Repetitive Transcranial Magnetic Stimulation (rTMS) and intravenous ketamine for treatment-resistant depression (TRD)

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Disclosures

◆ No possessions in medical companies

◆ Honoraria for lectures 2007 – 2017: Astra-Zeneca, Bayer, Bristol-Myers Squibb, Duodecim, Efeko, Eisai, GlaxoSmithKline, City of Helsinki, University of Helsinki, Finnish Research Council for Medical Industry, Lilly, Lundbeck, Nexstim, Orion Pharma, Pfizer, Professio Finland, Scandinavian Association of the Study of Pain, Schering-Plough, Finnish Dental Association, Finnish Medical Association, Finnish Psychiatric Association, City of Turku, University of Turku, UCB, Vesa Laukkanen Ltd, Jarkko Männistö Ltd, L Legal Ltd, Mega Electronics Ltd

Treatment-resistant depression (TRD)

◆ Many definitions

◆ Most common definition: failure to achieve response (50 % reduction in symptom severity) in trials with two antidepressants of different classes with adequate doses and sufficient period (Keitner and Mansfield 2012)

◆ TRD can be classified by different methods (Ruhé et al. 2012)

◆ Most used classification is Maudsley Staging Model (MSM, Fekadu et al. 2009

Table 1 Summary of scoring system and domain components of the Maudsley Staging Method

|	Score range
Domains	
Antidepressants	1–5
Failure of augmentations	0–1
Failure of electroconvulsive therapy	0–1
Chronicity	1–3
Severity	1–5
Total score	3–15
Severity categories	
Mild	3–6
Moderate	7–10
Severe	11–15

Prevalence and outcome of TRD

- Failure to achieve response in 20 – 30 % of patients with major depression (Keitner and Mansfield 2012)
- Only 40 % of patients achieve remission
- 12-month prevalence in Finland about 1 % (Taiminen 2013)
- In a tertiary centre (N = 118, mean MSM 10) 60 % achieved remission during the 8 – 84 months follow-up (Fekadu et al. 2012)

Sickness pensions in Finnish Private Companies in 1983–2009
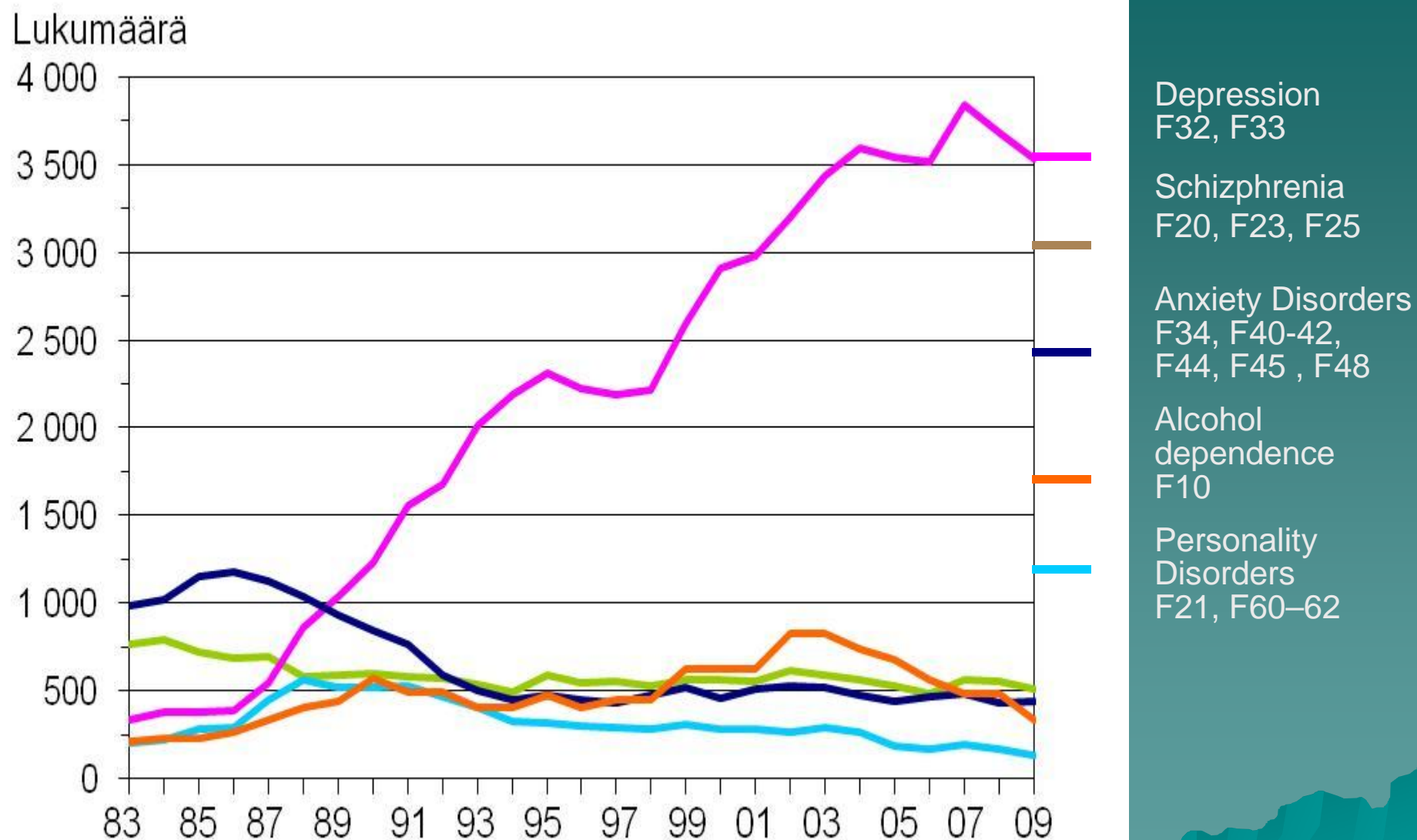
Costs of depression in Sweden (Sobocki et al. 2007)
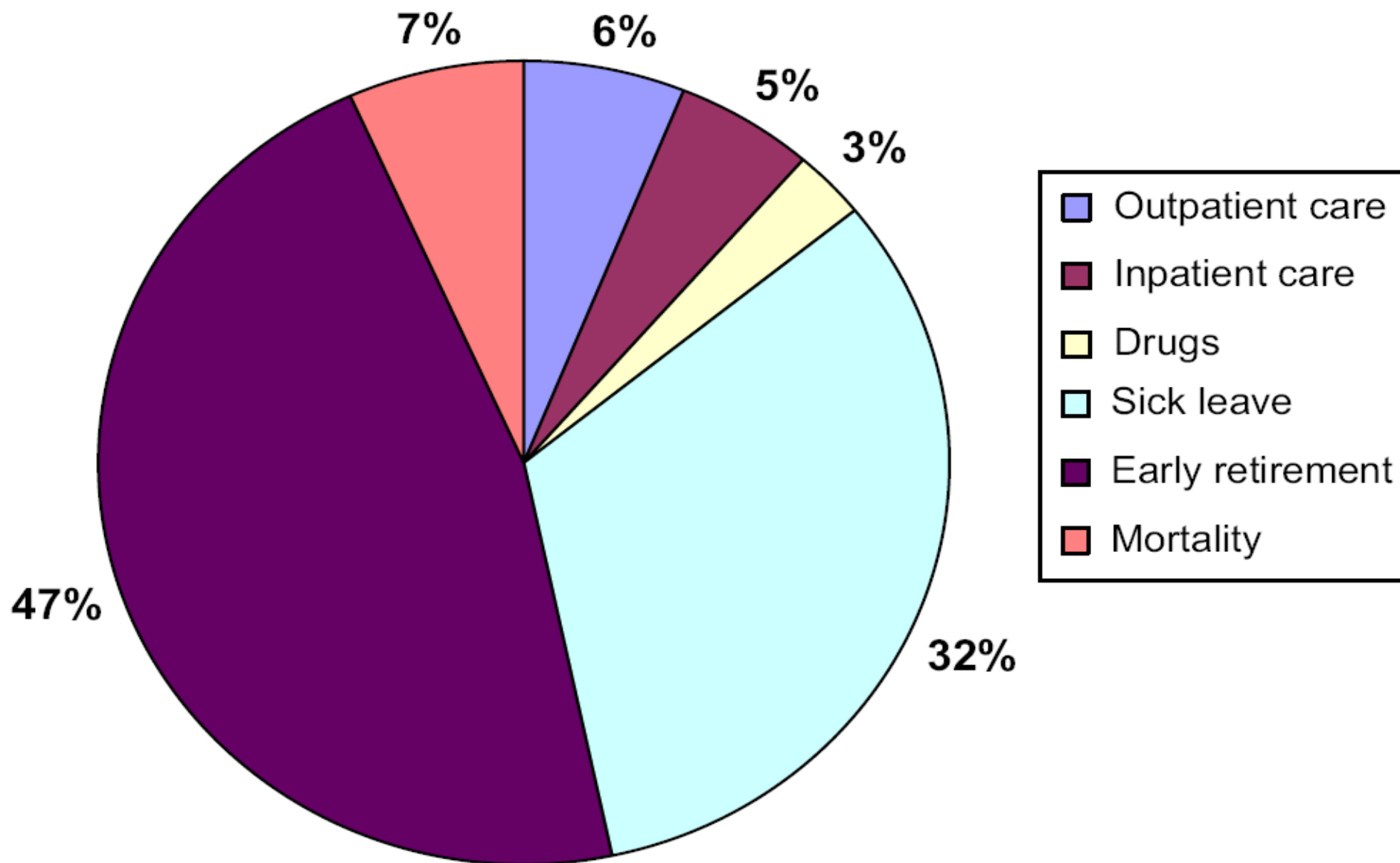
Effect size: examples of Cohen's d

- 0.2 = height difference (hd) between 15- and 16-year-old girls in population
- 0.5 = hd between 14- and 18-year-old girls
- 0.8 = hd between 13- and 18-year-old girls
- 1 = effect size of placebo response in depression studies
- 1.7 = hd between women and men

Cohen's d of depression treatments

- ◆ < 0.3 Second generation antipsychotic as an adjuvant
- ◆ 0.3 – 0.4 Antidepressant or tDCS
- ◆ 0.4 – 0.6 Lithium or thyroxin as adjuvants
- ◆ 0.6 – 0.7 rTMS
- ◆ 0.3 – 0.4 Cognitive psychotherapy
- ◆ 0.7 Antidepressant and psychotherapy combined
- ◆ 0.9 bilateral or high-energy unilat. ECT
- ◆ 1.2 – 1.4 ketamine i.v.

Responder curve of rTMS in depression is biphasic (Downar et al. 2014)
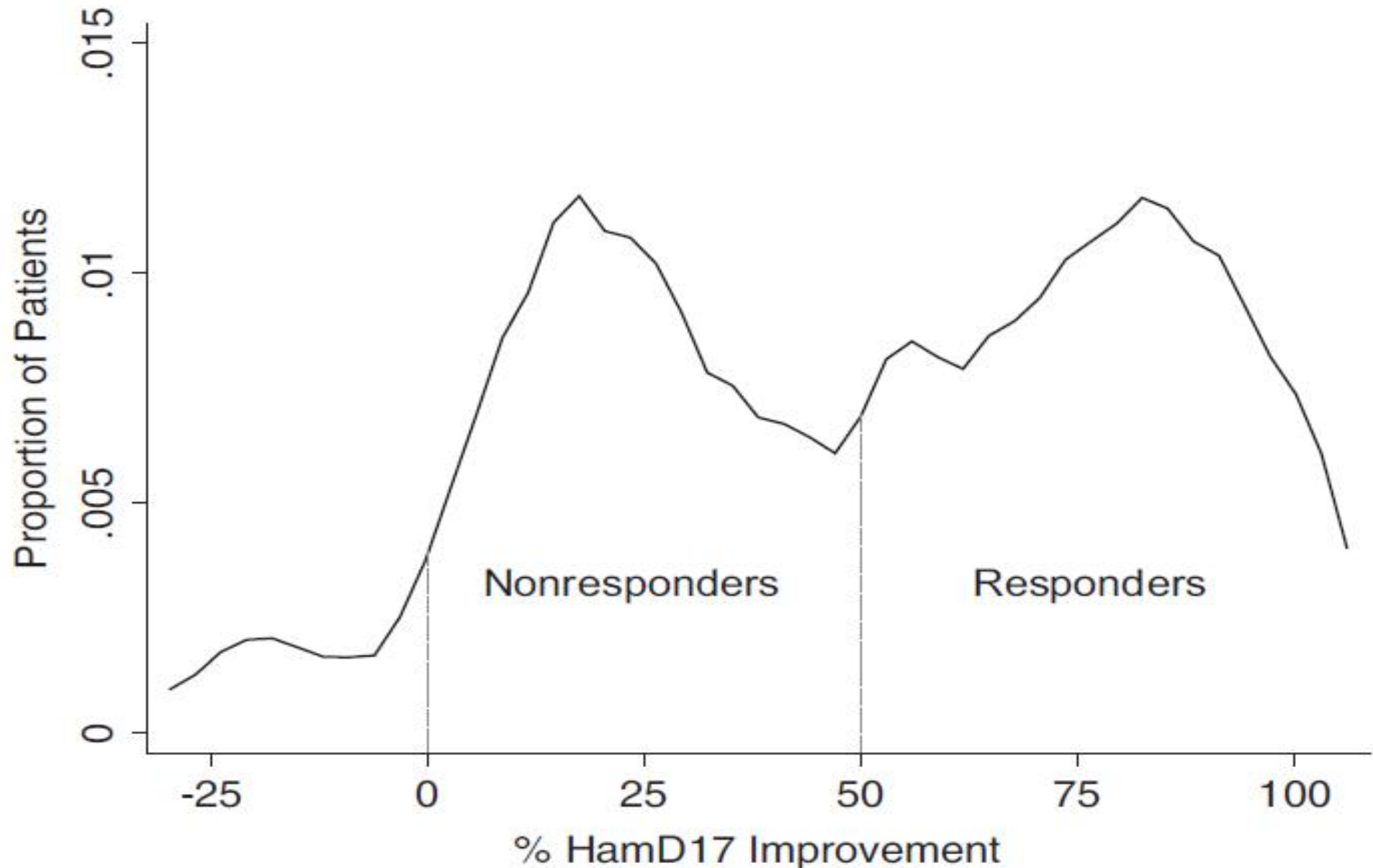
rTMS in depression – early (and primitive) theory

- In depression right DLPFC is hyperactive and left hypoactive
- Right hyperactivity is associated with depression severity and anxiety
- Left hypoactivity is associated with negative emotions
- rTMS aims at restoring balance

Some observations on rTMS in depression

- rTMS releases endogenic opioids (Lamusuo et al. 2017) and dopamine (Cho and Strafella 2009)

- rTMS increases white matter integrity in frontal middle gyrus (Peng et al. 2012) → enhancement of neuroplasticity

- rTMS normalizes brain energy consumption (Li et al. 2010)

- rTMS normalized hyperacticity of temporal areas associated with default mode network ("network of introspection", Richieri et al. 2017, Ge et al. 2017)

rTMS activates the endogenous opioid system in a wide network (Lamusuo et al. 2017)
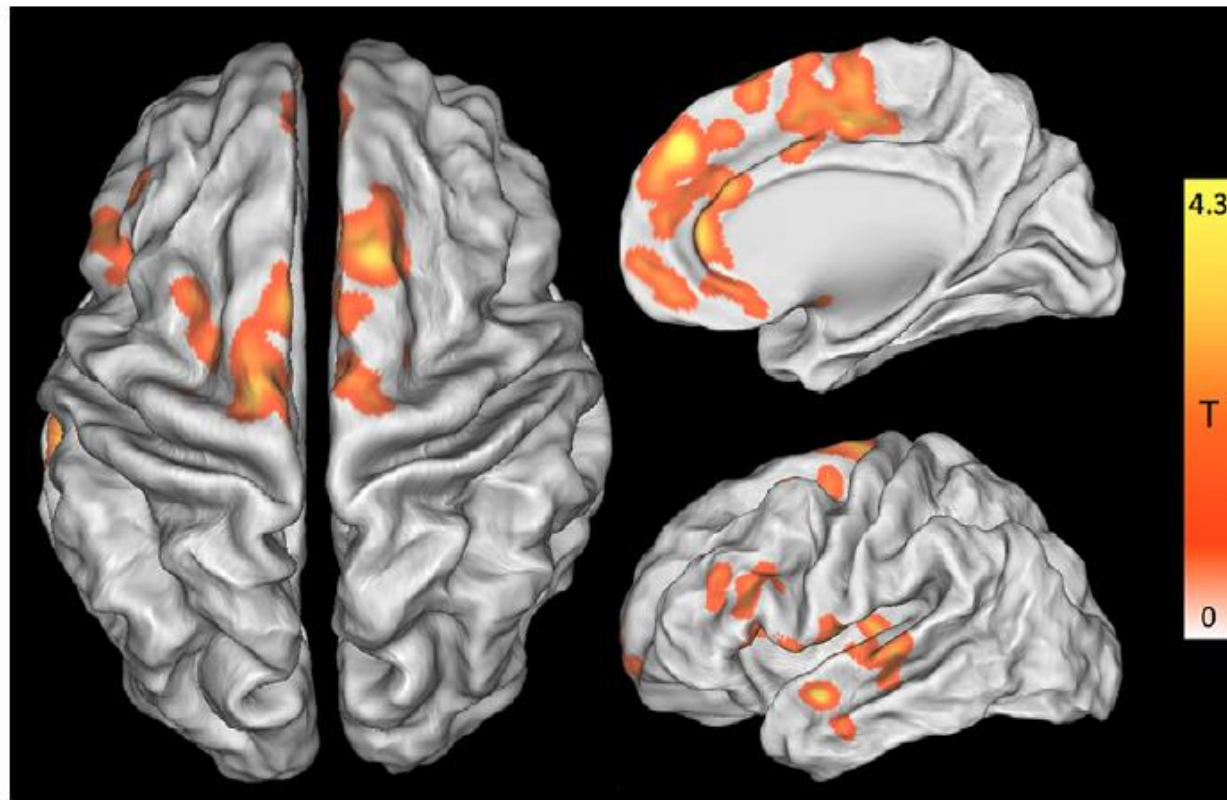

Figure 3 Statistical parametric mapping (SPM) analysis shows lower [^{11}C]carfentanil BP_{ND} after active rTMS treatment, compared with sham treatment, in multiple brain regions involved in pain processing ipsilateral and contralateral to rTMS treatment. The ipsilateral cluster comprised of 4477 voxels and had a maximum t value of 5.1 at [4, 48, 36] and a cluster-level corrected P-value of <0.001. The contralateral cluster comprised of 2101 voxels and had a maximum t value of 5.7 at [−54, 0, −14] and a cluster-level corrected P-value of 0.044. Colour bar represents t value in each voxel within the significant cluster. The MNI coordinates of the three slices are [3, 46, 6].

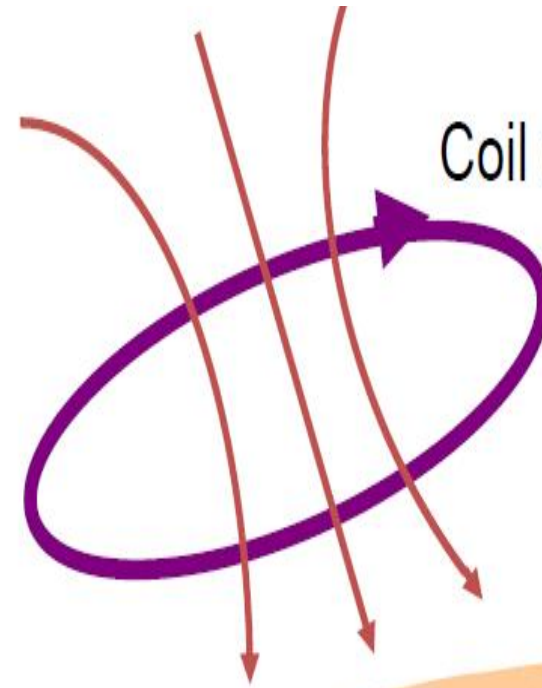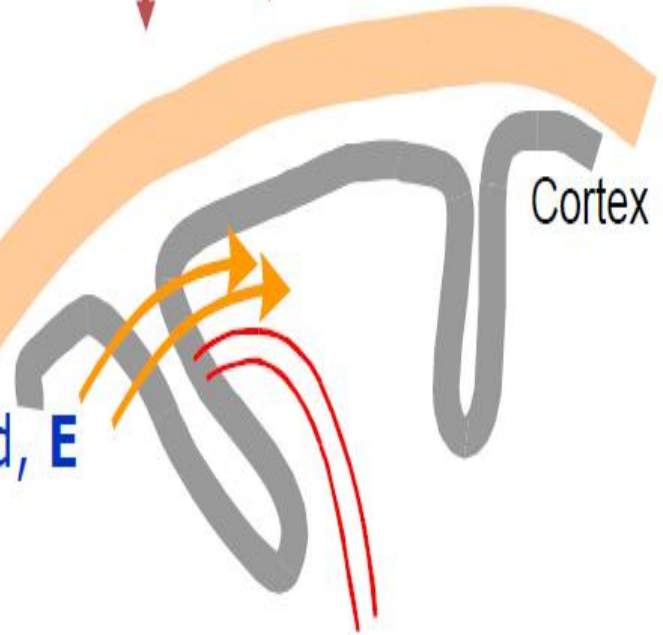Magnetic field, **B**

Coil

Electric field, **E**
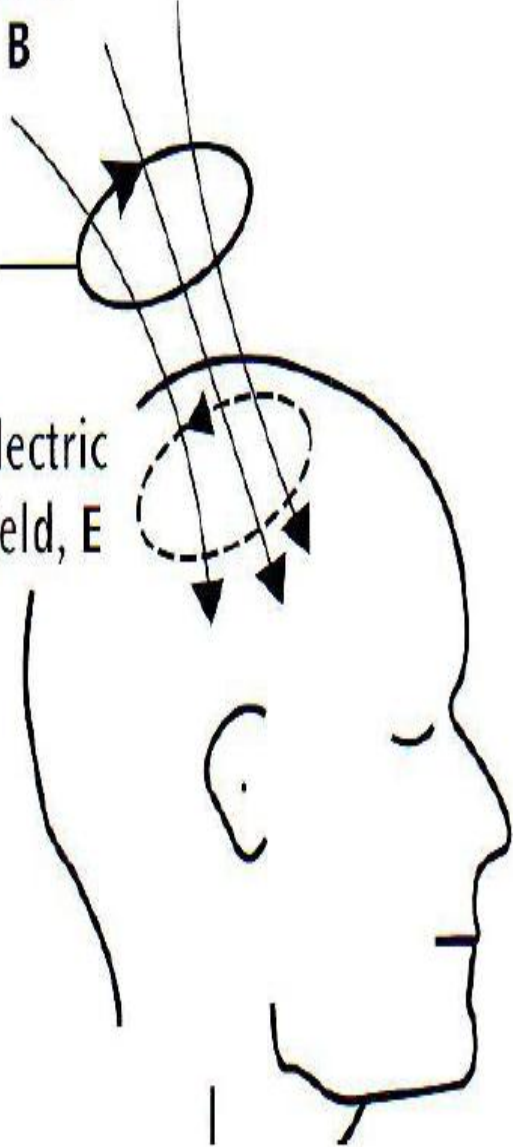
Coil current

Cortex

Electric field, **E**

Neuronal activation

Navigation with MRI

Crux helicis

Brodmann's areas
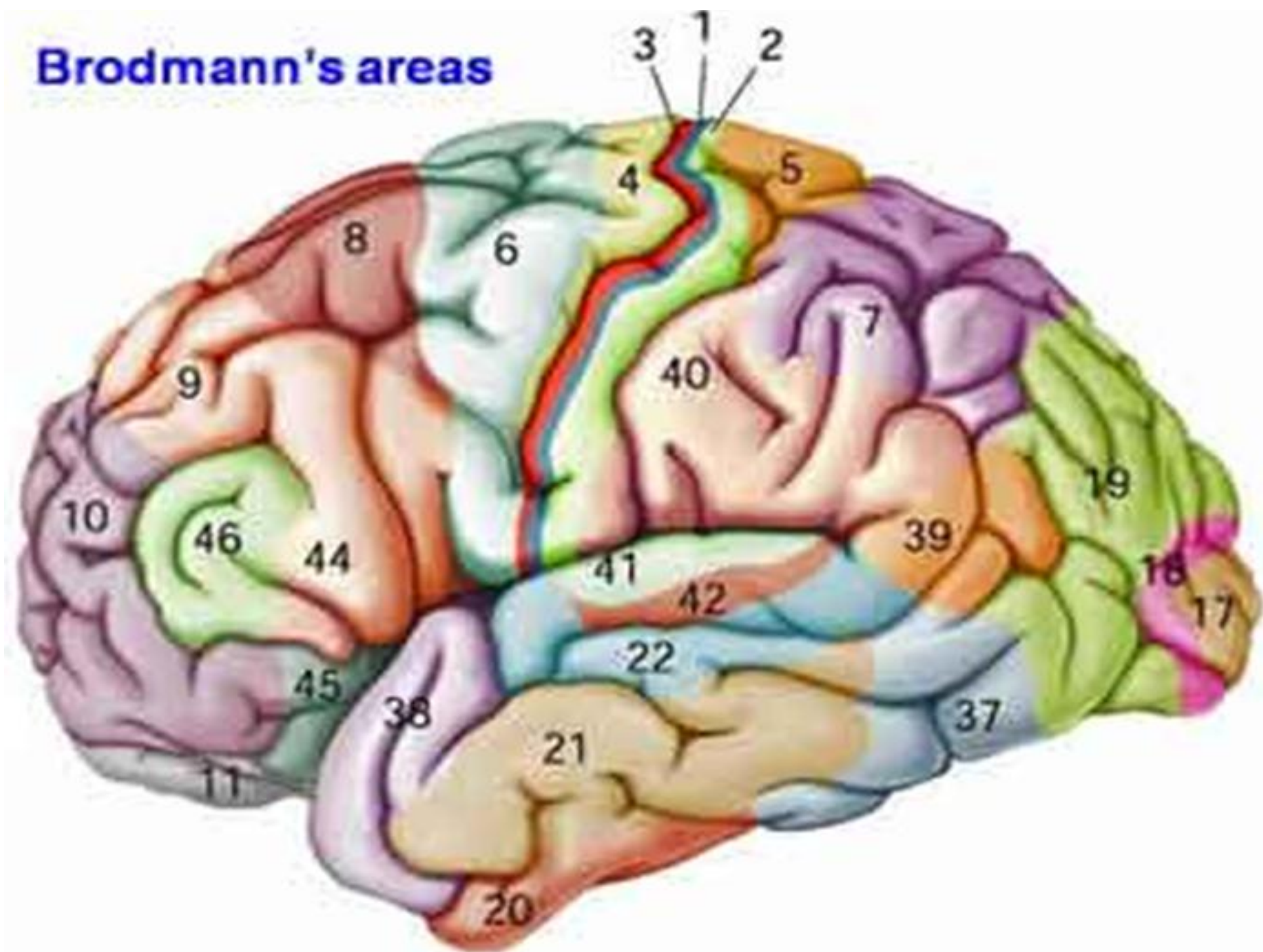
- Target in depression: border between BA9 and BA 46 (Mylius et al. 2013)
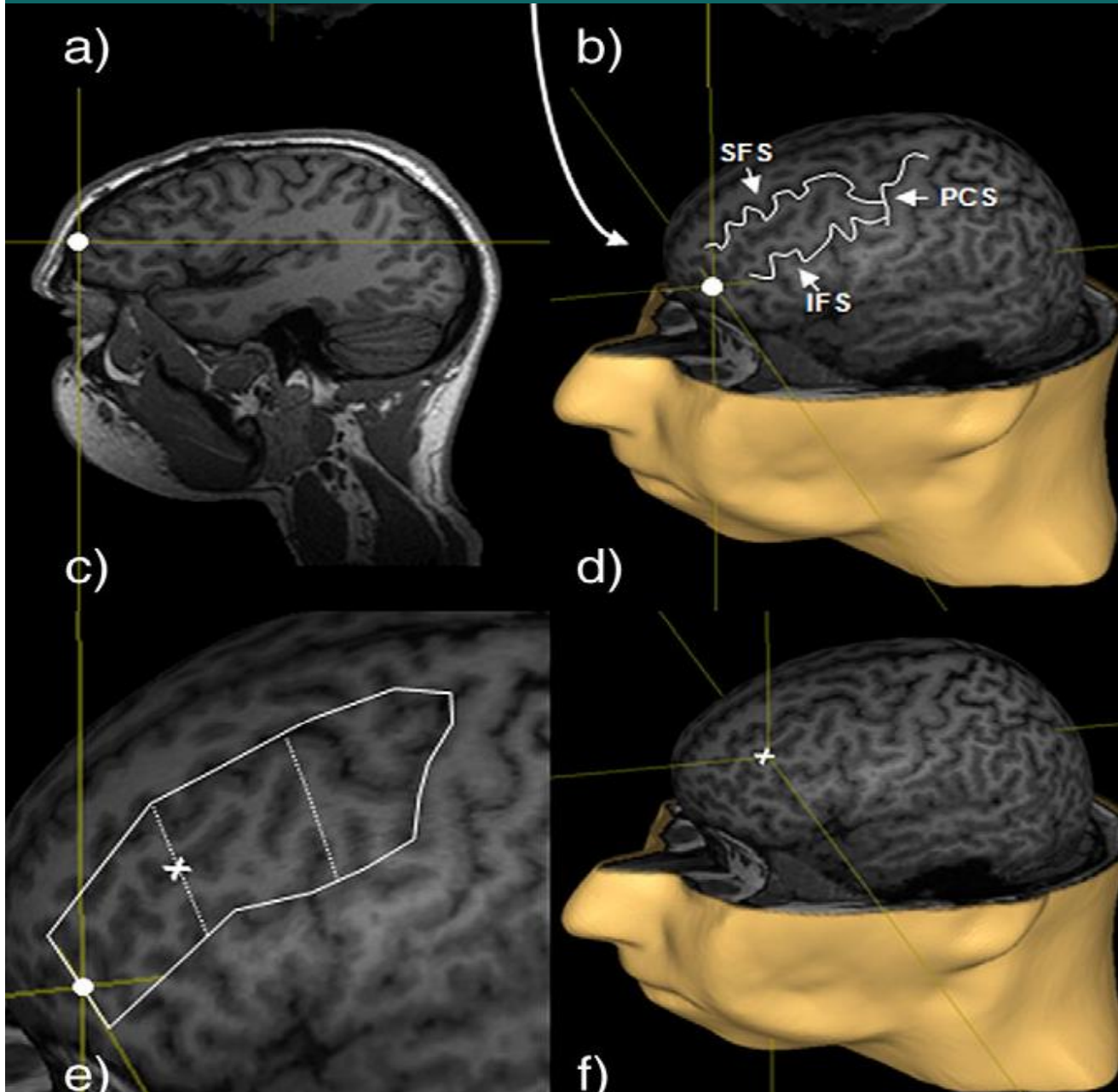
Techniques

◆ Activate left DLPFC with high frequency, e.g. 10 Hz –side effects with high energy

◆ Inhibit right DLPFC with low frequency, e.g. 1 Hz – efficacy also against anxiety (Diefenbach et al. 2016)

◆ Do both

◆ Theta burst stimulation with a robot – shorter sessions < 10 minutes

◆ Many sessions per day (Tor et al. 2016)

◆ Option to treat more than one indication per session, e.g. depression, chronic pain and tinnitus

10Hz

conventional rTMS

t

Patterend TMS
Theta Burst Stimulation (TBS)

200 ms

t
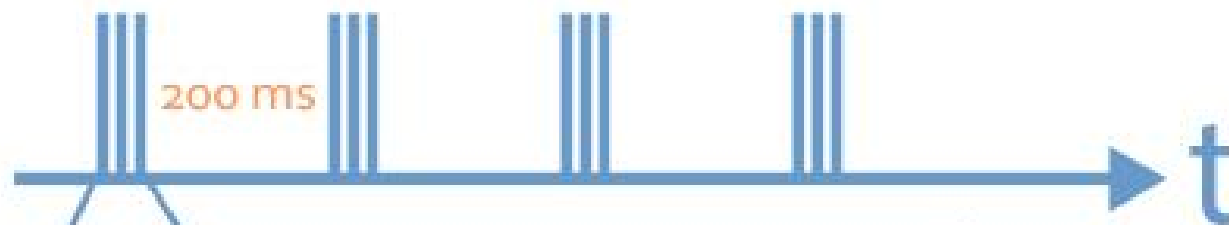
5 Hz repetition rate (Theta)

facilitating: iTBS: 2s on, 8s off, 20 Trains
inhibiting: cTBS: 40s on - 600 Pulses

20 ms
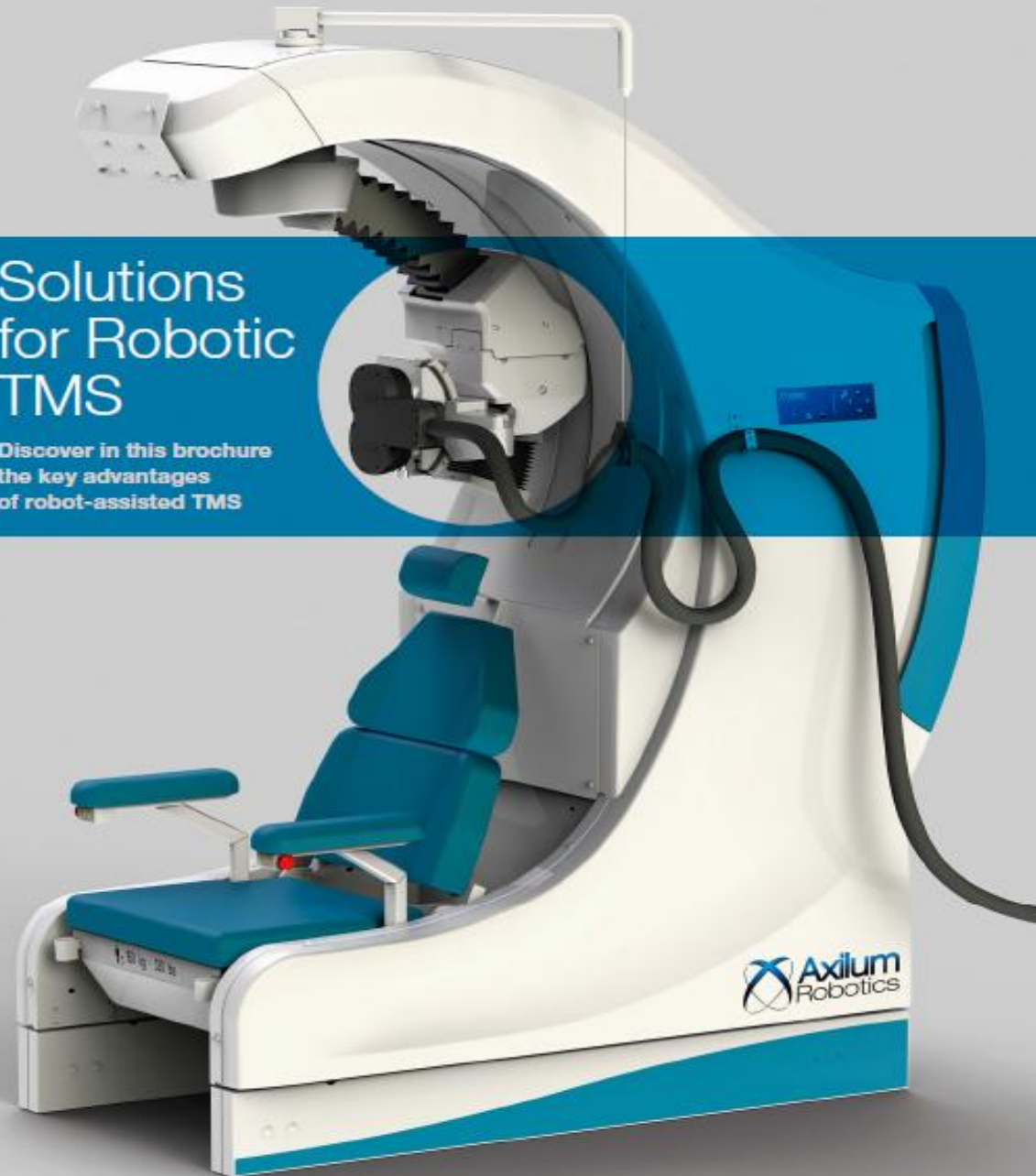
TABLE 1. Commonly used rTMS and TBS parameters in treating depression

Parameters	rTMS		TBS	
	Low-frequency rTMS	High-frequency rTMS	cTBS	iTBS
Intensity (motor threshold)	110% rMT	120% rMT	80% aMT/rMT	80% aMT/rMT
Frequency of stimulation	1 Hz	10 Hz	50 Hz	50 Hz
Interstimulus interval (ISI)	1 s	100 ms	20 ms	20 ms
Train duration	20 min	4 s	20 or 40 s	2 s
Intertrain interval (TTI)	–	25 s	200 ms	200 ms
Interblock interval (IBI)	–	–	–	10 s
Number of trains	-	75 trains	-	10 trains each block
Total number of stimulus[a]	1,200	3,000	300 or 600	600
Administration site	Right DLPFC	Left DLPFC	Right DLPFC	Left DLPFC

[a]Total number of stimulus given per day may vary.

aMT/rMT, active/resting motor threshold; DFLPC, dorsolateral prefrontal cortex; cTBS/iTBS, continuous/intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

Efficacy of rTMS in depression

◆ Good evidence → level A in Finland

◆ More than 20 meta-analyses: d has varied between 0.4 and 0.7

◆ In general, results are better in newer studies and with MRI-based navigation (Gross et al. 2007, Fitzgerald et al. 2009, Schönfeldt-Lecuona et al. 2010, Johnson et al. 2013)

ECT is more effective than rTMS in depression (Slotema et al. 2010)

Study	Hedges' g	P Value	Hedges' g and 95% CI
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	
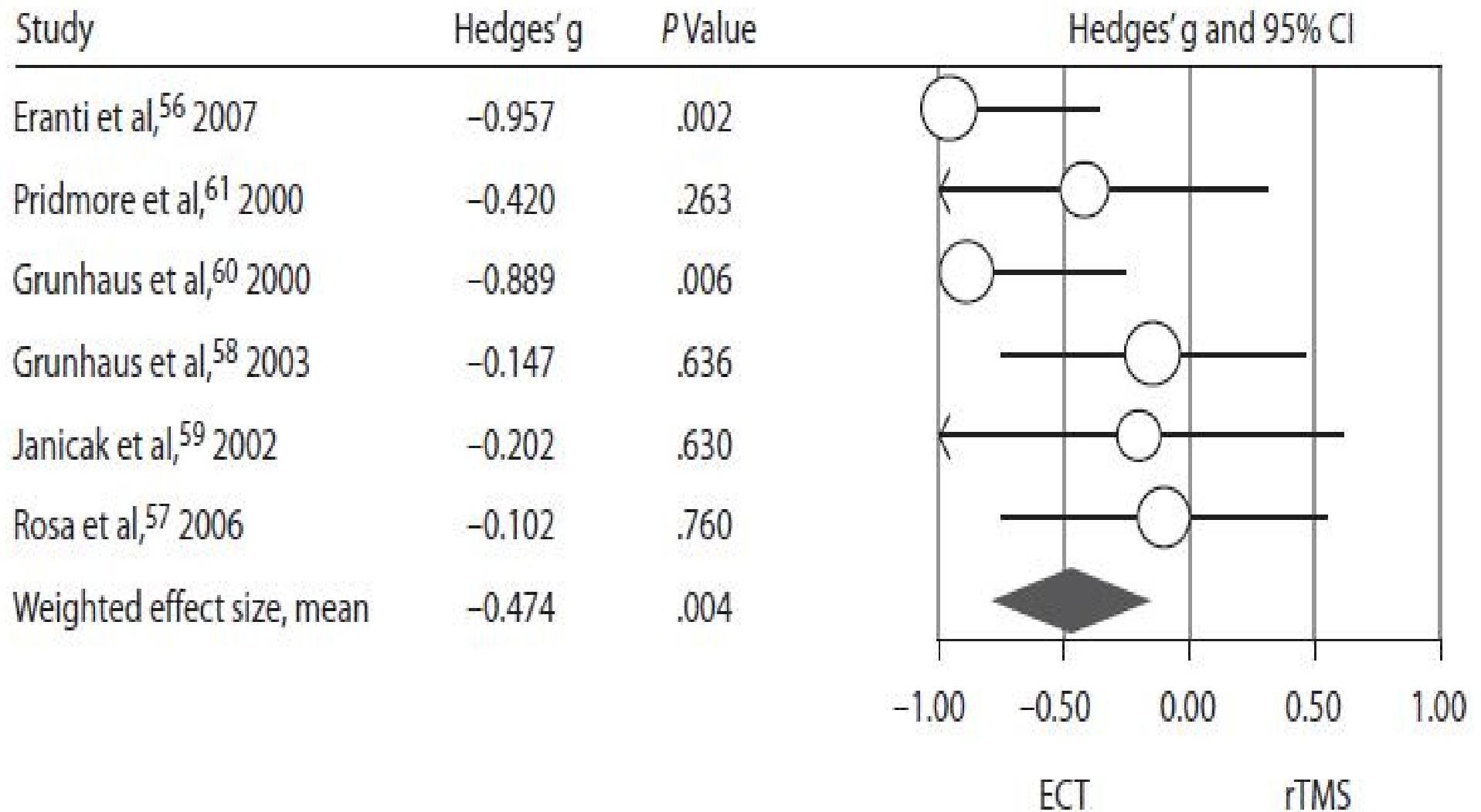
Prediction of response

◆ Young patients (Aguirre et al. 2010) ← neuroplasticity

◆ Effective also for psychotic depression (Ray et al. 2011)

◆ Effective also for ECT-refractory patients (Connolly et al. 2012)

◆ Ekstraversion predicts good response (Berlim et al. 2013)

rTMS in psychotic depression (N = 45, 67 % of patients were psychotic, Ray et al. 2011)
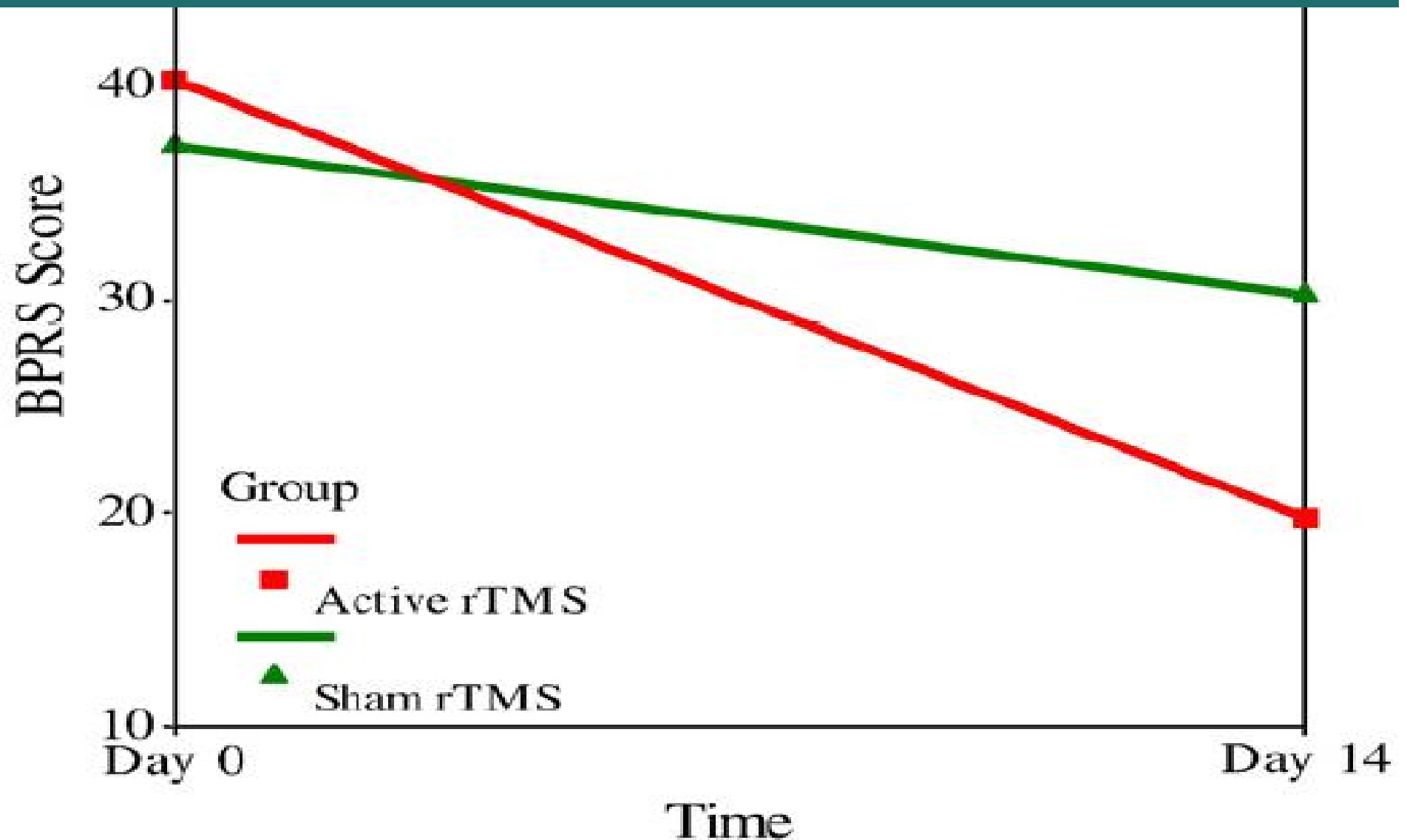
Maintenance treatment of depression

- Steady maintenance: one session per week, fortnightly sessions probably insufficient (Benadhira et al. 2017)

- Tapering down session frequency, c.f. ECT (Connolly et al. 2012)

- Clustered maintenance: 5 sessions during a weekend (Fitzgerald et al. 2012)

rTMS is more cost-effective than antidepressants in TRD (Nguyen and Gordon 2015)

Table 2 – Costs, effects, cost-effectiveness ratios, and net monetary benefit (2013–2014 AUD).

Mean values	3 y (base case)		5 y (sensitivity analysis)	
	Antidepressant	rTMS	Antidepressant	rTMS
Total cost	$31,190	$31,003	$41,009	$39,693
Incremental total cost	–	–$187	–	–$1,316
Total QALYs	1.18	1.25	1.53	1.63
Incremental total QALYS	–	0.07	–	0.10
Cost/QALY	$26,432	$24,803	$26,803	$24,352
Incremental cost per QALY	–	Dominant	–	Dominant

AUD, Australian dollar; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.

Ketamine in the treatment of depression 1

- Non-competative NMDA-antagonist: developed as an anaesthetic
- Fastest and most effective short-term treatment for major depression
- Activity of AMPA-receptors increases → mTOR-pathway activates → synaptic activity and number of dendritic spines increases → enhancement of brain plasticity (Maeng et al. 2008, Li et al. 2010, Tizabi et al. 2012, Cornwell et al. 2012, Zunszain et al. 2013)
- Used as a club-drug
- Most common method: racemic ketamine 0.5 mg/kg/45 min i.v. once a week
- Short-term treatment (< 2 weeks) is evidence-based, long-term treatment is still experimental
- Reliefs pain
- APA consensus statement (Sanacora et al. 2017)
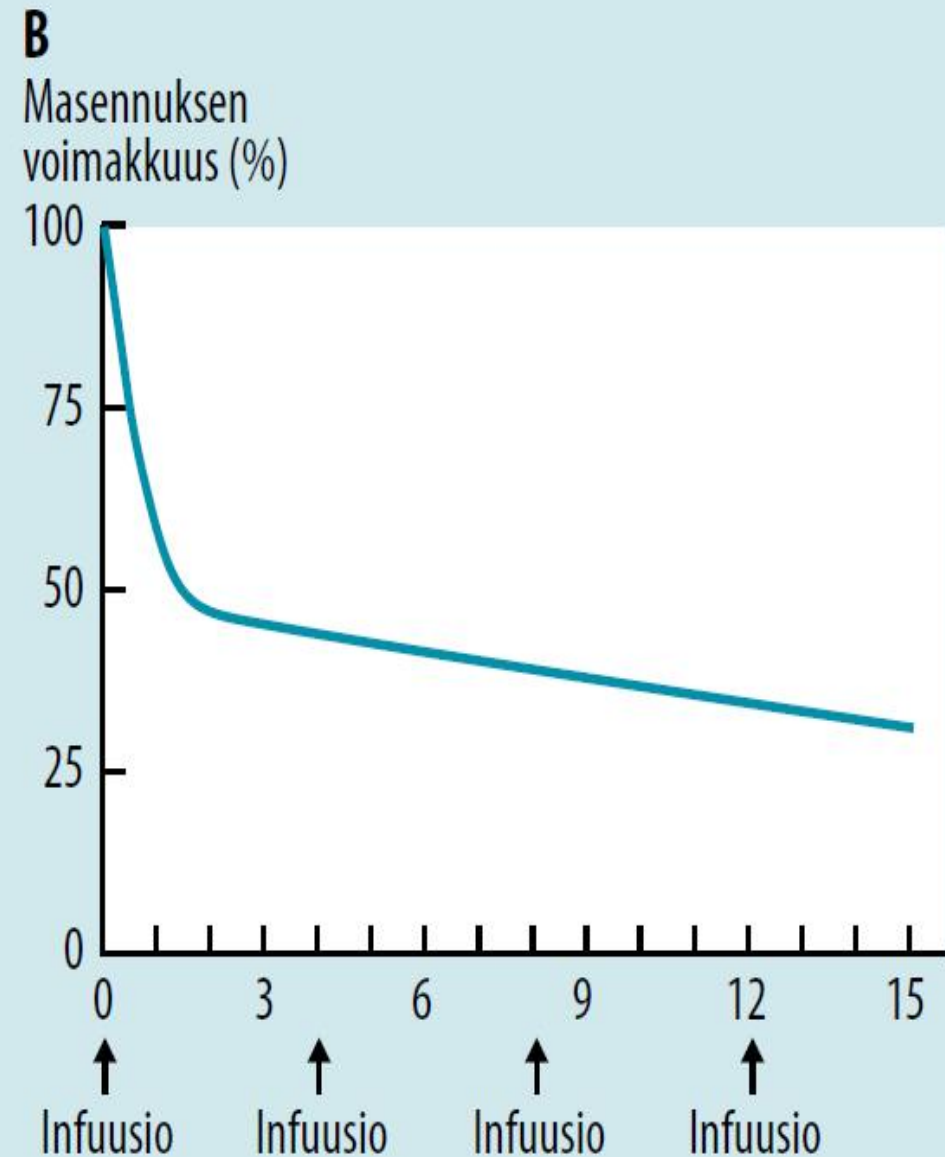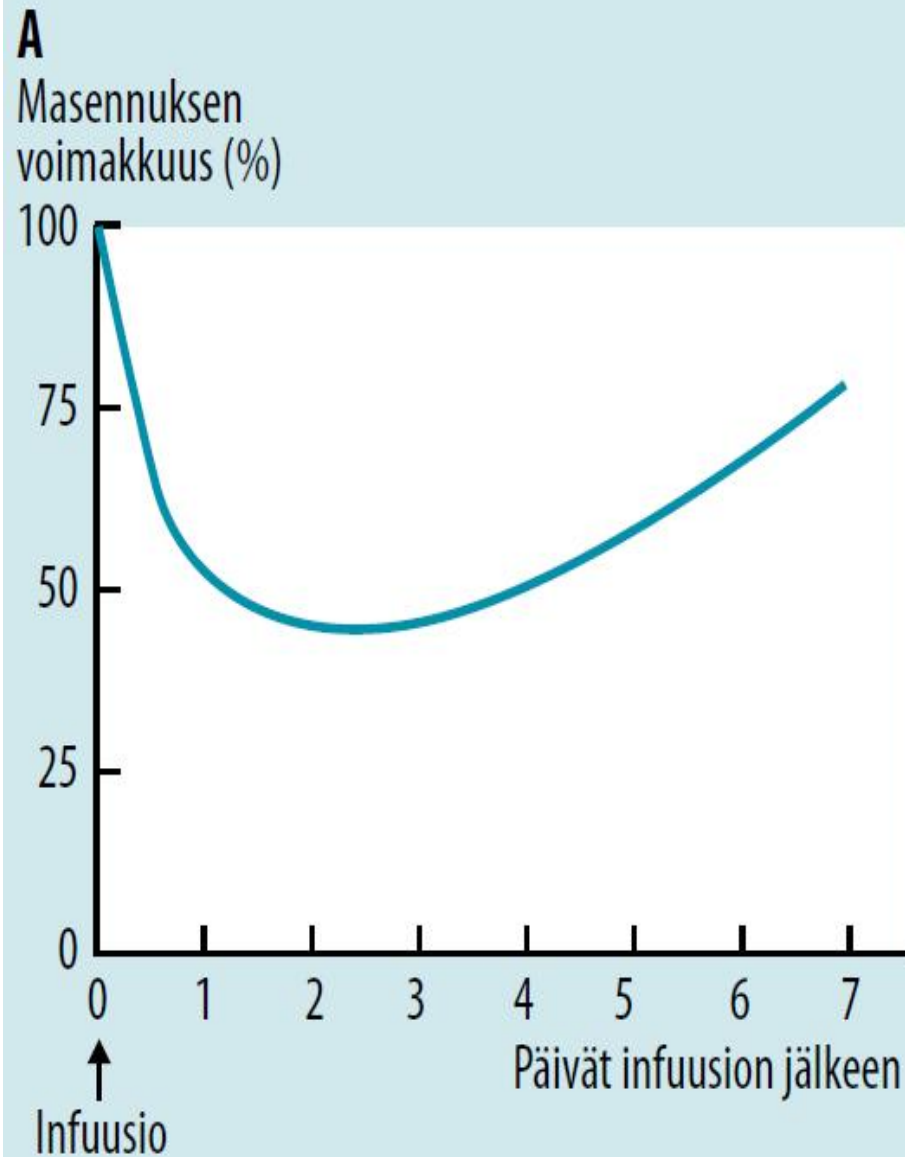
Ketamine once *vs.* twice a week

FIGURE 2. Response Rates Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]
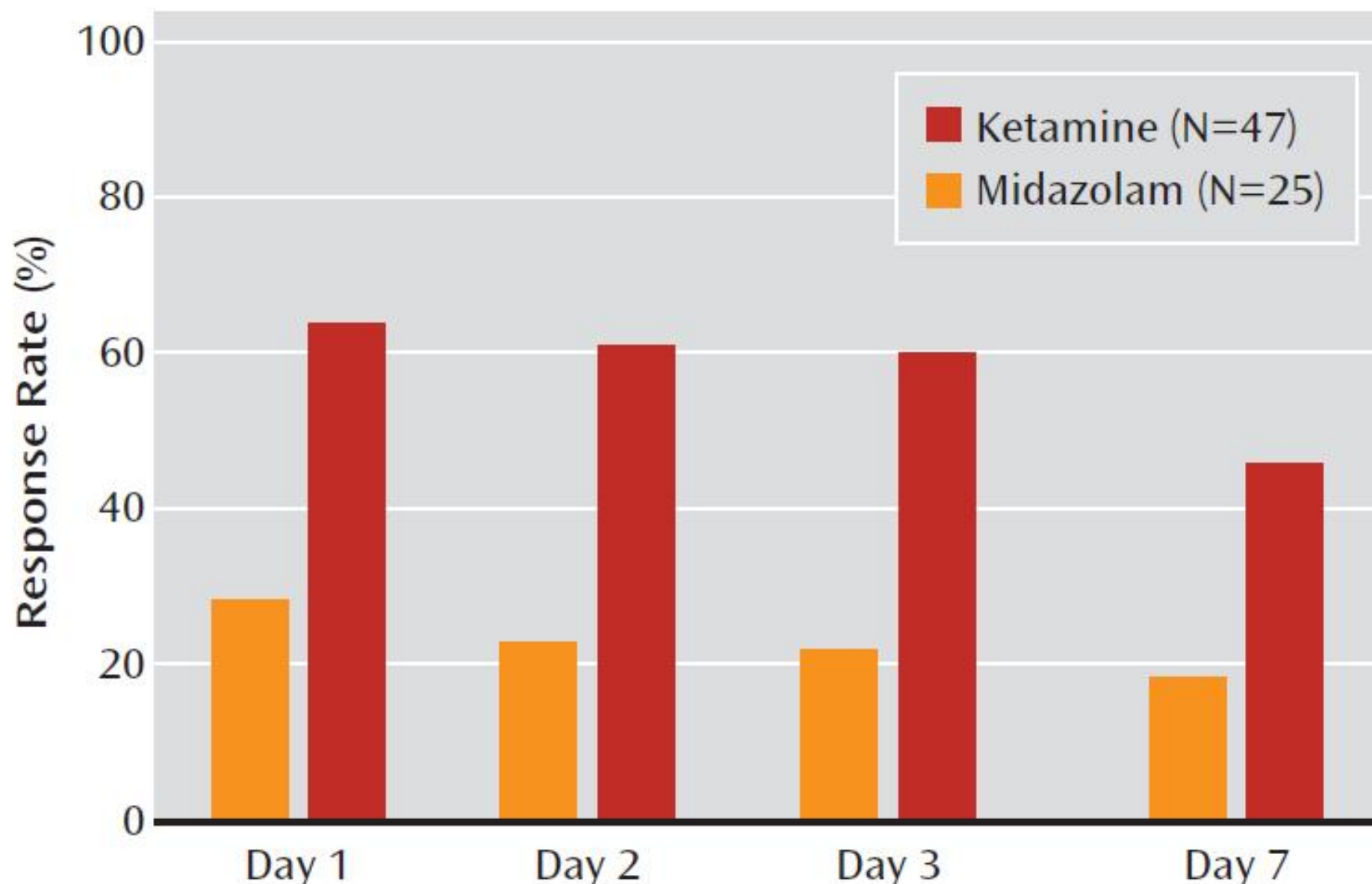
Ketamine in the treatment of depression 2

◆ Effective also for ECT-refractory patients (Ibrahim ym. 2011)

◆ Long-term safety in unknown - our hospital has limited length of treatments to 3 months

◆ In apes, ketamine is neurotoxic in doses > 10 mg/kg (Slikker et al. 2007)

◆ Ketamine abusers have impaired memory (Morgan et al. 2009) and decline of grey-matter volume in DLPFC (Liao et al. 2011)

◆ Main contraindications: previous schizophreniform psychosis, abuse history, blood in urine, risk of pregnancy, psychological incapacity to stand cessation of treatment

Ketamine-dependence and grey-matter decline: particularly right middle frontal gyrus (Liao et al. 2011)

Regions of smaller GM volume in ketamine-dependent group
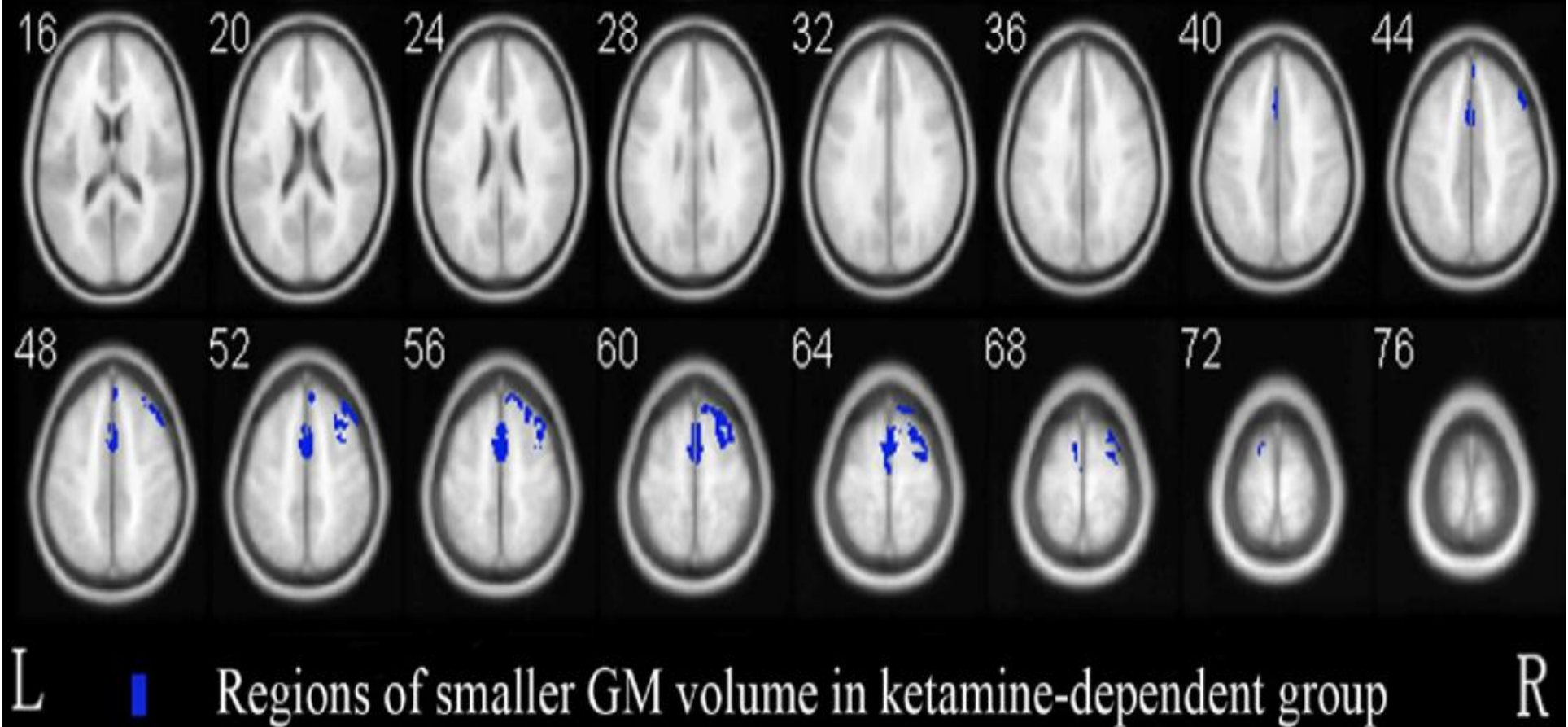
Combinations

◆ Many possibilities, e.g. venlafaxine + mirtazapine + bupropion + psychotherapy + 1 Hz rTMS + ketamine (rTMS and ketamine on different days)

◆ Various combinations may have long-term additive effects (Castren 2013)

◆ Ketamine anaesthesia does not increase the efficacy of ECT (McGirr et al. 2017), but may boost the response (Li et al. 2017) – how about ECT and ketamine on separate days?

Single Ketamine infusion and escitalopram (Hu et al. 2015)
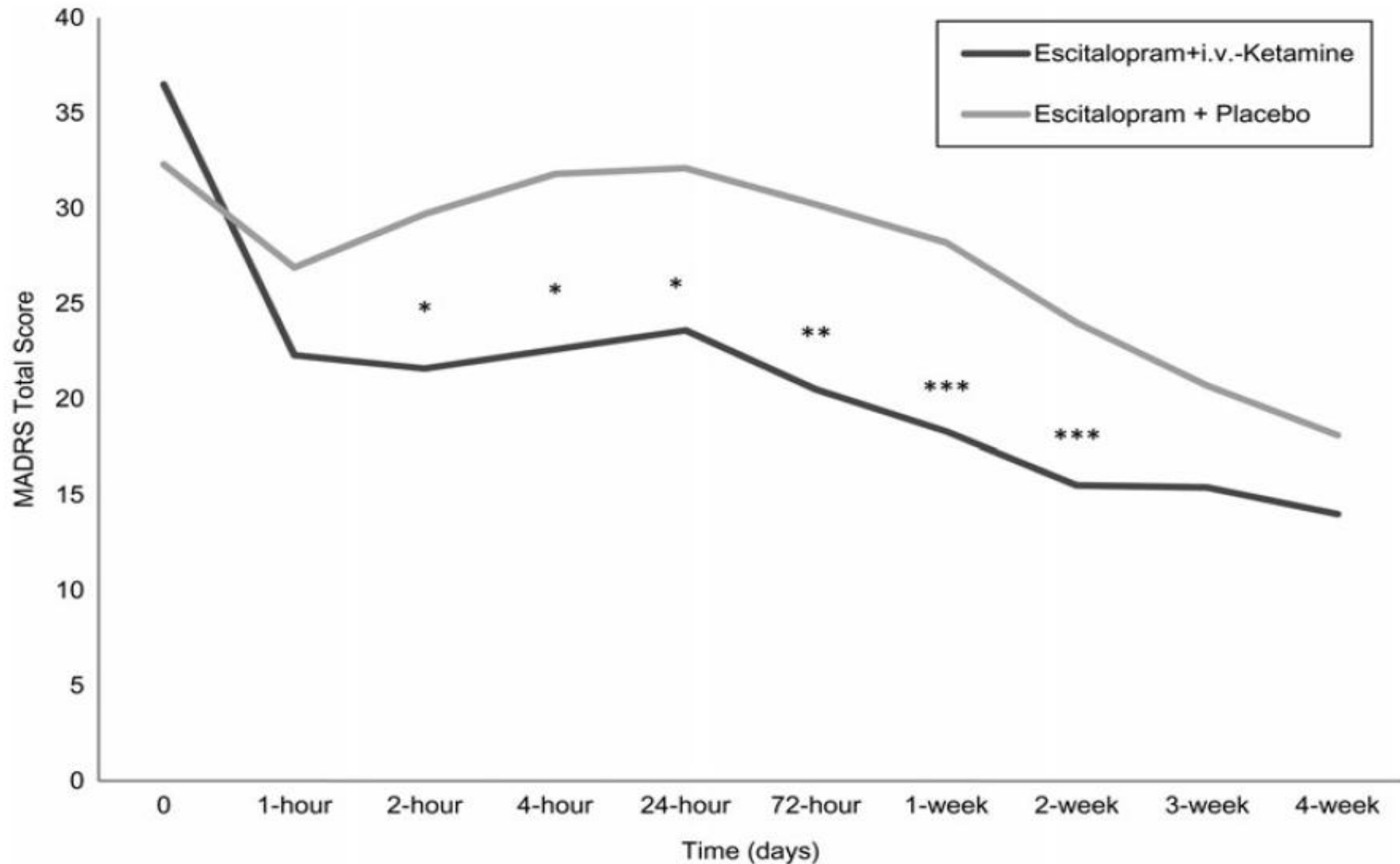
Ketamine anaesthesia does not boost ECT (McGirr et al. 2017)

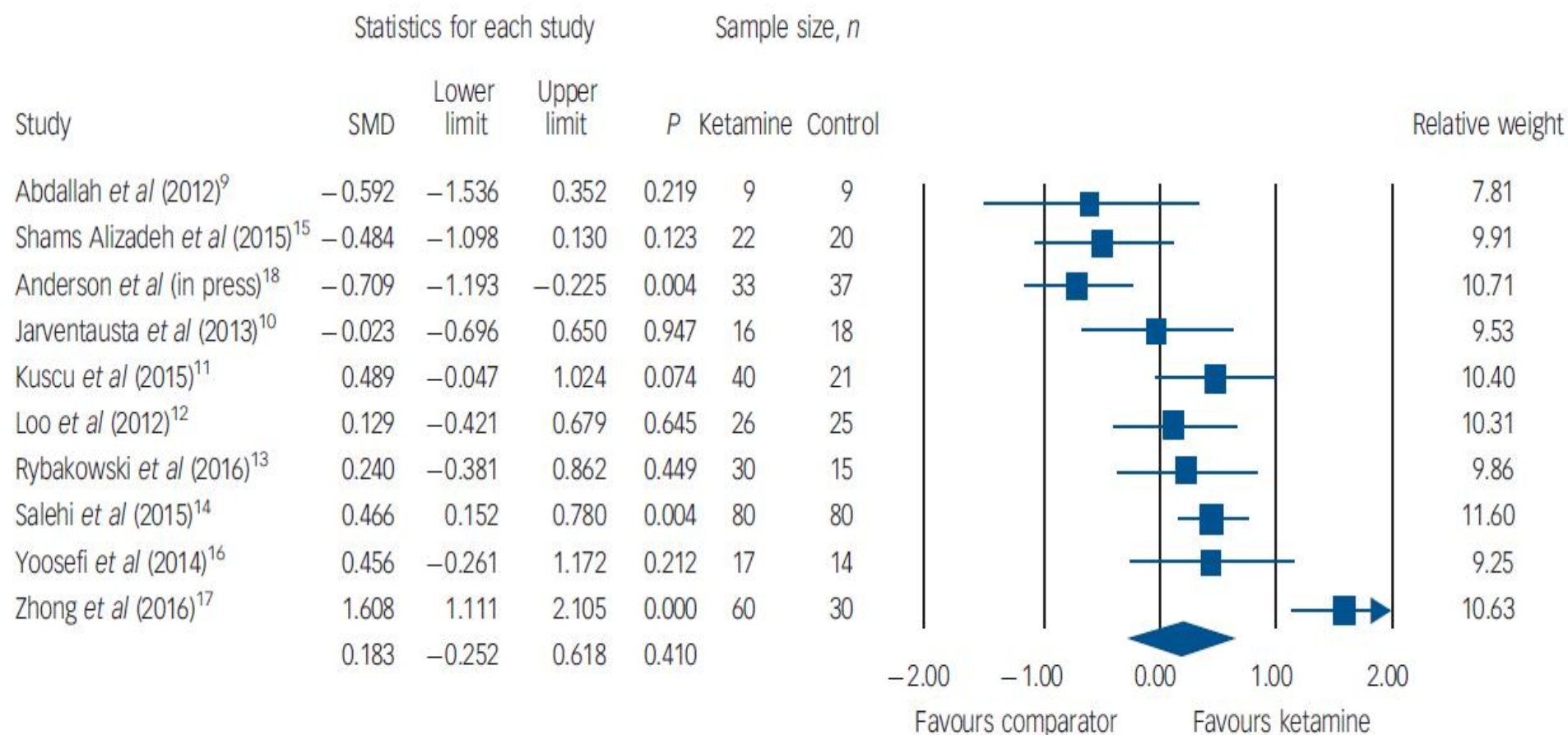| Study	Statistics for each study				Sample size, n			Relative weight
	SMD	Lower limit	Upper limit	P	Ketamine	Control		
Abdallah et al (2012)[9]	− 0.592	− 1.536	0.352	0.219	9	9		7.81
Shams Alizadeh et al (2015)[15]	− 0.484	− 1.098	0.130	0.123	22	20		9.91
Anderson et al (in press)[18]	− 0.709	− 1.193	− 0.225	0.004	33	37		10.71
Jarventausta et al (2013)[10]	− 0.023	− 0.696	0.650	0.947	16	18		9.53
Kuscu et al (2015)[11]	0.489	− 0.047	1.024	0.074	40	21		10.40
Loo et al (2012)[12]	0.129	− 0.421	0.679	0.645	26	25		10.31
Rybakowski et al (2016)[13]	0.240	− 0.381	0.862	0.449	30	15		9.86
Salehi et al (2015)[14]	0.466	0.152	0.780	0.004	80	80		11.60
Yoosefi et al (2014)[16]	0.456	− 0.261	1.172	0.212	17	14		9.25
Zhong et al (2016)[17]	1.608	1.111	2.105	0.000	60	30		10.63
	0.183	− 0.252	0.618	0.410				

Favours comparator   Favours ketamine

Fig. 2 Change in clinician-administered depression rating scores. SMD, standardised mean difference.