

The use of non invasive brain stimulation in the treatment of mood and cognitive disorders

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Psychiatric illness and Treatment Resistance

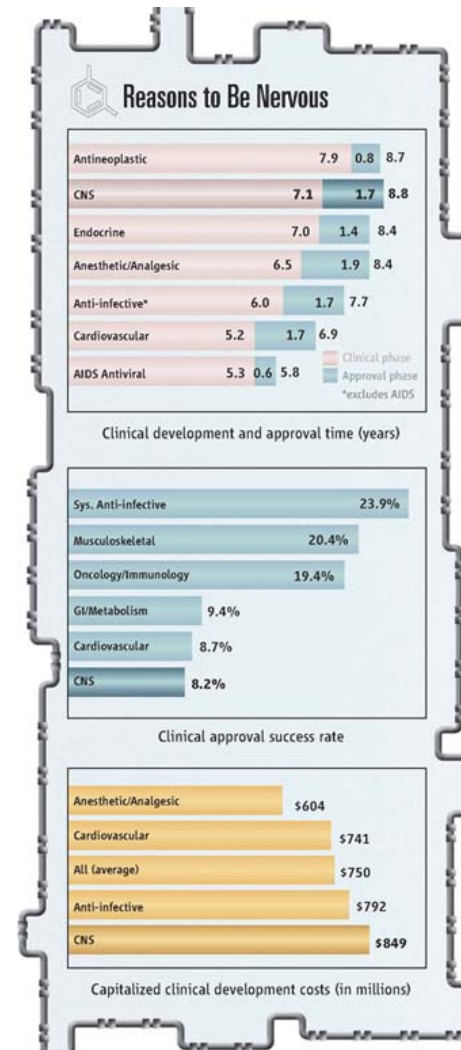
Depression is:

- Common (~7% of Australians every year)
- Highly disabling
- Costly to treat
- Frequently unable to be treated or respond poorly to treatment (30% TRD)

Neuropsychiatric Drug development:

"This is hardly a rich pipeline...It suggests a sad dearth of ideas and involves lots of attempts at patent extensions and new indications for old drugs."

(Steven Hyman, former NIMH director, Provost Harvard)





Editorial

Acute Continuation and Maintenance Treatment of Major Depressive Episodes With Transcranial Magnetic Stimulation

**Table 1**

Rate of acute remission, likelihood of completing 12-months without relapse, and probability of sustained benefit at each level of STAR*D [19].







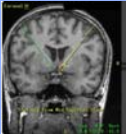

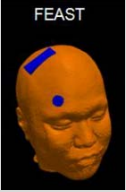

	Acute remission rate	Probability of remaining well for 12 months after acute remission	Probability of sustained benefit
Level 1	36.80%	69.90%	25.72%
Level 2	30.60%	44.70%	13.68%
Level 3	13.70%	35.40%	4.85%
Level 4	13.00%	28.90%	3.76%

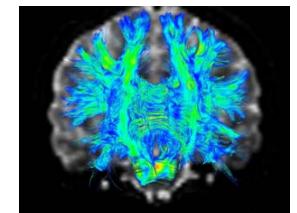
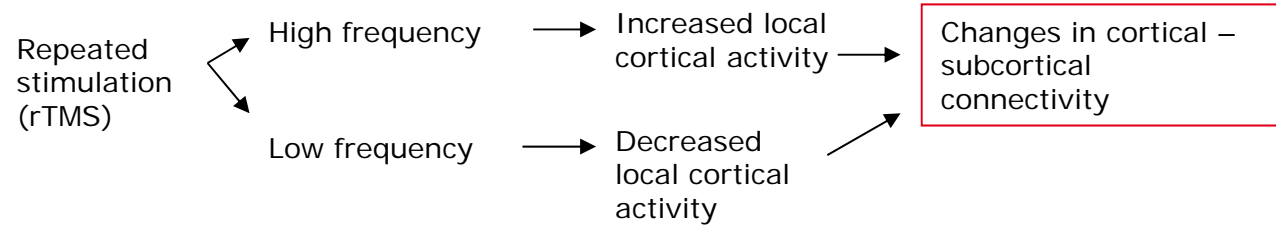
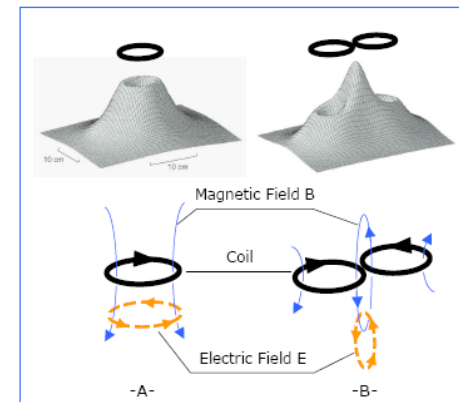
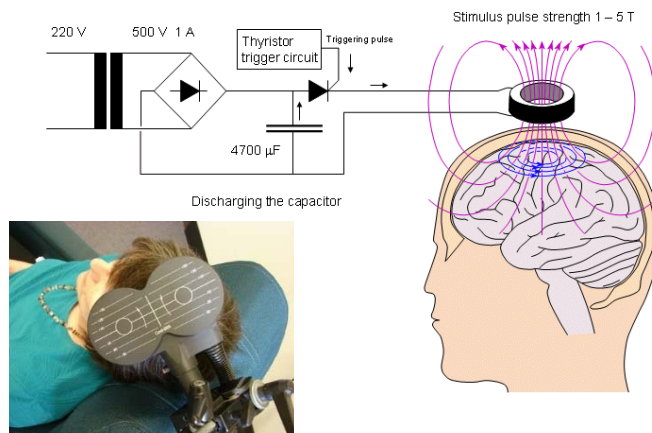
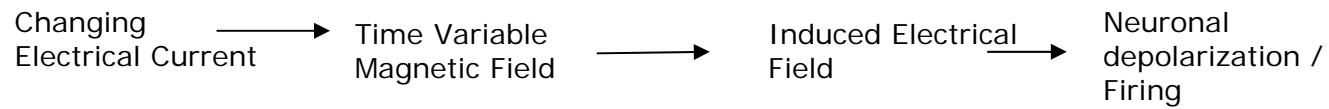


The answer...ask Magnus



Novel Brain Stimulation Treatments in Psychiatry

	Non Invasive	Convulsive	Surgical
Established	 <p>TMS - depression</p>  <p>Deep TMS - depression</p>  <p>tDCS - depression</p>	 <p>ECT</p>	<p>Vagal nerve stimulation - depression</p> 
Undergoing clinical trials	<p>TMS – other disorders: e.g. OCD, Alzheimer's disease</p> <p>tDCS – cognitive enhancement</p> <p>Trigeminal nerve stimulation - PTSD</p> <p>Caloric nerve stimulation - mania</p> <p>EMF pulse stimulation – depression</p> <p>External vagal nerve stimulation – multiple applications</p>	 <p>MST - depression</p>	<p>DBS – neurological, OCD</p>  <p>DBS – Depression</p>
Early stage development	 <p>Ultrasound stimulation</p> <p>Optogenetics</p>	<p>FEAST</p>  <p>FEAST</p>	 <p>Epidural cortical stimulation</p>



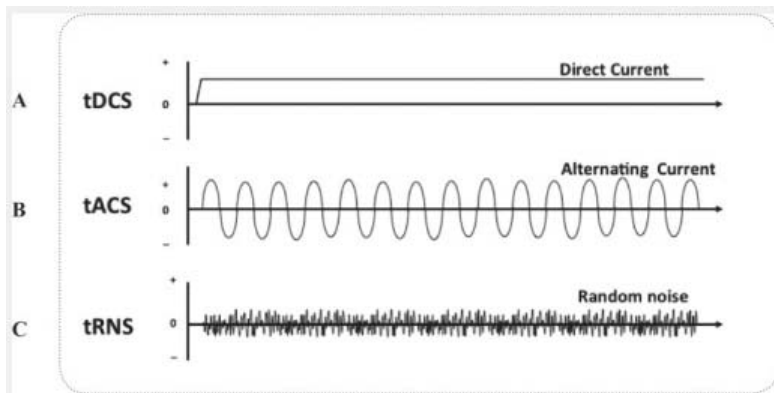
What does TMS for depression involve?

- Daily, Monday to Friday treatment
- 20-45 minutes a day, for a number of weeks
- Sitting in reclining chair
- Coil placed on head
- 'Tapping' sensation

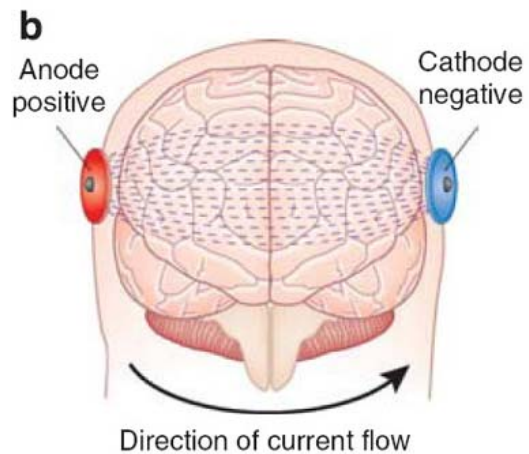


Non invasive electrical stimulation

- Existing technology:
 - tDCS – direct current stimulation
 - tACS – alternating current stimulation
 - tRNS – random noise stimulation



Transcranial Direct Current Stimulation

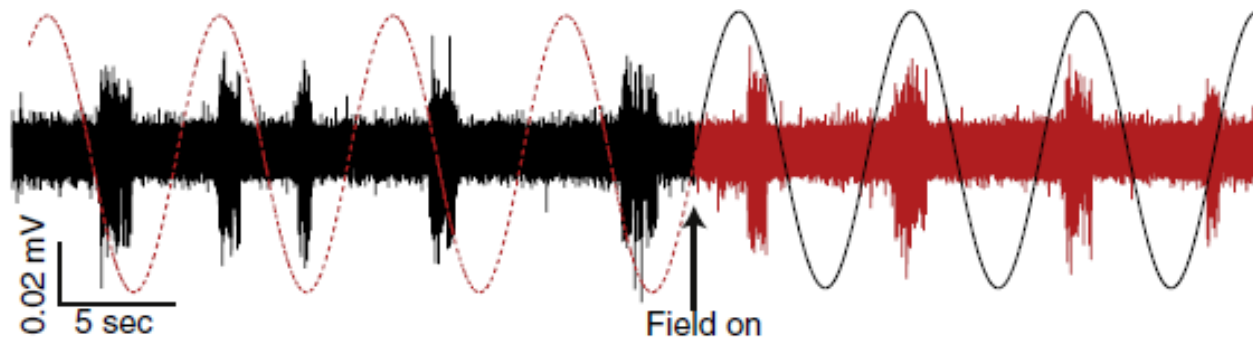
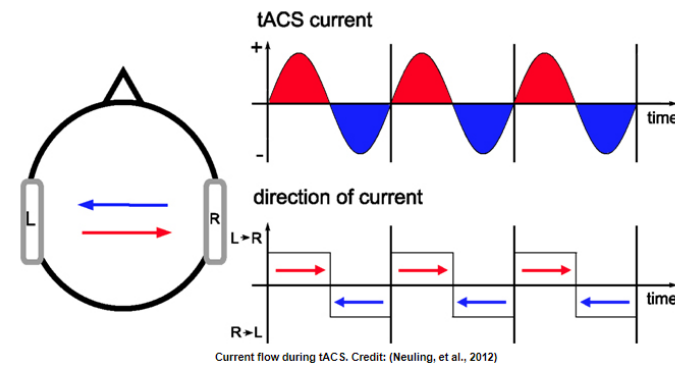


- tDCS involves the application of a weak electrical current (1-2mA) to the scalp via two surface electrodes,

- **Anode** = hyperpolarisation leading to increases in neuronal activity
- **Cathode** = depolarisation leading to decreases in neuronal activity



Transcranial Alternating Current Stimulation: entraining brain waves



Fröhlich & McCormick

NEST® (NeoSync-EEG Synchronized TMS)



Low Field magnetic Stimulation



Ultrasound



Trigeminal Nerve Stimulation

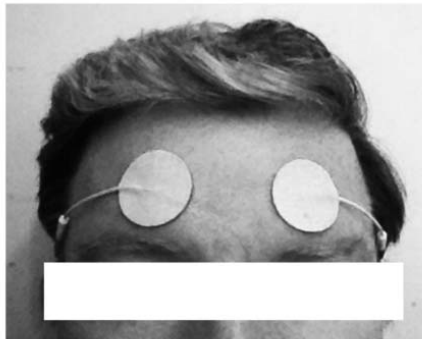


Fig. 1. Placement of electrodes over the V₁ branch of the trigeminal nerve. Self-adhering electrodes were specifically placed on the forehead as shown to achieve bilateral stimulation of the supraorbital and supratrochlear nerves of the V₁ division of the trigeminal nerve.

Vagal Nerve Stimulation



rTMS as a Therapeutic Tool in Depression

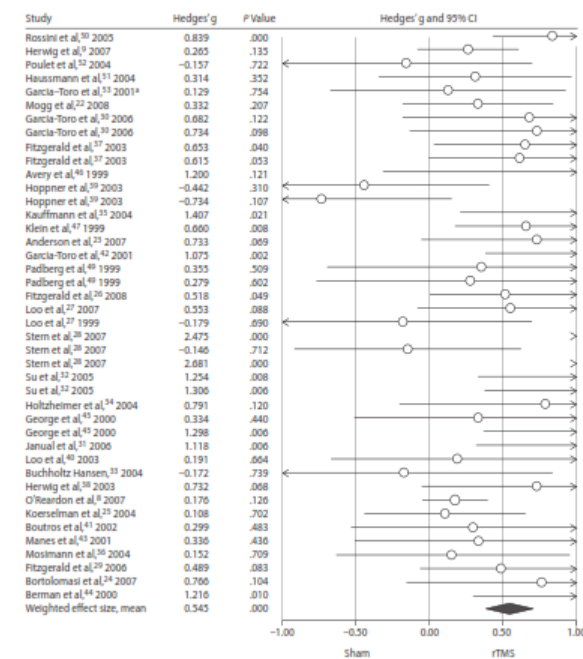
- Initial case reports in early 1990's: vertex then Left DLPFC stimulation
- First controlled studies mid 90's [Pascual-Leone, 1996] [George, 1997]
- Initial studies for 1 week, cross over designs
- Gradually longer duration and increased pulse number
- Predominant focus on Left DLPFC

Evidence for Efficacy of Left PFC rTMS in adults

- 30 + clinical trials
 - Numerous meta-analyses
 - Greater effects in more recent studies
 - Longer duration of treatment
 - Increased intensity
 - Increased pulse number
 - Most recent
 - 34 individual trials, 1383 patients and found
 - rTMS to be more effective than sham rTMS
 - Large effect size = 0.55.
- (Slotema et al 2010)

- Moderate effect sizes
- Increase in efficacy over time

Figure 1. rTMS for Depression, Results of the Meta-Analysis



Slotema et al 2010

rTMS in Depression: what are the overall outcomes?

A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION

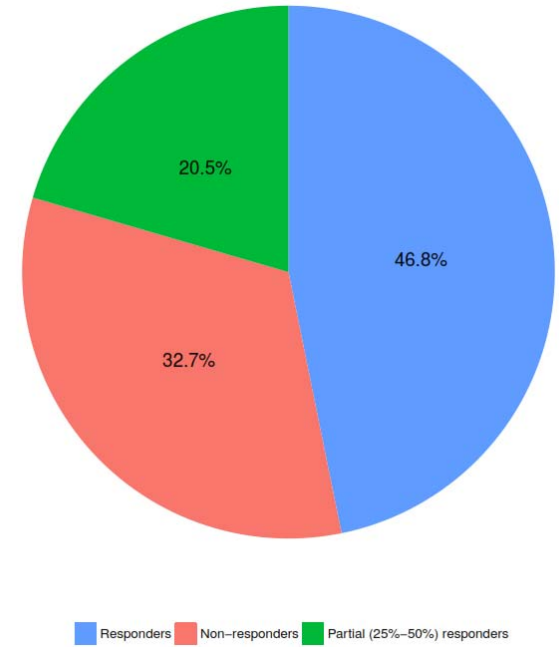
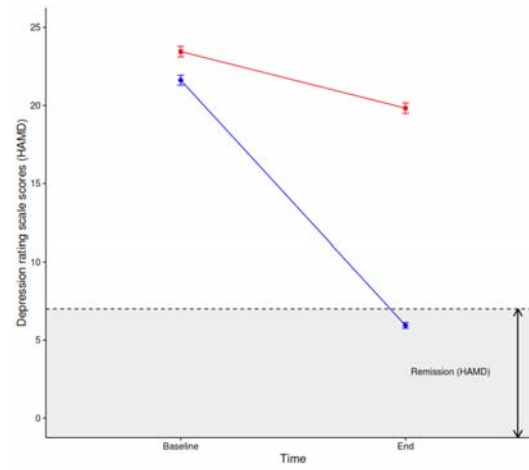
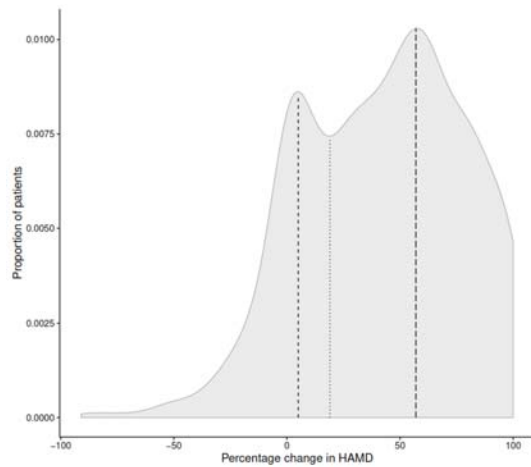
Paul B. Fitzgerald, M.B.B.S., M.P.M., Ph.D., FRANZCP,^{1*} Kate E. Hoy, B.B.N.Sc. (Hons.),
D.Psych. (Clin. Neuro.),¹ Rodney J. Anderson, B.Sc. (Hons.), G.Dip.Psych.,¹ and
Zafiris J. Daskalakis, M.D., Ph.D., FRCP (C)²

TABLE 1. Demographic and baseline clinical variables

		Responders		Non responders		t/ χ^2	Significance
		Mean	SD	Mean	SD		
Age		47.7	13.0	45.1	14.0	3.2	.001
Sex (M/F)		189/309		202/357		0.18	.67
Diagnosis (number of subjects)	MDD—single episode	121		208		21.9	.000
	MDD—relapse	287		277			
	BPAD	78		65			
Number of failed antidepressant trials		5.7	9.0	6.1	6.5	0.48	.49
Age of illness onset		28.7	13.8	26.1	14.0	2.4	.02
Number of episodes		5.5	5.9	5.0	6.1	1.0	.32
Illness duration (years)		9.7	13.7	15.3	15.2	−3.7	.000
Baseline HAMD/MADRS		21.6	7.2	23.7	8.5	−4.3	.000
Left-sided resting motor threshold		48.9	17.2	48.3	15.4	0.39	.71
Right-sided resting motor threshold		52.9	14.2	53.7	11.7	−0.5	.62
Concurrently taking antidepressant medication (yes/no)		421/70		437/121		9.7	.002
Concurrently taking mood stabilizer medication (yes/no)		176/289		154/351		5.8	.02
Concurrently taking antipsychotic medication (yes/no)		203/232		279/325		0.02	.88
Comorbid diagnoses (number of subjects)	Panic disorder	36		67		18.9	.002
	PTSD	22		67			
	GAD	86		98			
Type of TMS	Left-sided	121		188		13.1	.02
	Right-sided	232		256			
	Bilateral	132		132			

MDD, major depressive disorder; BPAD, bipolar affective disorder; OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

Pattern of Response

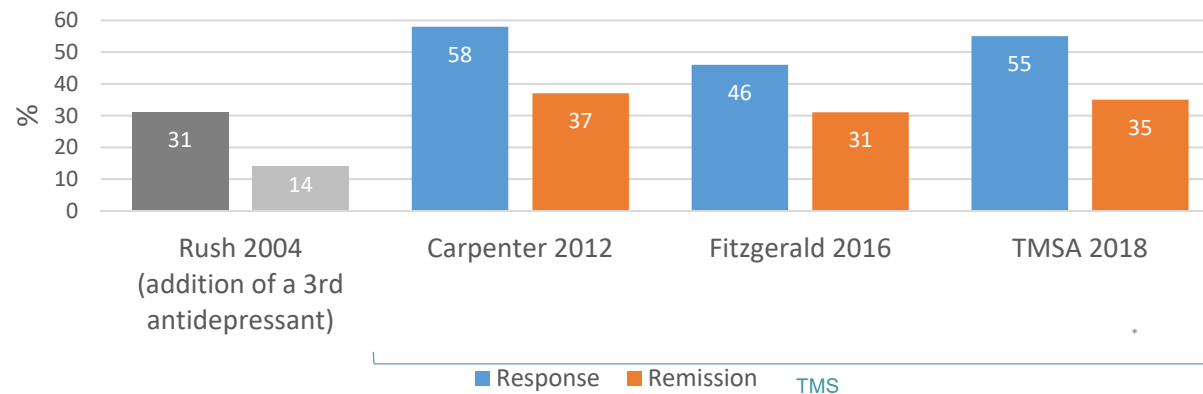


Data from 11 clinical trials (n = 1132)

TMS vs Medication

Treating with TMS early is more effective than adding a 3rd antidepressant

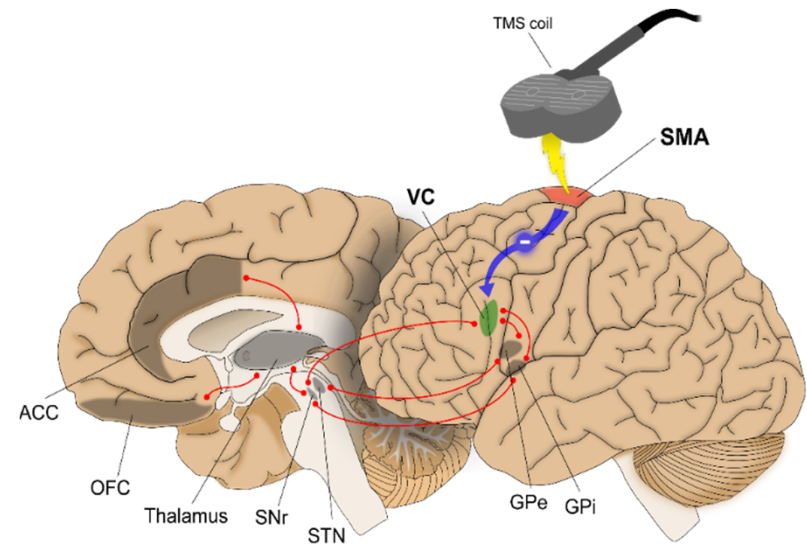
Efficacy of TMS or medication in MDD

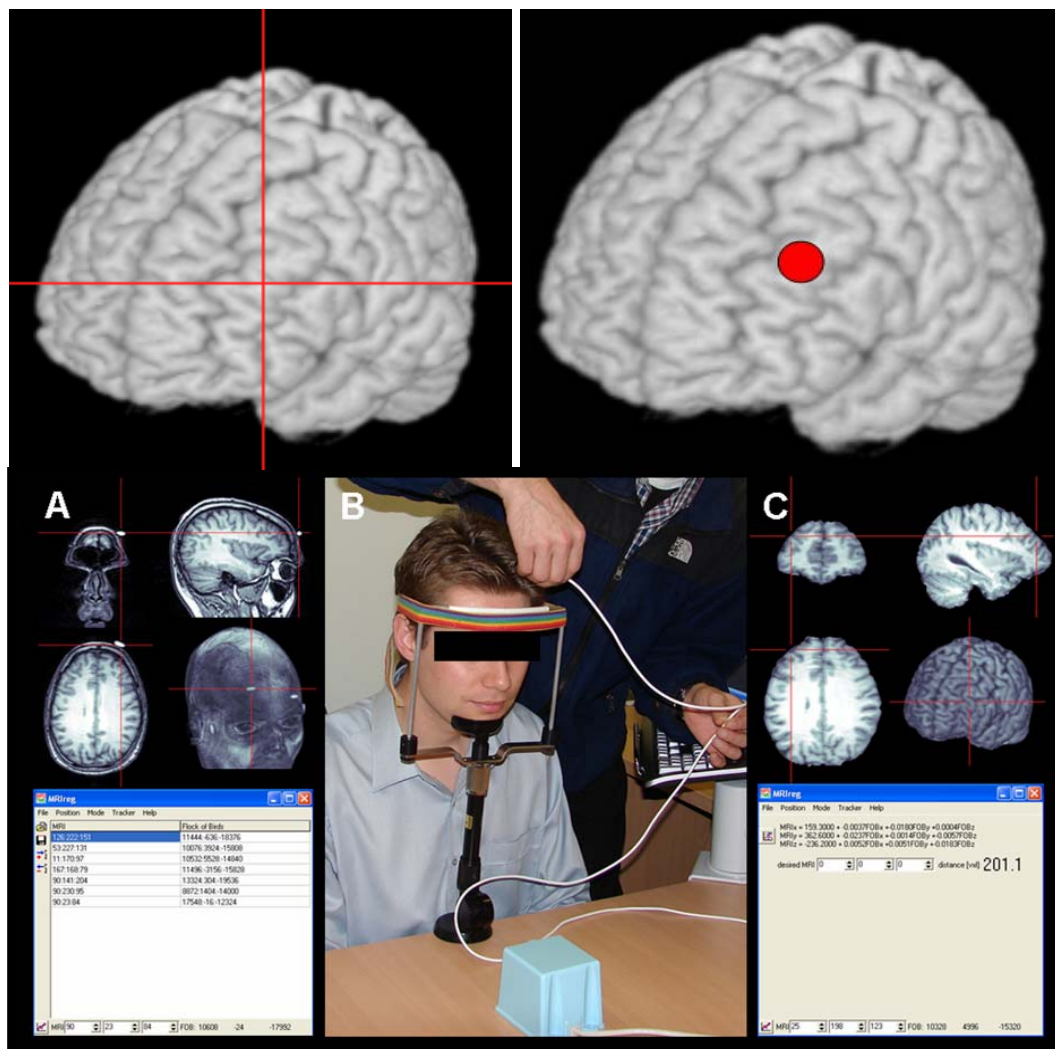


* TMS Australia Preliminary Internal Data (n=130)

Future Targets

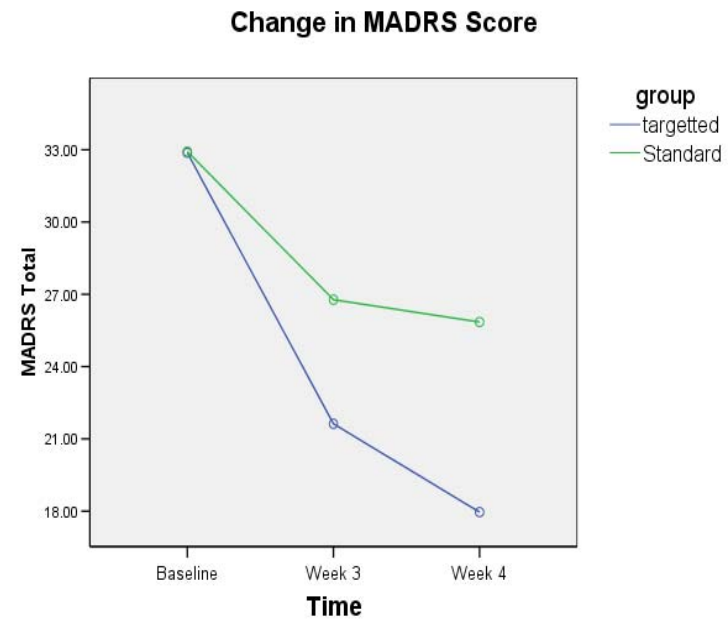
Efficacy
Utility
Application





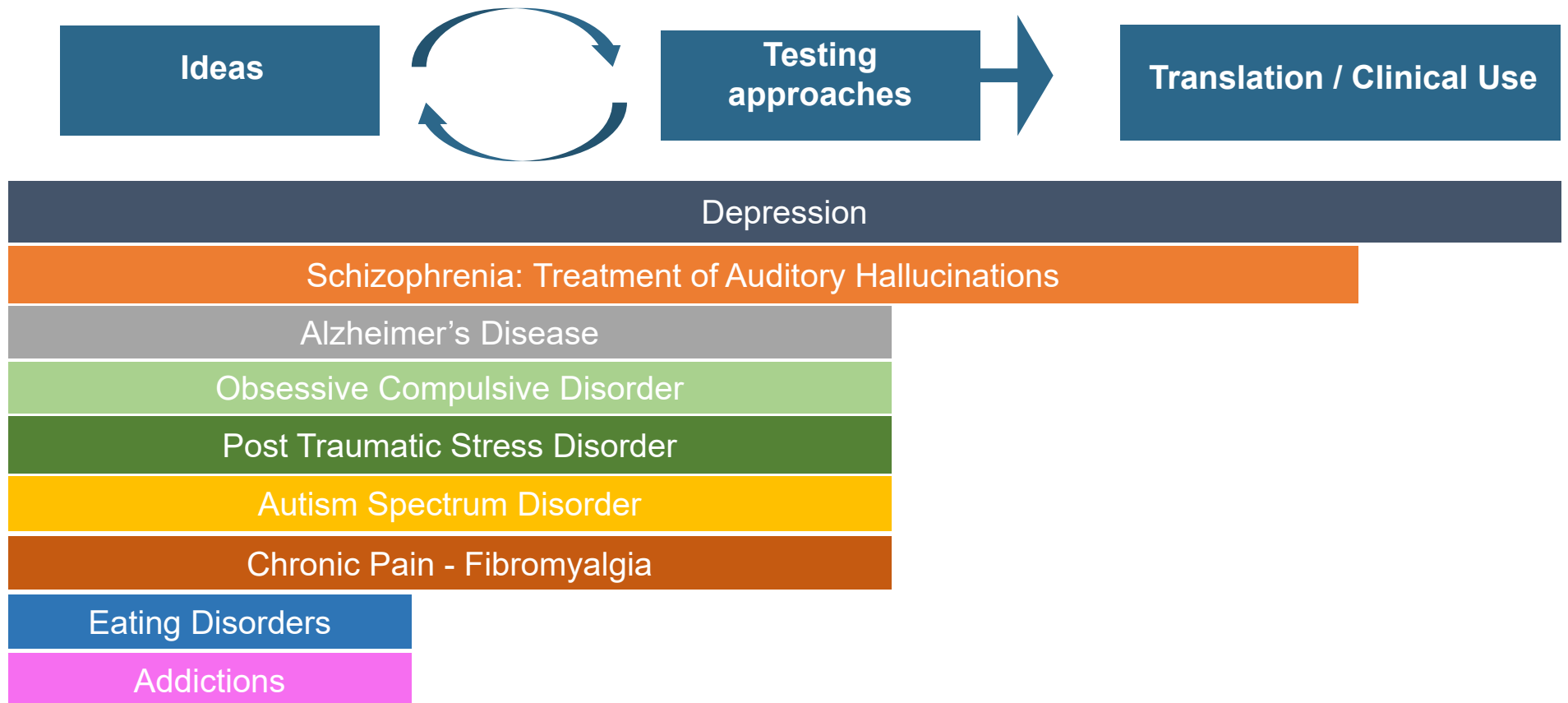
Does improved treatment targeting enhance response to rTMS?

- Randomised double blind
- 52 subjects
- Targeted or '5 cm method'
- Target = Middle FG / border BA 48 and 9
- $x,y,z=-45, 45,35$



Sign time vs group $p < 0.05$

Future Targets: Applications of TMS

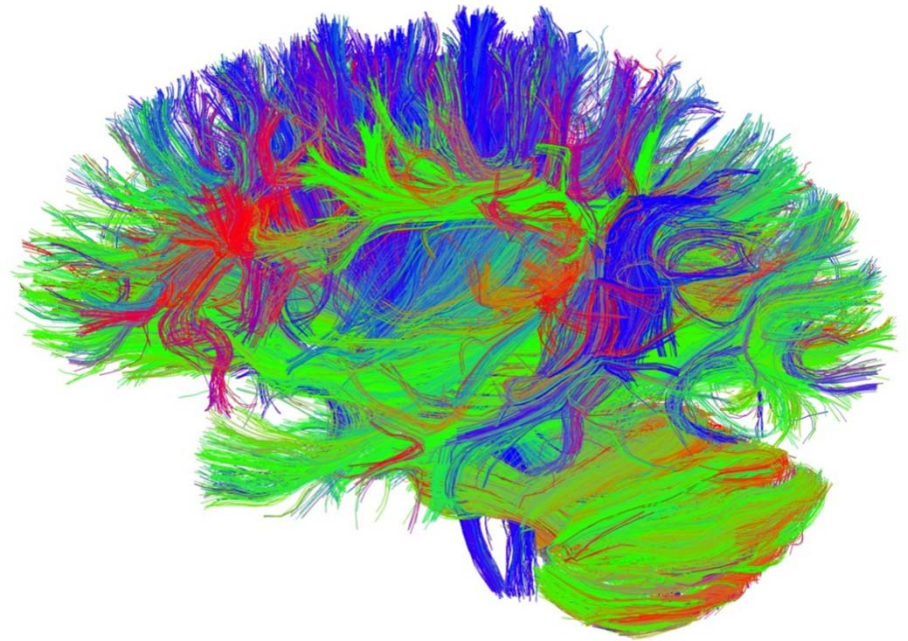


Brain Stimulation and Cognitive Disorders

Cognitive functions are represented by dynamic activity occurring throughout neural networks, both locally and globally.

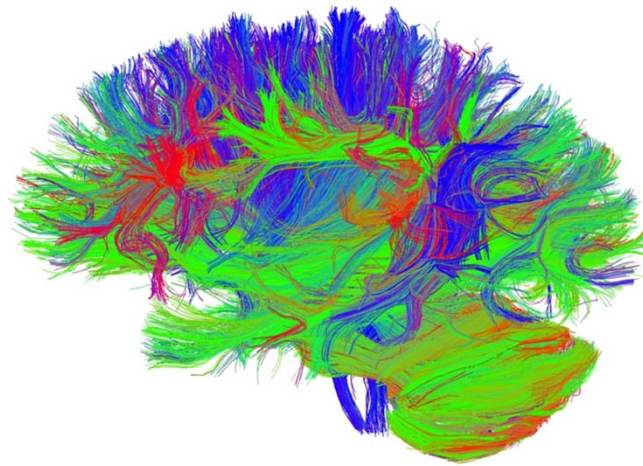
Activity of interconnected networks of synapses throughout the brain is crucial

There are number of 'index' ways in which these fundamental processes can be disturbed...



rTMS in Dementia

- Multi-focal versus critical node
- Frequency specific activation of task related oscillations
- Interaction of stimulation with cognitive activation



Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: clinical experience

Jose Martin Rabey^{1,2} · Evgenia Dobronevsky^{1,2}

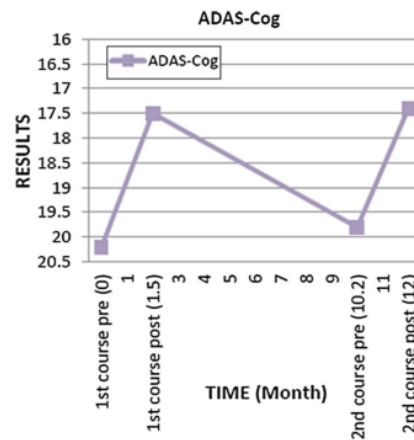


Fig. 1 ADAS-Cog results for the first and second treatment course (5 patients)

Table 4 ADAS-Cog percentile improvement (%) per ADAS-Cog improvement points

ADAS-Cog improvement (points)	Patients' improvement percentile (%)
−5	21.4
−4	25.0
−3	42.9
−2	60.7
−1	71.4
0	78.6



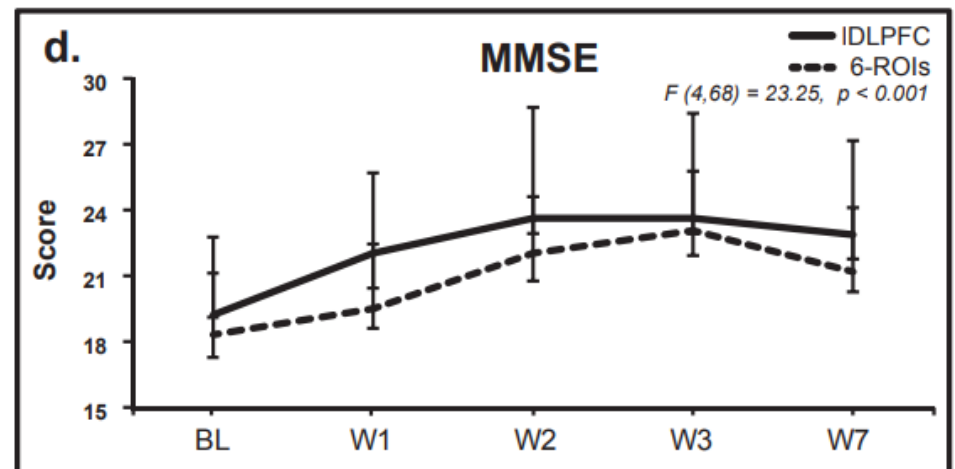
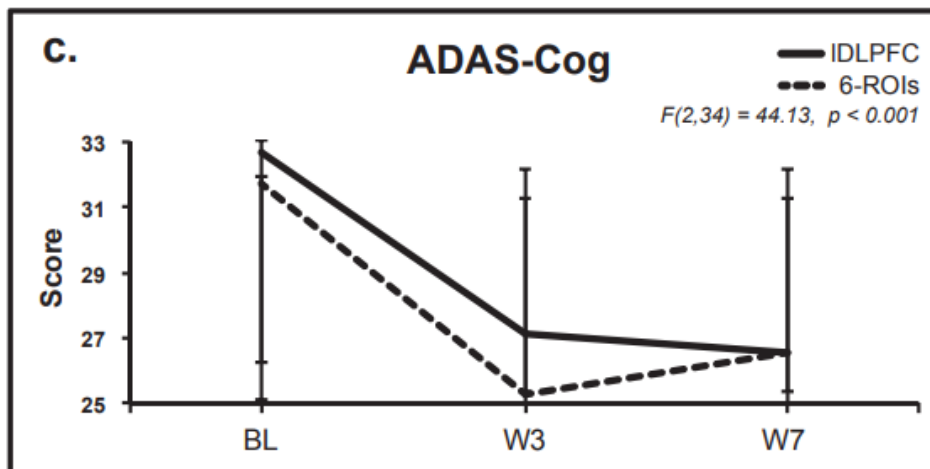
Contents lists available at ScienceDirect

Brain Stimulation

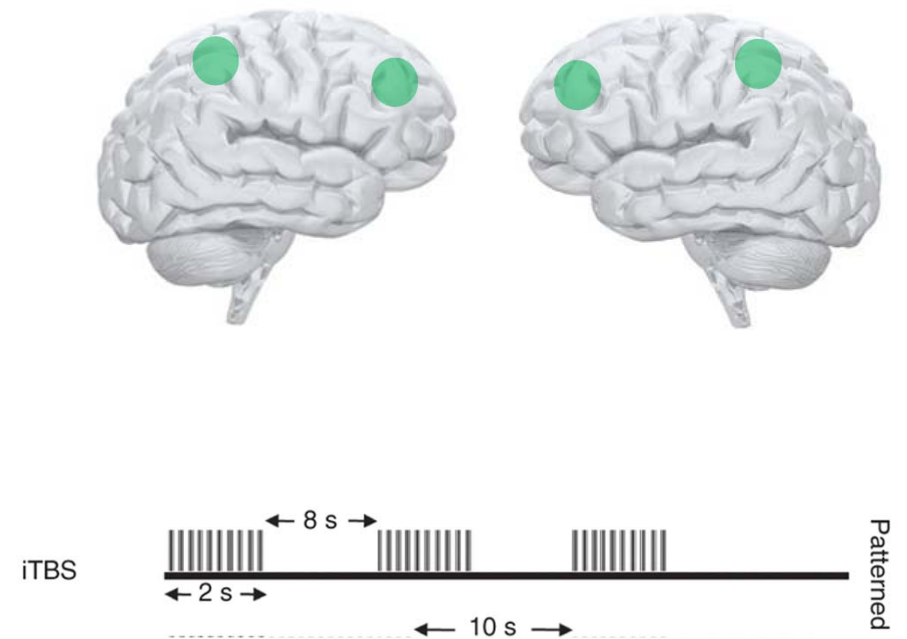
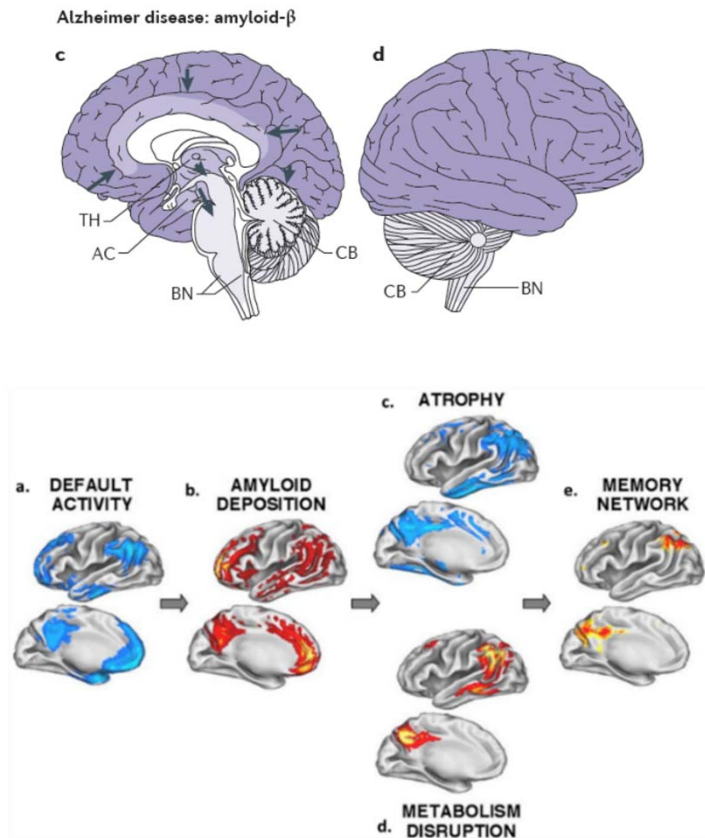
journal homepage: <http://www.journals.elsevier.com/brain-stimulation>



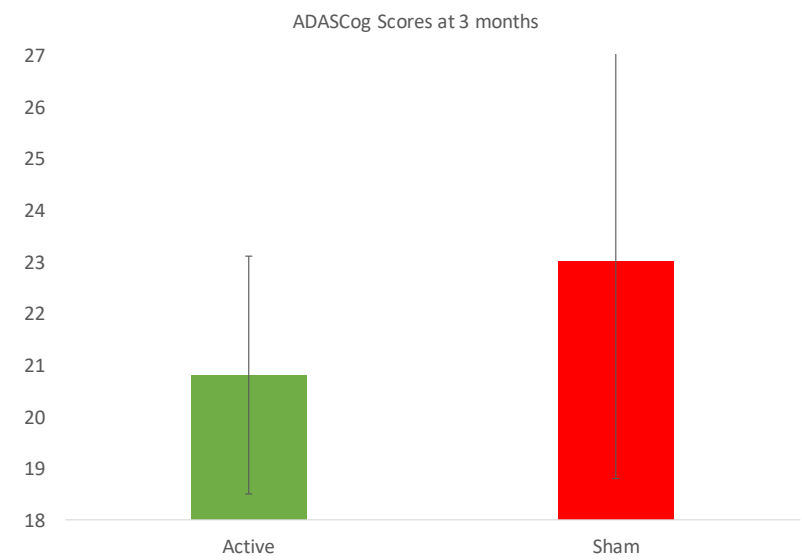
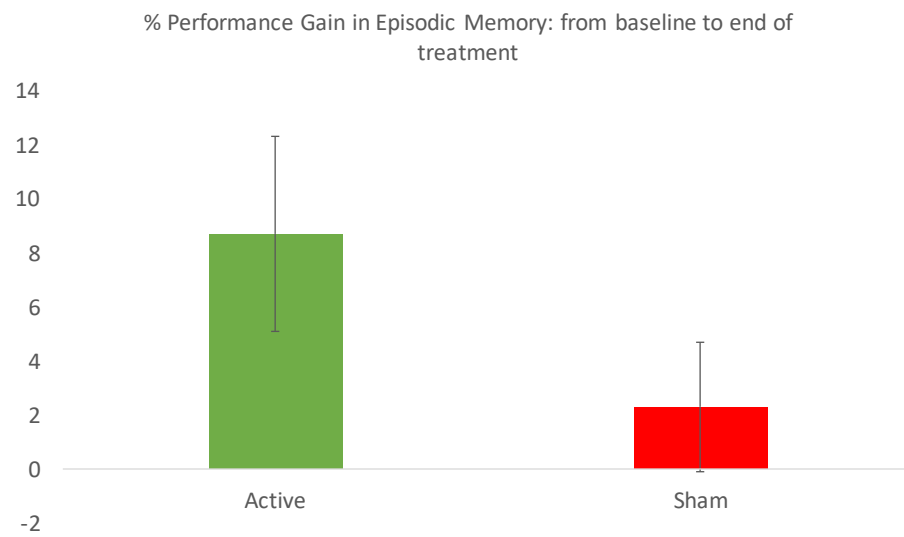
Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer's disease



RCT of Theta Burst Stimulation for Mild to Moderate Alzheimer's



Alzheimer's RCT: Preliminary data

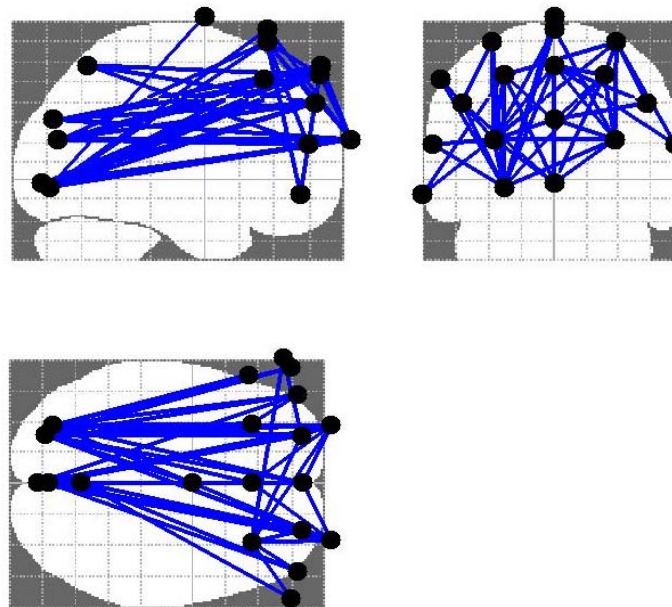


Alzheimer's RCT: Preliminary data

Resting EEG data from 13 patients in active and 13 in sham.

Active iTBS significantly reduced theta connectivity at rest, from bilateral frontal regions to left and central occipital regions ($p = 0.025$). No change in sham group

Image of the endpoint network differences, right



Conclusions

- rTMS is an established, safe and effective treatment for depression
- rTMS shows evidence of preliminary efficacy in cognitive disorders
- rTMS presages the use of potentially a wide range of non invasive brain stimulation techniques



Thanks

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