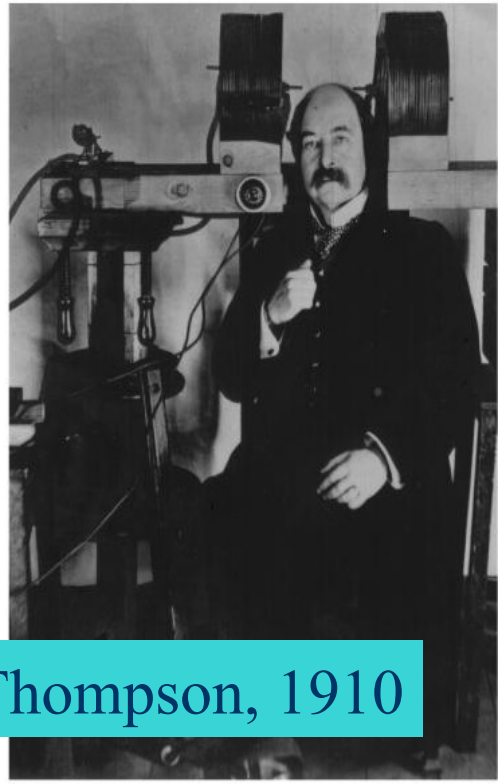
  - Principes de ces techniques
  - Effets sur l'humeur
  - Effets sur la cognition

rTMS et PA

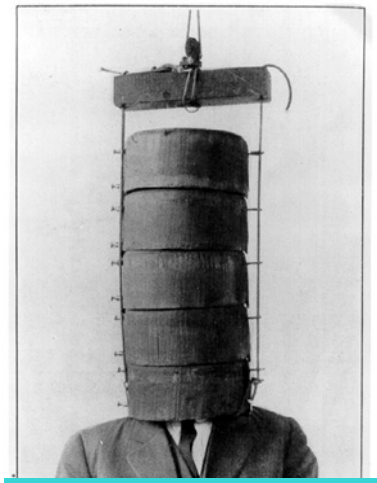
rTMS : principes



d'Arsonval (1896/1911)



Thompson, 1910



Magnusson & Stevens, 1911

Principes de la r-TMS

Condensateur
Courant alternatif (5000 A)

↓

Bobine couplée à un système de refroidissement

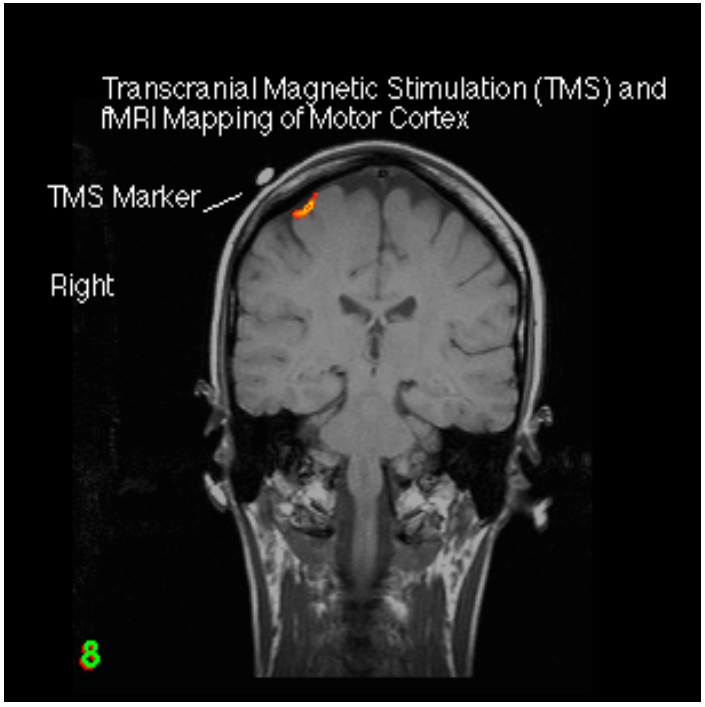
↓

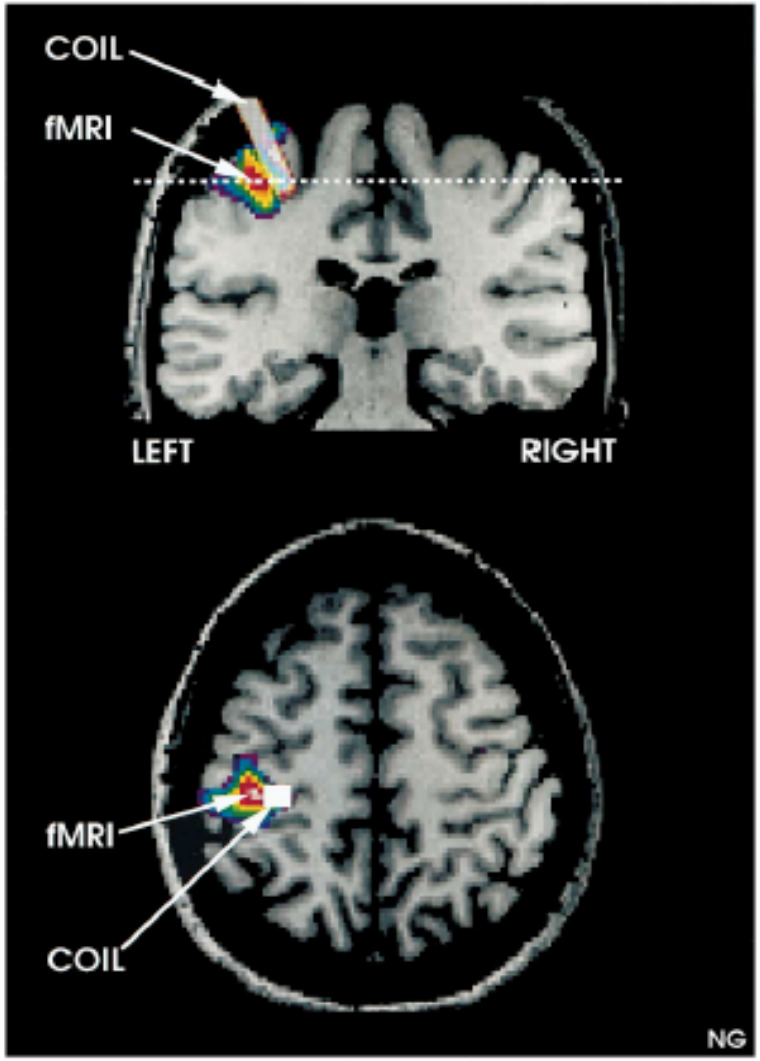
Champ magnétique

↓

Courant électrique
Excitation des neurones corticaux sous le scalp

rTMS : principes





rTMS : les indications

- traitement des acouphènes *(Kleinjung, Eichhammer et al. 2005; Kleinjung, Steffens et al. 2007),*
- douleurs chroniques *(Passard, Attal et al. 2007),*
- hallucinations auditives de la schizophrénie *(Freitas, Fregni et al. 2009)*
- dépression *(Rachid and Bertschy 2006; Haffen and Galinowski 2007).*

rTMS et dépression PA

- Des données anciennes et contradictoires chez la PA : rôle de l'atrophie corticale

Table 1 Previous findings of rTMS effect on depression in elderly populations

Authors	N	Age range	Number of sessions	% MT	Hz	Response/outcome
Figiel 1998	50	22–89 (mean 60)	5	110	10	23% responded to Tx. Well-tolerated
Manes 2001	20	60.7 ± 9.8	5	80	20	No significant change in HDRS scores with Tx
Mosimann 2004	24	62 ± 12	10	100	20	No addn'l antidepressant effects vs sham
Fabre 2004	11	67.9 ± 6.7	10	100	10	5 patients had clinically meaningful improvement in HDRS scores
Pradberg et al 1999	18	51.2 ± 16	5	90	0.3 or 10	19% decline in HDRS score for slow rTMS and 6% decline for fast rTMS
Nahas et al 2004	18	61.2 ± 7.3	15	114 (103–141)	5	35% decline over 3 weeks in HDRS score
Grunhaus et al 2000	20	58.4 ± 15.7	20	90	10	27% decline over 4 weeks in HDRS score

Table 2 Studies on rTMS efficacy comprising elderly samples

Authors	Study type	Mean age (SD) Age range	TMS parameters[b]	Percentage improvement on HDRS scores (SD)	Response/remission (%)	Findings
Hizli Sayar et al. [90•] (n=65)	Open-label	66.6 (5.8) 60–83	L, 18 treatments, 25 Hz, 100 %, 1000 stimuli	48.6	58.5/29.2	58.5 % response rate.
Milev et al. [94]						
Overall (n=49)						
(n=31)	Case series from two sites, raters not blinded	69 (7) 58–89	L, 10 sessions, 10 Hz, 80–110 %[c]	26.1	22.6/9.7	Modest reduction in HDRS scores. Similar improvements were found for both low and high frequency rTMS.
(n=14)			R, 10 sessions, 1 Hz, 80–110 %[c]	26.7	14.3/0	
(n=4)			"Combination" (L, 10 Hz or R 1 Hz), 80–110 %[c]	6.5	0/0	
Jorge et al. [91]						
Overall (n=92)						Increasing the number of treatments resulted in more patients with vascular depression responding. Older participants (≥65 years) benefited more from additional sessions than younger participants (<65 years).
(n=30)	Double-blind RCT across two sequential cohorts	62.9 (7.2)[a]	L, 10 sessions, 10 Hz, 110 %, 1200 stimuli	33.1	33.3/13.3	
(n=62)		64.3 (9.4)[a] ≥50	L, 15 sessions, 10 Hz, 110 %, 1800 stimuli	42.4	39.4/27.3	
Abraham et al. [93] (n=20)	Open label	66.8 (.5) 60–80	L, 10 sessions, 10 Hz, 100 %, 1600 stimuli	31.6	30/10	Statistically significant reduction in depression scores across all patients.
Fabre et al. [95] (n=11)	Open label	67.9 (6.7) 56–77	L, 10 sessions, 10 Hz, 100 %, 1600 stimuli	20.6	45.5/NR	Five patients with vascular depression showed clinically significant but not statistically significant antidepressant response.
Jorge et al. [92] (n=20)	Double-blind RCT	63.1 (8.1)[a] NR	L, 10 sessions, 10 Hz, 110 %, 1000 stimuli	38	30/10	Active treatment was more effective than sham in treating post-stroke depression. This was not influenced by age.
Manes et al. [106] (n=20)	Double-blind RCT	60.7 (9.8) ≥50	L, 5 sessions, 20 Hz, 80 %, 800 stimuli	39.7	30/20	Difference between active and sham group not statistically significant. No significant differences between responders and non-responders in age.

RCT randomised-controlled trial, *DLPFC* dorsolateral prefrontal cortex, *SD* standard deviation

[a] Mean age for active rTMS group, as overall mean average not reported

[b] Percentage (%) refers to stimulus intensity (relative to resting motor cortical threshold) and hertz (Hz) refers to frequency. *R* right, *L* left. The total number of stimuli per session is given

[c] Number of stimuli not stated

rTMS/ECT

Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls

Priyadharshini Sabesan, Sudheer Lankappa, Najat Khalifa, Vasudevan Krishnan, Rahul Gandhi, Lena Palaniyappan

Sabesan P *et al*. TMS in geriatric depression 2015

Table 4 Summary of meta-analyses comparing transcranial magnetic stimulation and electroconvulsive therapy in depression

Meta-analysis	No. of studies/sample size	Mean age range	Summary of effect
Berlim *et al*[47] 2013	7/294	31.0-63.6	NNT = 6 favouring ECT for short-term response; at baseline, ECT samples had shorter illness duration and higher HAMD scores than rTMS samples. Age has no moderating effect on the differences
Ren *et al*[46] 2014	9/425	31.0-63.6	NNT = 7 for response; 6 for remission favouring ECT; No significant group difference when continuous change in HAMD scores is considered as outcome; In the absence of psychosis, rTMS as efficacious as ECT; Cognitive domains are better preserved after rTMS than ECT
Micallef-Trigona[49] 2014	9/384	34.0-63.6	Hedges'g = 1.28 for rTMS and 2.15 for ECT. rTMS produces a mean reduction of 9.3 points; ECT produces a mean reduction of 15.42 points on the HDRS
Xie *et al*[48] 2013	9/395	31.0-63.6	OR = 0.55 for response and 0.49 for remission in favour of ECT; rTMS is better tolerated than ECT (OR = 0.70); rTMS > 1200 stimuli/d is as efficacious as ECT

NNT: Number needed to treat; TMS: Transcranial magnetic stimulation; ECT: Electroconvulsive therapy; HAMD: Hamilton Depression Rating Scale.

rTMS et cognition PA

- Le traitement par la rTMS de patients souffrants de dépression *(Rachid et al., 2006 ; Haffen et al., 2007)* ou atteints de la maladie de Parkinson *(Epstein et al., 2007)* montre une capacité de cette technique à améliorer certaines fonctions cognitives.

- **r-TMS et cognition**
  - ↑ mémoire de travail, fonctions exécutives (flexibilité, planification +++), vitesse traitement information *(Guse et al., 2010)*

- **r-TMS et MA: lors d'une tâche cognitive**
  - ↑ dénomination actions et objets *(Cotelli et al., 2006, 2008)*
    (1 stimulation unique à haute fréquence CPFDL droit ou gauche)

  - **1 séance / jour / 5 jours / semaine / 2 semaines / CPFDL D ou G**:
    ✓ préservation de l'amélioration des performances de compréhension orale jusqu'à 2 mois après la stimulation *(Cotelli et al., 2010)*

	Site de stimulation	Impact cognition	auteur
Mémoire de travail (verbale et visuo-spatiale)	DLPFG ou D (1 Hz) : pas d'effet sur la mémoire de travail	Pas d'effet délétère	Koren et al., 2001, N= 50
	Aires frontales et temporales inférieures et pariétales (8 Hz)	Implication +++ de HD>HG (dans la mémoire visuelle)	Hong et al., 2000, N= 8
	Cortex Pariéto-temporal (50 Hz)	pas d'effet sur la mémoire verbale immédiate et visuospatiale	Hufnagel et al., 1993, N= 11
	Gyrus frontal moyen bilatéral (4Hz) :	amélioration des performances en mémoire de travail verbale	Mottaghy FM. Et al., 2003 N= 14
Mémoire spatiale	Cortex Pariétal Postérieur Droit (25 Hz, 115%)	diminution du temps de réaction	Kessels RP et al., 2000
Mémoire à long terme	DLPFG et D, cortex moteur	meilleures performances au rappel différé de mots lorsque le cortex moteur est stimulé seul	Pascual Leone et al., 1994
	Cortex moteur bilatéral (1, 5, 10, 20, 25 Hz)	amélioration de la mémoire verbale et du temps de réaction	Pascual- Leone et al., 1996
	Temporal et DF gauche (20 Hz, 120%)	capacités de rappel des mots altérées	Grafman et al., 1994
	cortex moteur, régions pariétales D et G (15 Hz, 20% SM)	diminution des scores dans les tâches de rappel	Flitman et al, 1998

MALADIE D'ALZHEIMER: EFFETS DE LA r-TMS (2)

A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer disease

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Table Cognitive performances for the patient at baseline (time 0), 1 month (time 1), and 5 months (time 2) after the rTMS treatment

				Change scores	
	Time 0	Time 1	Time 2	Difference T1-T0[a]	% of improvement from baseline[b]
Neuropsychologic tests					
Mini-Mental State Examination (range 0-30)	20	22	19	2	10
Memory Impairment Screen (range 0-8)	3	7	4	4	133
Free and Cued Recall Test					
Immediate recall (range 0-16)	10	12	9	2	20
Free recall (range 0-48)	5	13	6	8	160
Total recall (range 0-48)	32	43	37	11	34
Recognition (range 0-16)	14	16	15	2	14
Isaacs Set Test	15	17	21	2	13
Trail-Making Test					
Part A (range 0-150)	220	135	316	−85	39
Part B (range 0-300)	Failed	Failed	Failed	–	–
Picture naming (range 0-30)	29	29	26	0	0
Copy (range 0-6)	4	1	1	−3	−75

[a] Changes in cognition were calculated by subtracting scores at time 1 from scores at time 0 for each test (eg, time 1 Free recall-time 0 Free recall).
[b] Percentages of improvement from baseline (time 0) were calculating by dividing the difference score (T1-T0) by the score at time 0 (eg, [T1 − T0]/T0 × 100). A positive percentage score means that performance increased at time 1 and a negative percentage score indicates that performance decreased.

SYNTHÈSE

ETUDES	RESULTATS	PUBLICATIONS
Case Report MA	Mémoire épisodique Vitesse de traitement Activités de la vie quotidienne	Haffen et *al.*, 2012, Brain Stimulation
« Case Report » 3 APP	Fluences Fonctions exécutives Vitesse de traitement	Béreau et *al.*, article soumis
ALSTIMAG	Mémoire épisodique verbale Mémoire visuelle	Haffen et *al.*, article en cours de rédaction

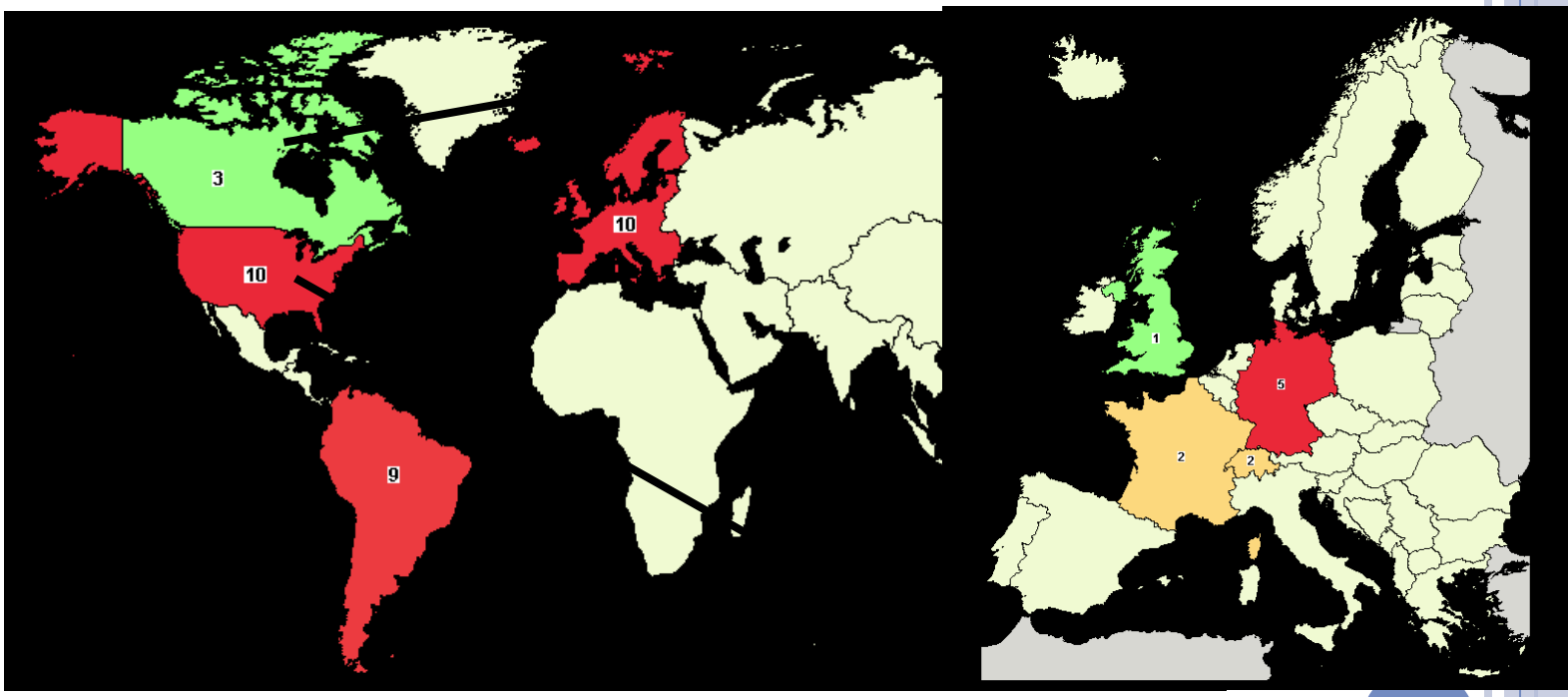
Les hypothèses

- potentialisation du CPFDL par la rTMS
  - pourrait faciliter les processus cognitifs notamment par le biais d'une activation cortico-sous corticale induite *(Grady, McIntosh et al. 2003).*
- ↗ dopamine / glutamate dans nucleus accumbens par rTMS *(Zangen 2002)*
- Récepteurs NMDA et induction des effets à long terme rTMS *(Hoogendam 2010)*
- Amélioration des symptômes dépressifs qui induisent un déclin cognitif plus important *(Levy-Cooperman, Burhan et al. 2008)* et sont associés à une hypoperfusion du cortex préfrontal

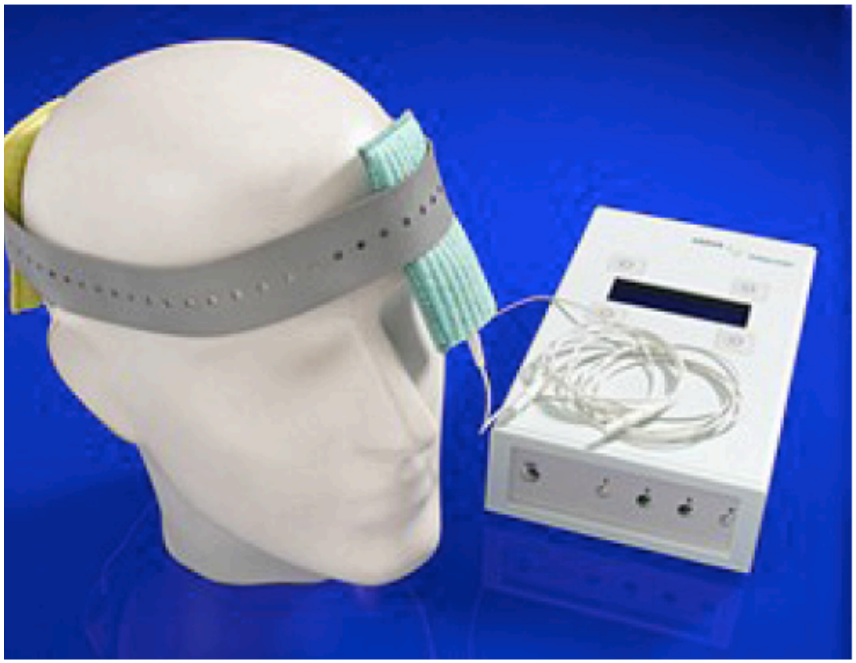
tDCS et PA

tDCS

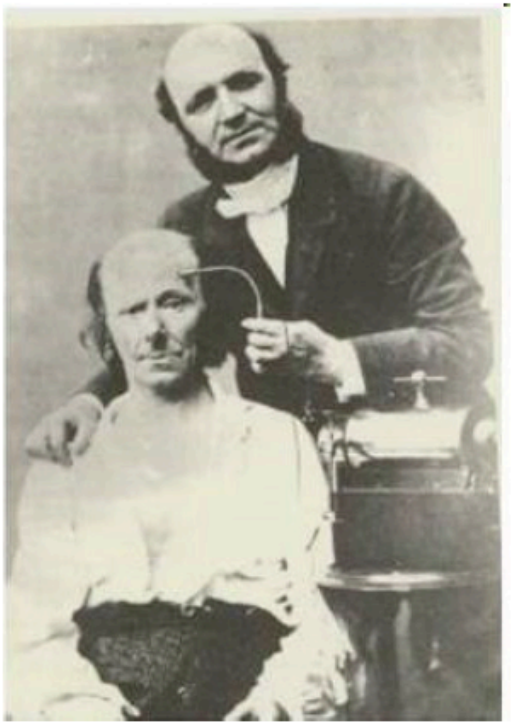
- Nouvel essor depuis une dizaine d'années
- Etudes cliniques tDCS/EDM : 44 études sur CT.gov



tDCS : principes



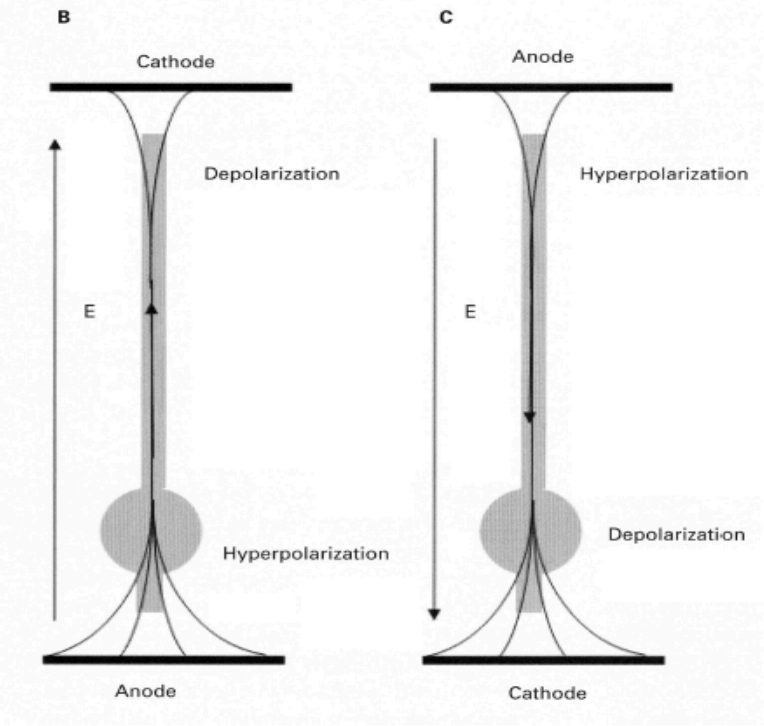
tDCS - 2010



1871, galvanisation
Beard and Rockwell

tDCS : PRINCIPES

Modulation du potentiel membranaire de repos



Bindman et al, 1964

tDCS : les effets

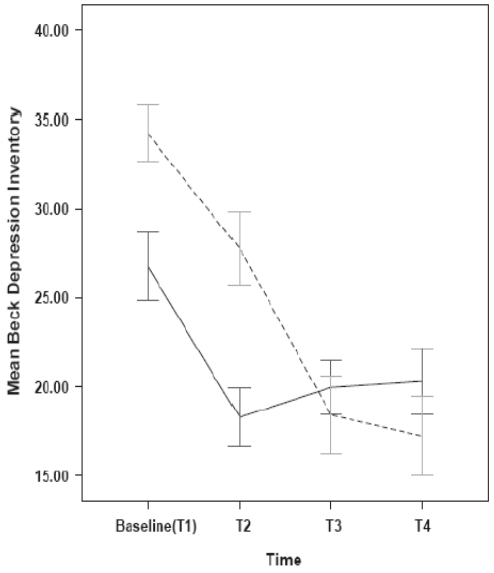


Fig. 1. The mean Beck Depression Inventory (BDI) scores in patients with bipolar depression and unipolar depression at 4 evaluation times: Baseline (T1), after the fifth transcranial direct current stimulation (tDCS) session (T2), one week later (T3) and one month later (T4). Error bars represent 95% confidence intervals. The continuous line represents the major depressive disorder (MDD) group; the dashed line represents the bipolar depressive disorder (BDD) group.

17 patients MDD
14 patients BDD

2 mA, 20 min
Anode : left DLPF cortex
Cathode : right DLPF cortex
Twice-daily, 5 days

Brunoni et al, 2010

- tDCS et EDM :
  - ✓Fregni et al, 2006 :
    - Diminution score HDRS et amélioration mémoire de travail
  - ✓Loo, 2012 :
    - Diminution score HDRS (13% rémission) et amélioration mémoire de travail et attention

tDCS : LES EFFETS

Table 1
Summary of previous transcranial direct current stimulation clinical trials.

Study	Design	Subjects	Sample size	Target area*	Cathode	Current strength (mA)	Electrode size (cm2)	Duration/ session (min)	Number of sessions	Side-effects	Results
Fregni et al. (2006)	Randomized, double-blinded, sham-controlled	MDD	10	F3	Contra-lateral supra-orbital	1	35	20	5 alternate days	not reported	Reduction of depressive symptoms
Boggio et al. (2008)	Randomized, double-blinded, sham-controlled	MDD	40	F3	Contra-lateral supra-orbital	2	35	20	10 consecutive days	mild transient effects distributed equally in active and sham groups	Reduction of depressive symptoms
Rigonatti et al. (2008)	Open arm of Boggio et al. (2007)	MDD	42	F3	Contra-lateral supra-orbital	2	35	20	10 consecutive days	not reported	reduction of depressive symptoms – tDCS was faster than fluoxetine
Ferrucci et al. 2009	Open trial	Severe MDD – referred for ECT	14	F3	F4	2	35	20	5 twice a day		30% of mood improvement that persisted after 4 weeks after ttm ended
Loo et al. (2009)	Randomized, double-blinded, sham-controlled	MDD	40	F3	Contra-lateral supra-orbital	1	35	20	a) 5 alternate days b) 10 active sessions		No effect in the 5-session phase Improvement on depression after 10 active sessions

The table shows the study design, the sample characteristics (MDD = major depressive disorder; ECT = electroconvulsive therapy); sample size; position of the anode (target area, F3 is over the left dorsolateral prefrontal cortex according to the International EEG 10/20 System); position of the cathode (either right supra-orbital area or F4 that is over the right dorsolateral prefrontal cortex); parameters of current delivery (current strength, electrode size, duration of session and number of stimulation days); and the reported side effects and results.

tDCS : les effets

Bystad *et al. Alzheimer's Research & Therapy* (2016) 8:13
DOI 10.1186/s13195-016-0180-3

Alzheimer's Research & Therapy

RESEARCH Open Access

Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial

Martin Bystad[1,3*], Ole Grønli[3], Ingrid Daae Rasmussen[1,3], Nina Gundersen[1], Lene Nordvang[1], Henrik Wang-Iversen[1] and Per M. Aslaksen[1,2]

- t-DCS et maladie d'Alzheimer:
  - ✓ Ferrucci et al, Neurology 2008:
    - Amélioration des performances lors d'une tâche de reconnaissance de mots
  - ✓ Boggio et al, JNNP 2009:
    - Amélioration des performances lors d'une tâche de reconnaissance visuelle
  - ✓ Bystad et al, Alz Research and therapy 2016
    - ✓ 25 patients
    - ✓ Mémoire verbale
    - ✓ Pas de différence entre groupes

Table 3 Frequency table

	Active tDCS ($n = 12$)	Placebo tDCS ($n = 13$)
CVLT-II immediate recall	9	6
CVLT-II delayed recall	4	1
CVLT-II recognition	7	4

CVLT-II California Verbal Learning Test–Second Edition, *tDCS* transcranial direct current stimulation
The data represent the number of patients showing improvement on primary outcome measures. Improvement was displayed as positive changes from baseline to posttest

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DOI 10.1007/s11920-015-0592-y

Neuromodulation Therapies for Geriatric Depression

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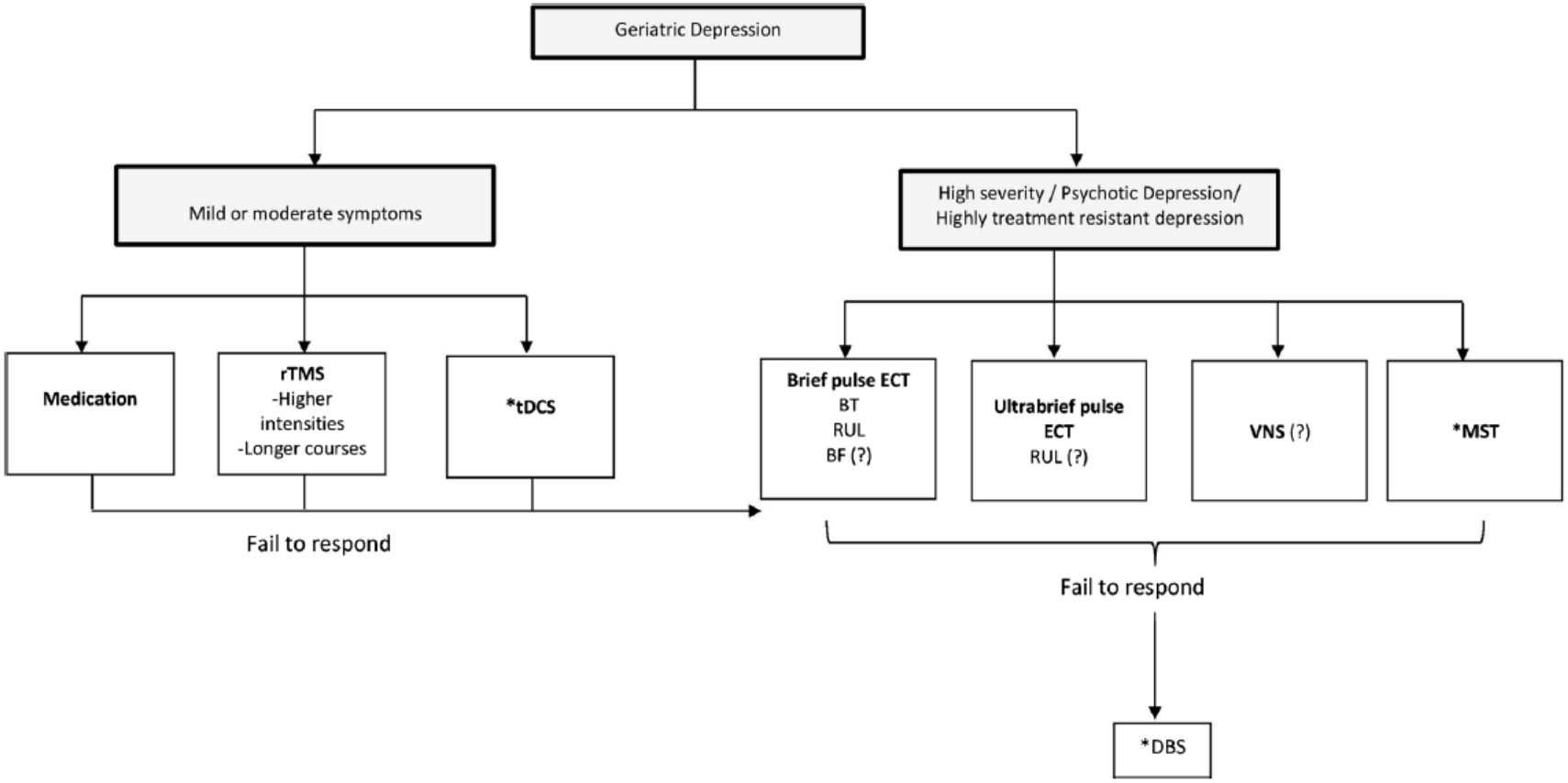

Fig. 1 Proposed algorithm for the treatment of geriatric depression with neuromodulation techniques. Treatment currently considered experimental for depression (*). Limited evidence specific to geriatric depression (?). *rTMS* repetitive transcranial magnetic stimulation, *tDCS* transcranial direct current stimulation, *ECT* electroconvulsive therapy, *BT* bitemporal, *RUL* right-unilateral, *BF* bifrontal, *VNS* vagus nerve stimulation, *MST* magnetic seizure therapy, *DBS* deep brain stimulation

Conclusion

- Manque d'études chez les PA
- Aucune étude sur l'effet de ces techniques à moyen et long terme sur les performances cognitives chez des patients atteints de MA au stade léger
- Recherche de facteurs prédictifs de réponse : âge, atrophie corticale, profil clinique, résistance…
- il est de plus en plus évident que ces paramètres doivent être adaptés aux patients traités, notamment en fonction de leur âge ou de leur degré d'atrophie corticale
- Études chez les PA