Repetitive transcranial magnetic stimulation (rTMS) for depression

Will Stageman

Northumberland Tyne and Wear NHS Foundation Trust

RADS Regional Affective Disorder Service

NCMD Northern Centre for Mood Disorders

Newcastle University Institute of Neuroscience

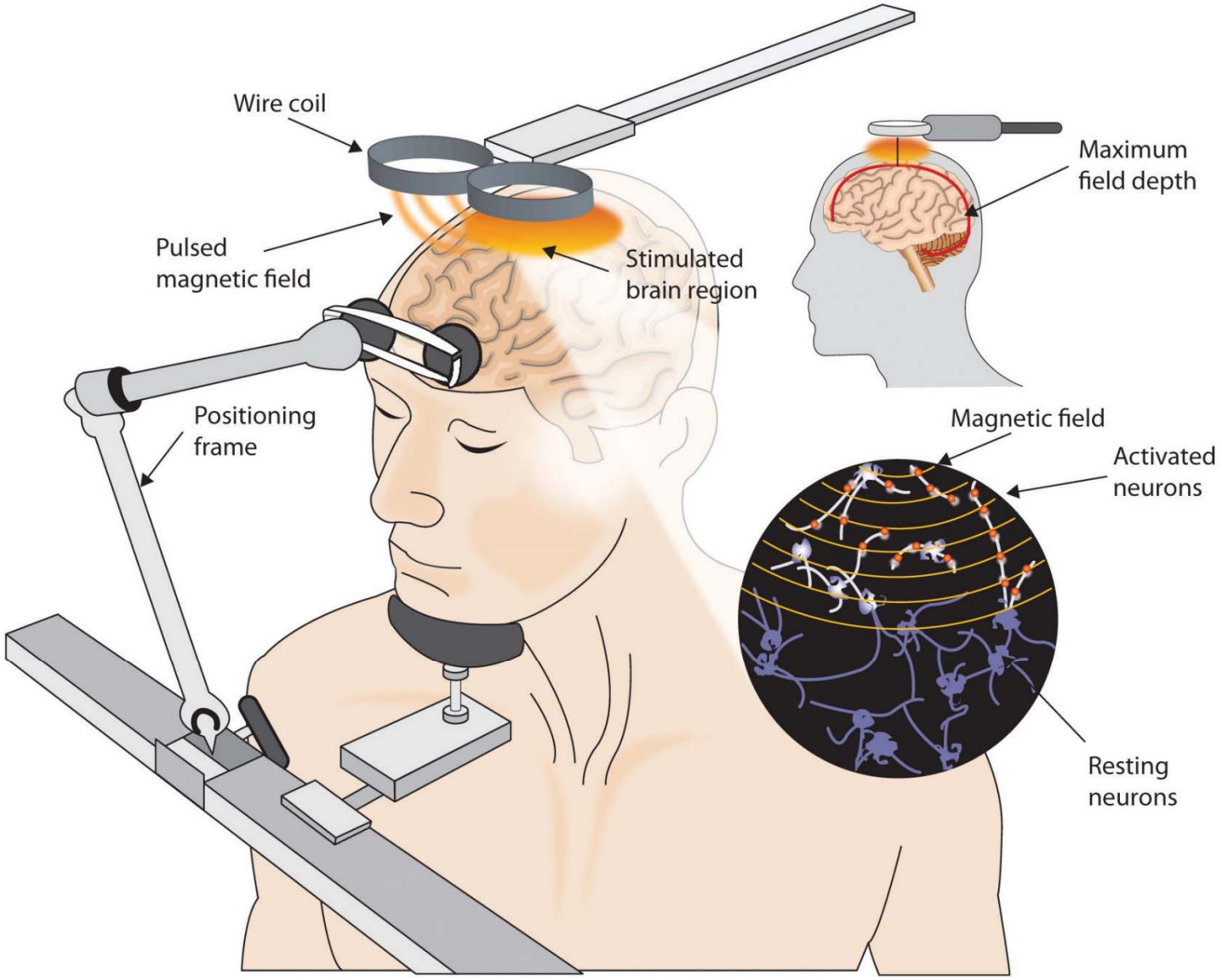
Restoring Hope

Hope through Research and Education

Outline

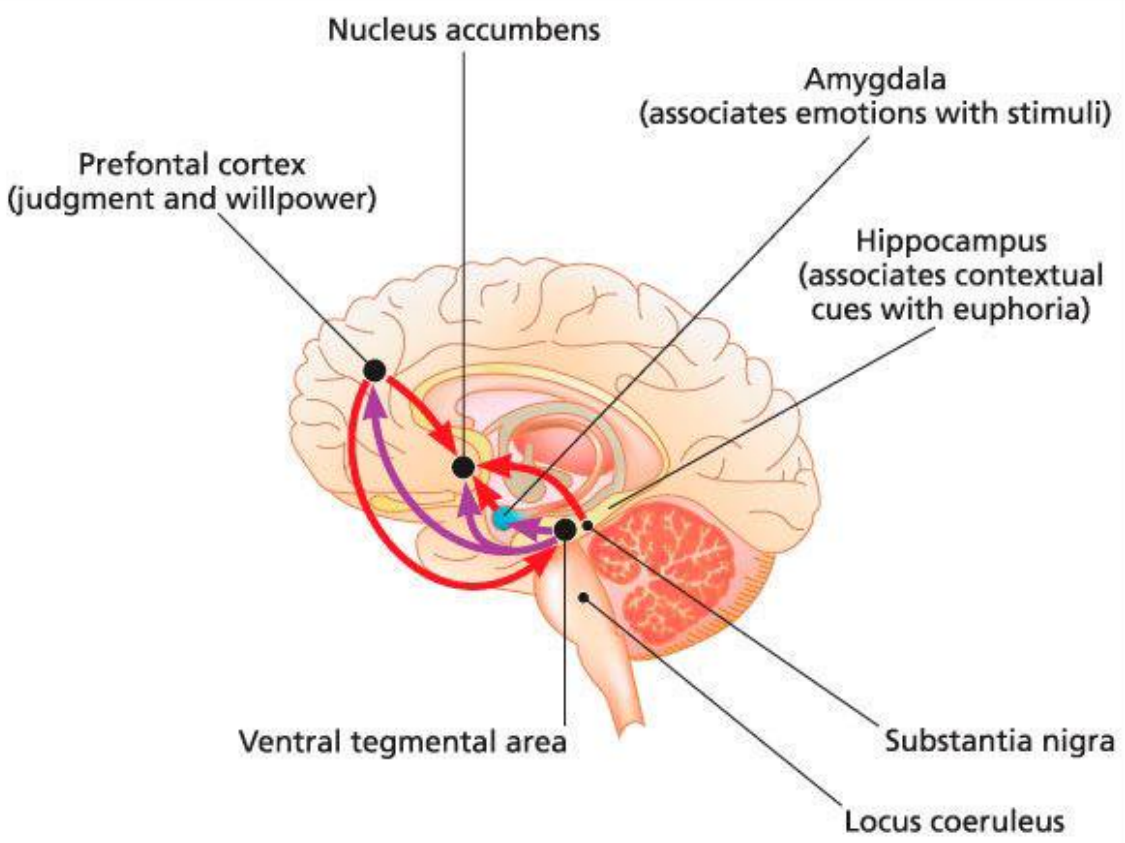
- What is rTMS?
- Why might it work in depression?
- Why has it only recently been NICE approved?
- What is the evidence base?
- Who might it benefit?
- What could be the future direction of rTMS?

What is rTMS?


Wire coil
Pulsed magnetic field
Stimulated brain region
Positioning frame
Maximum field depth
Magnetic field
Activated neurons
Resting neurons

Why might this work in depression?

1. rTMS appears to modulate neuronal plasticity
2. Stimulating left dorsolateral prefrontal cortex may strengthen cortico-striatal-thalamic connections



History of rTMS

- Initially developed in Sheffield in 1985
- Used for depression since 1990
- Approved Health Canada 2002
- FDA approval 2008
- In the USA over 500 clinics as of 2013
- Approved NICE in 2015
- Currently 4 NHS rTMS centres in UK

NICE Guidance IPG542 (December 2015)

"The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit"

NICE National Institute for Health and Care Excellence

Why has it only recently been NICE approved?

Modest Efficacy

- Large number of differing treatment protocols included in meta-analysis
- 50-60% of the *n* within the meta-analysis are for trials where they did 10-15 sessions of stimulation

Time and Cost Intensive Procedure

- 3000 10Hz pulses per session, each 4 seconds long with 26 second pause (30 second cycle), each “train” lasts 37.5 minutes
- Daily sessions 5 days per week for 4-6 weeks (26-28 sessions)

Is active rTMS more effective than sham?

Sclotema (2010)

Netherlands (1990 to 2008)

Depression (type unspecified)

751 rTMS vs 632 sham

Between 5 and 25 treatments of rTMS

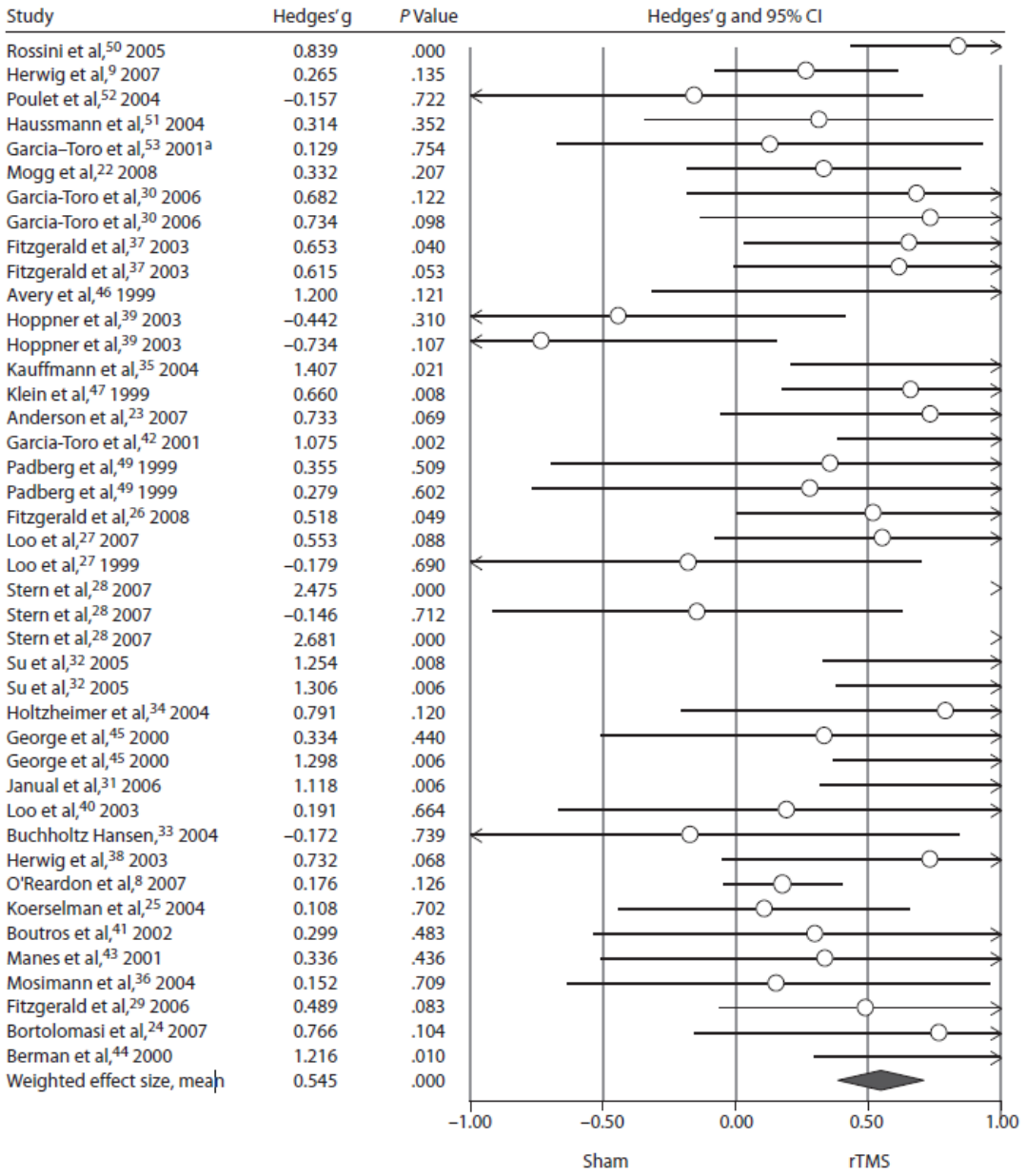
Different cranial sites

Unilaterally or bilaterally

Frequency between 1 and 20 Hz

80% to 120% of motor thresholds

Hedges' g value of 0.55, p<0.001

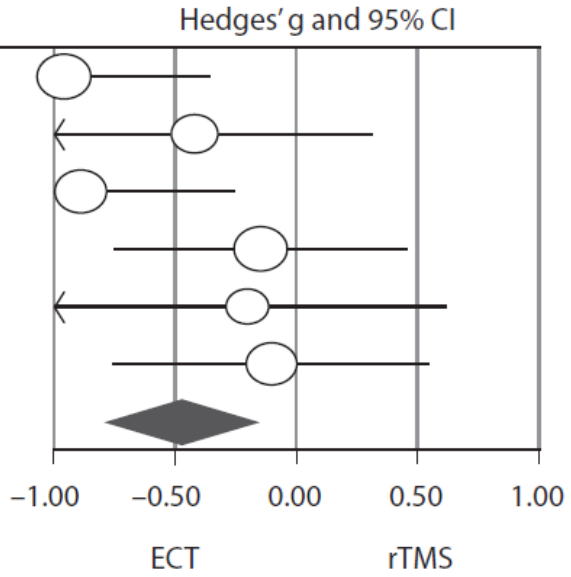


Is rTMS more effective than ECT?

Sclotema (2010)

113 rTMS vs 102 ECT

Study	Hedges' g	*P* Value
Eranti et al,[56] 2007	−0.957	.002
Pridmore et al,[61] 2000	−0.420	.263
Grunhaus et al,[60] 2000	−0.889	.006
Grunhaus et al,[58] 2003	−0.147	.636
Janicak et al,[59] 2002	−0.202	.630
Rosa et al,[57] 2006	−0.102	.760
Weighted effect size, mean	−0.474	.004



	rTMS	ECT*
Response	50%	80%
Remission	30%	75%

*Husain (2004)

Is rTMS more effective in treatment resistant cases?

Lepping P (2014)

United Kingdom

2330 rTMS vs 806 sham

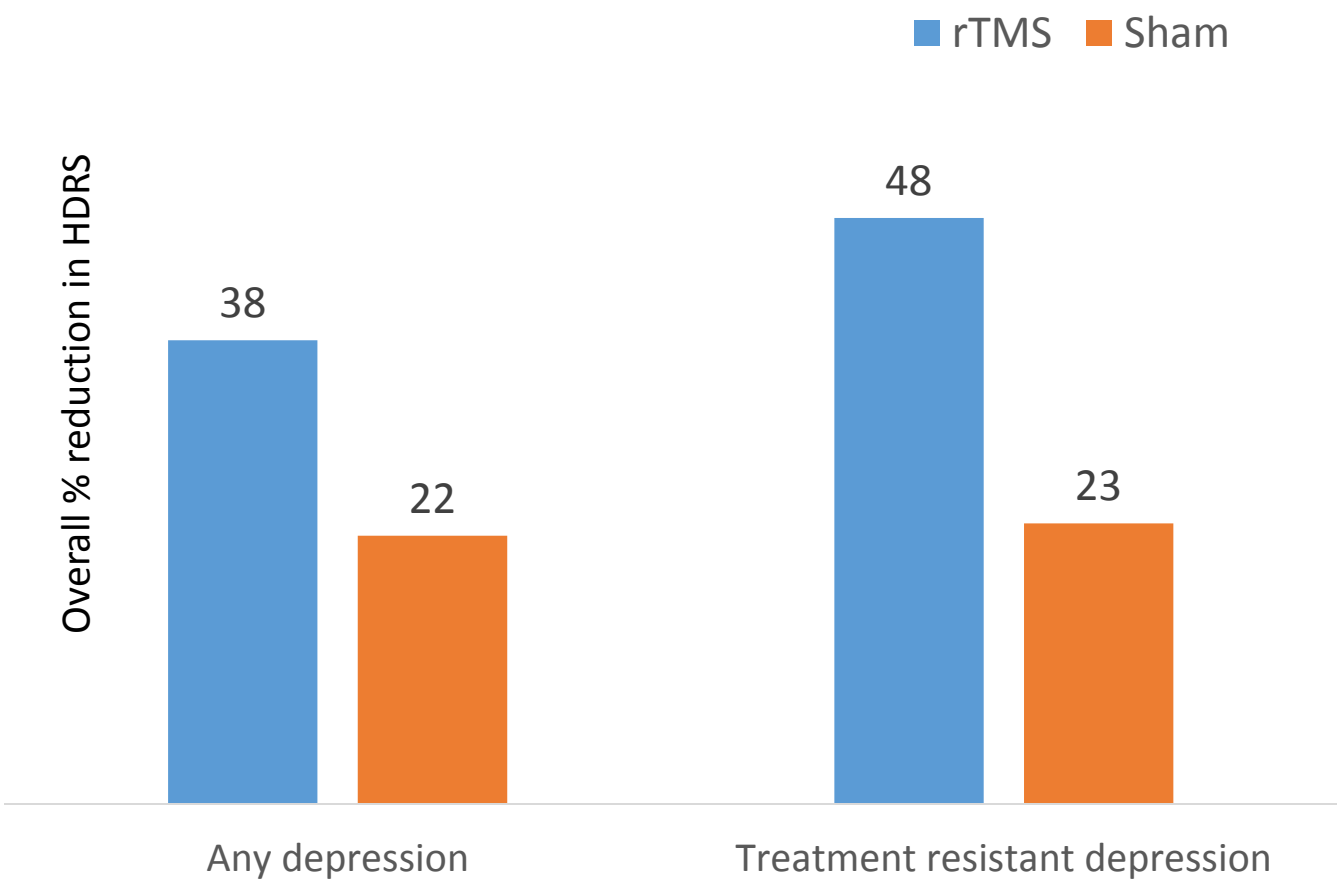
Between 1 and 12 weeks (only week 4 results analysed)

Different cranial sites

Unilaterally or bilaterally

Frequency between 1 and 20 Hz

80% to 120% of motor thresholds



Are the effects durable?

Janicak PG (2010)

United States

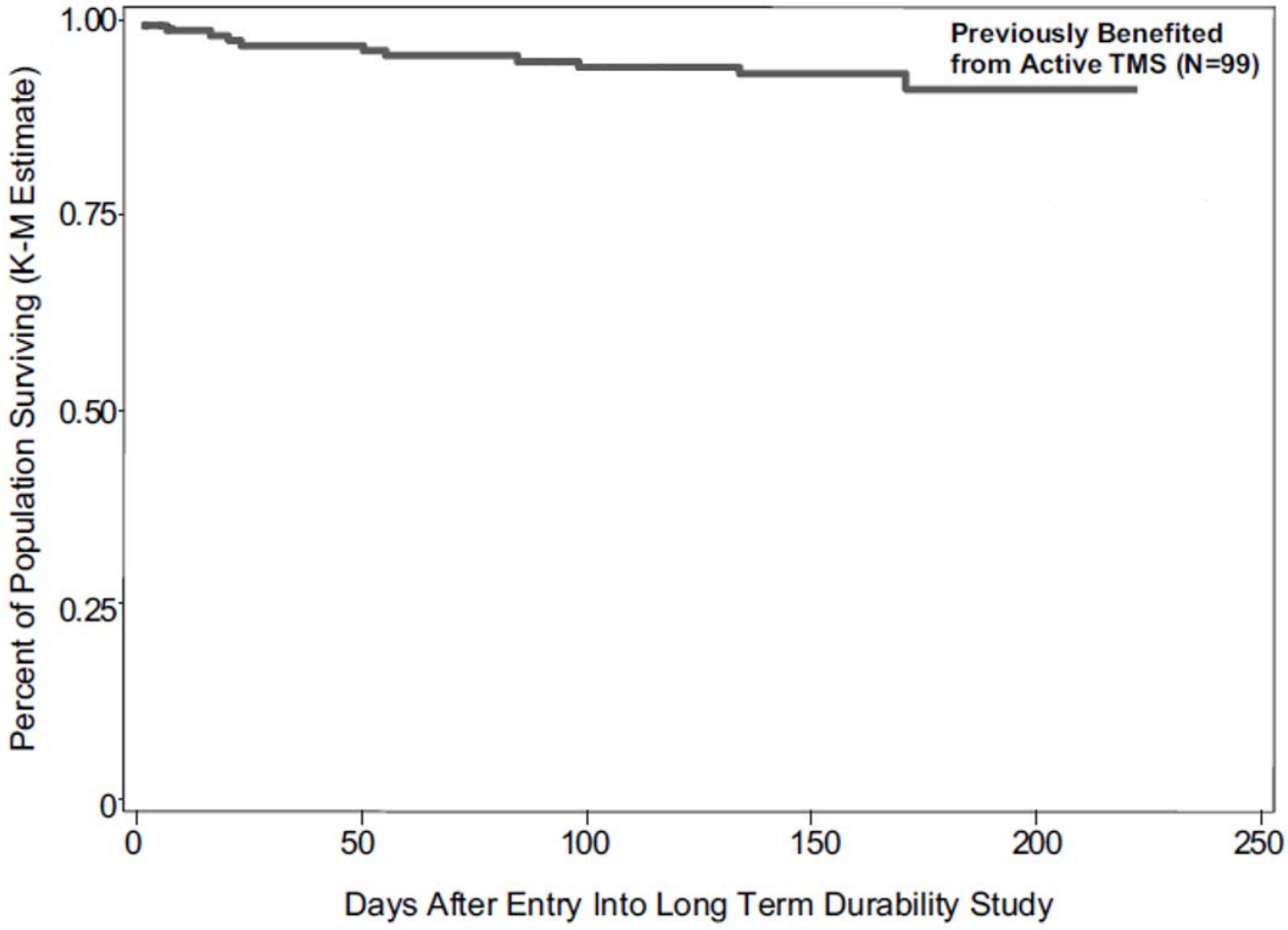
MDD

Partial response to 6 weeks rTMS

10/99 (Kaplan Mier survival estimate 13%) relapsed at 6 months

37% of patients on continuation pharmacotherapy relapsed at 6 months following successful initial treatment with ECT

Jelovac (2013)



Is rTMS safe and tolerable?

Risk of seizure 1 in 10,000

95% of patients who start a course of treatment make it the end

No long term side effects known

	Low frequency	*High frequency*	*Sham*
Headache	4% (4/109)	10% (46/472)	3% (12/461)
Scalp discomfort	2% (2/109)	9% (45/472)	2% (9/461)
Facial twitching	0% (0/109)	2% (9/472)	0% (0/461)
Eye watering	0% (0/109)	2% (7/472)	0% (0/461)
Drowsiness	0% (0/109)	3% (12/472)	0% (0/461)

Short term side effects

Sclotema CW (2010)

Indications

Unipolar treatment resistant depression without psychotic symptoms

Alternative to ECT

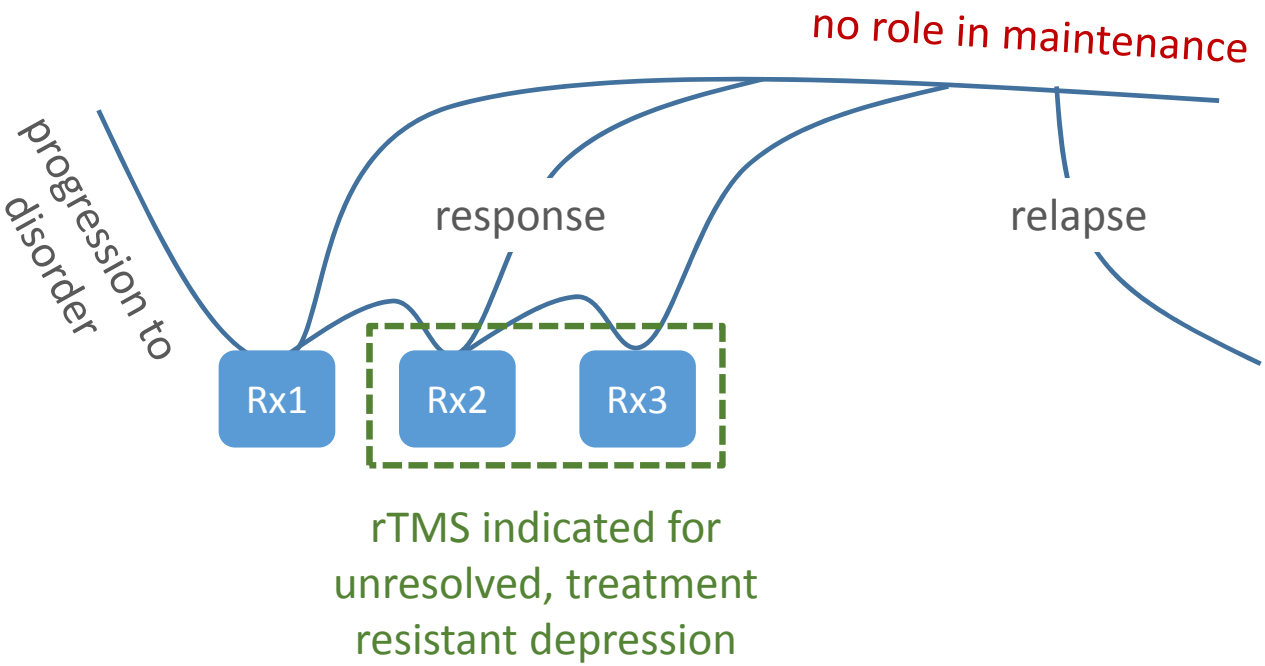
Sensitivity to side-effects

Cautions

A history of epilepsy or organic brain pathology

Acute alcohol dependence syndrome

Presence of surgically placed ferromagnetic material (e.g cardiac pacemaker, cochlear implant)

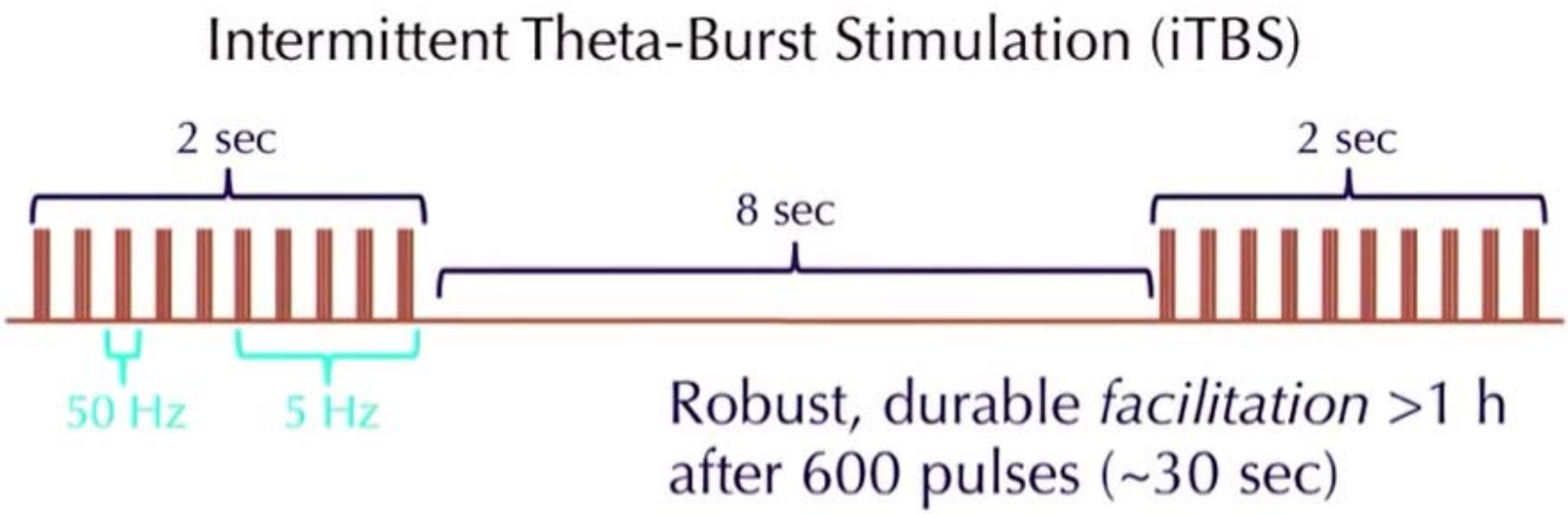


Future Directions

- Safe, tolerable and durable
- Modest effectiveness, time and cost intensive

What is needed?

- Faster sessions
- Shorter courses
- More remitters
- Predictive test


Intermittent Theta-Burst Stimulation (iTBS)
2 sec
8 sec
2 sec
50 Hz
5 Hz
Robust, durable *facilitation* >1 h
after 600 pulses (~30 sec)

Is theta-burst as effective as conventional rTMS?

Bakker N (2015)

Canada (2011 to 2014)

Non-randomised comparative study

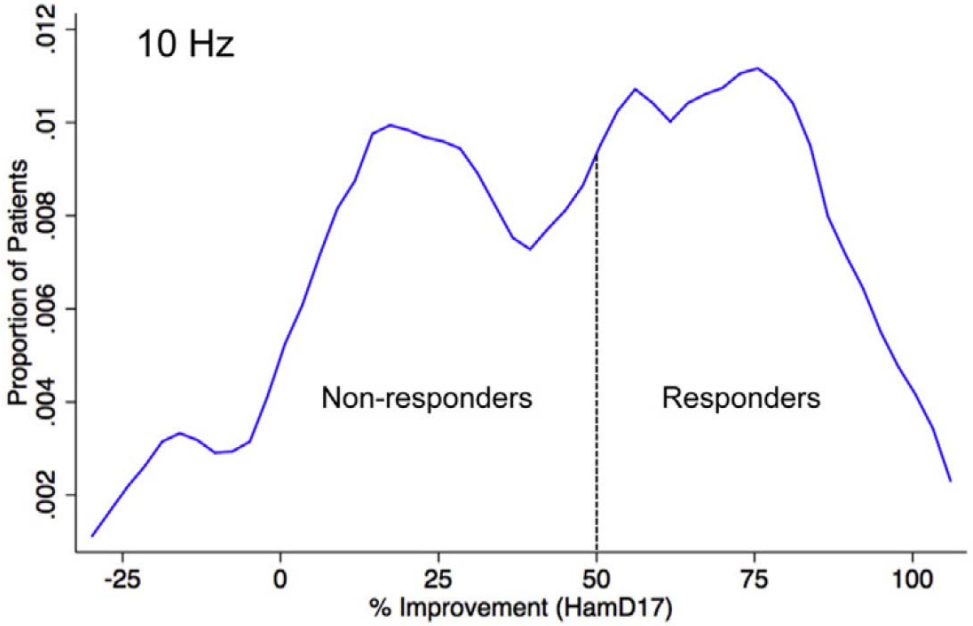
Included unipolar and bipolar, no comorbidities excluded

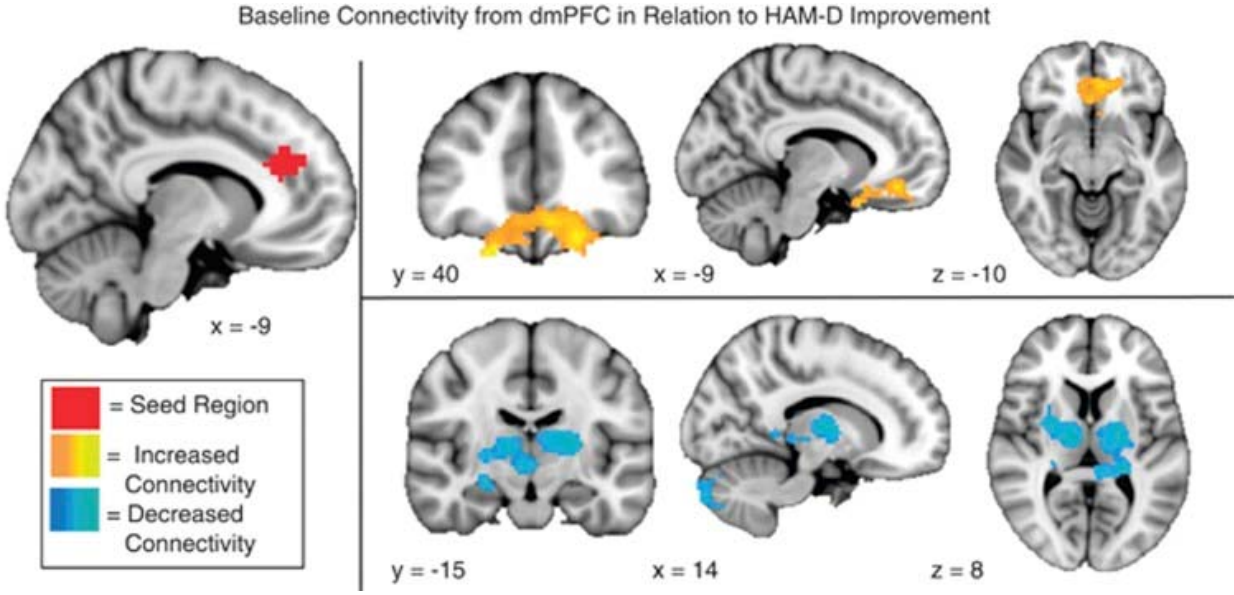
98 conventional vs 87 theta-burst

DMPFC (left and right)

	Response rates (%)		
Outcome	rTMS (n/N)	TB-rTMS (n/N)	p value
HDRS scores	50.6 (42/83)	48.5 (32/66)	0.869

	Remission rates (%)		
Outcome	rTMS (n/N)	TB-rTMS (n/N)	p value
HDRS scores	38.5 (37/96)	27.9 (24/86)	0.157





Questions?

Northumberland Tyne and Wear NHS Foundation Trust

RADS Regional Affective Disorder Service

NCMD Northern Centre for Mood Disorders

Newcastle University Institute of Neuroscience

Restoring Hope

Hope through Research and Education