Treatment resistant depression: Beyond the basics- exploring old and new treatment options

This webinar will start shortly.

Treatment resistant depression: Beyond the basics- exploring old and new treatment options

Hybrid event – 8 September 2025, 6:00pm – 8:00pm

Acknowledgement of traditional owners

We acknowledge the Tasmanian Aboriginal people as the traditional owners and ongoing custodians of the land on which we are meeting today. We pay our respects to Elders past and present.

We would also like to acknowledge Aboriginal people who are joining us today.

Learning outcomes

After this session, I will be able to:

1. Outline a clinical approach to the assessment and management of treatment resistant depression (TRD).
2. Compare available treatment options for TRD based on efficacy, adverse effects, accessibility, and cost.
3. Identify available public and private sector referral pathways for advice and management of patients with TRD with reference to the Tasmanian HealthPathways.

Some housekeeping

- Tonight's webinar is being recorded
- Please use the Zoom Q&A feature to ask questions
- At the end of the webinar your browser will automatically open an evaluation survey. We appreciate you taking the time to complete this to help us improve our events programme
- Please don't forget to register for your next webinar at: https://www.primaryhealthtas.com.au/for-health-professionals/events/

Continuing Professional Development

2 hours of Educational Activities CPD for participants attending tonight's session live (online and f2f)

(optional) 5 hours of Measuring Outcomes CPD for post-session activity.

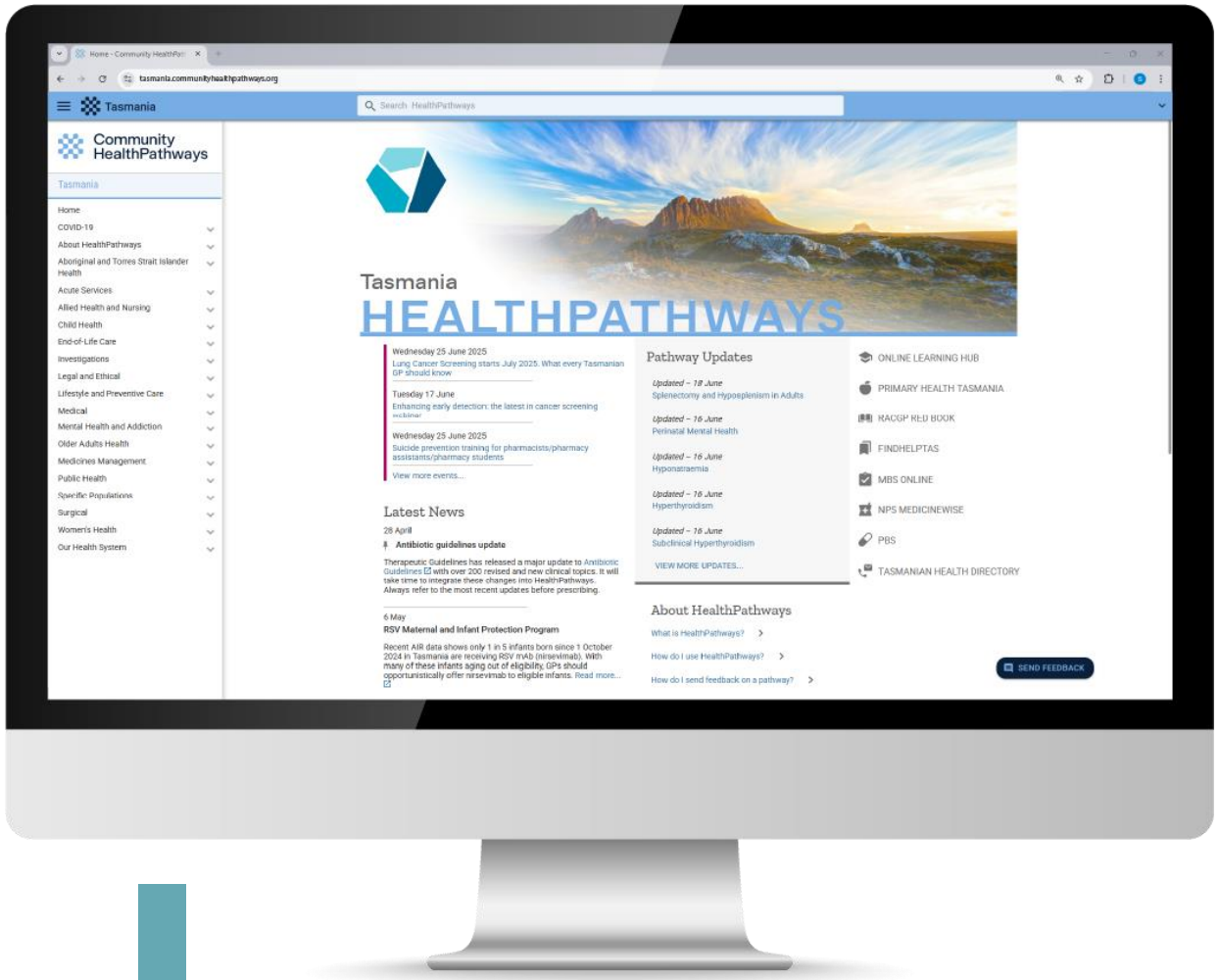
Will be sent after the session via email.

Tasmanian HealthPathways

Tasmanian HealthPathways

is a web-based information portal developed by Primary Health Tasmania. It is designed to help primary care clinicians plan local patient care through primary, community and secondary healthcare systems.

tasmania.communityhealthpathways.org



Tasmanian HealthPathways

Medications for Depression in Adults

See also:

- Depression in Adults
- Medications for Depression in Older Adults
- Medications for Perinatal Depression and Anxiety

Management

1. Aim to use antidepressants as part of a comprehensive management plan at an effective dose to support functionally meaningful recovery, not just remission of symptoms.

   See Depression in Adults for details of non-pharmacological management.

2. Provide patient education.
3. Consider:
   - initial choice of medication.
   - potential adverse effects:
     - Common adverse effects of SSRIs and SNRIs
     - Common adverse effects of tricyclic antidepressants (TCAs)
     - Common adverse effects of mirtazapine
     - Common adverse effects of agomelatine
     - Transient increase in suicidal ideation or behaviour with antidepressants
     - Serotonin toxicity risk
     - QT prolongation risk with some SSRIs and TCAs
     - Bleeding risk with SSRIs and SNRIs
     - Hyponatraemia with SSRI, SNRI, TCA, and Mirtazapine
     - bone density and fracture risk with SSRIs, SNRIs, and TCAs

SEND FEEDBACK

To gain access to HealthPathways, please email
healthpathways@primaryhealthtas.com.au

Presenter:

Prof. Malcolm Hopwood

TRD: Beyond the basics - exploring old and new treatment options

Professor Mal Hopwood

Professorial Psychiatry Unit, Albert Road Clinic

And University of Melbourne

RAMSAY MENTAL HEALTH

People caring for people

RAMSAY HEALTH CARE

THE UNIVERSITY OF MELBOURNE Australia

Background

In Australia:

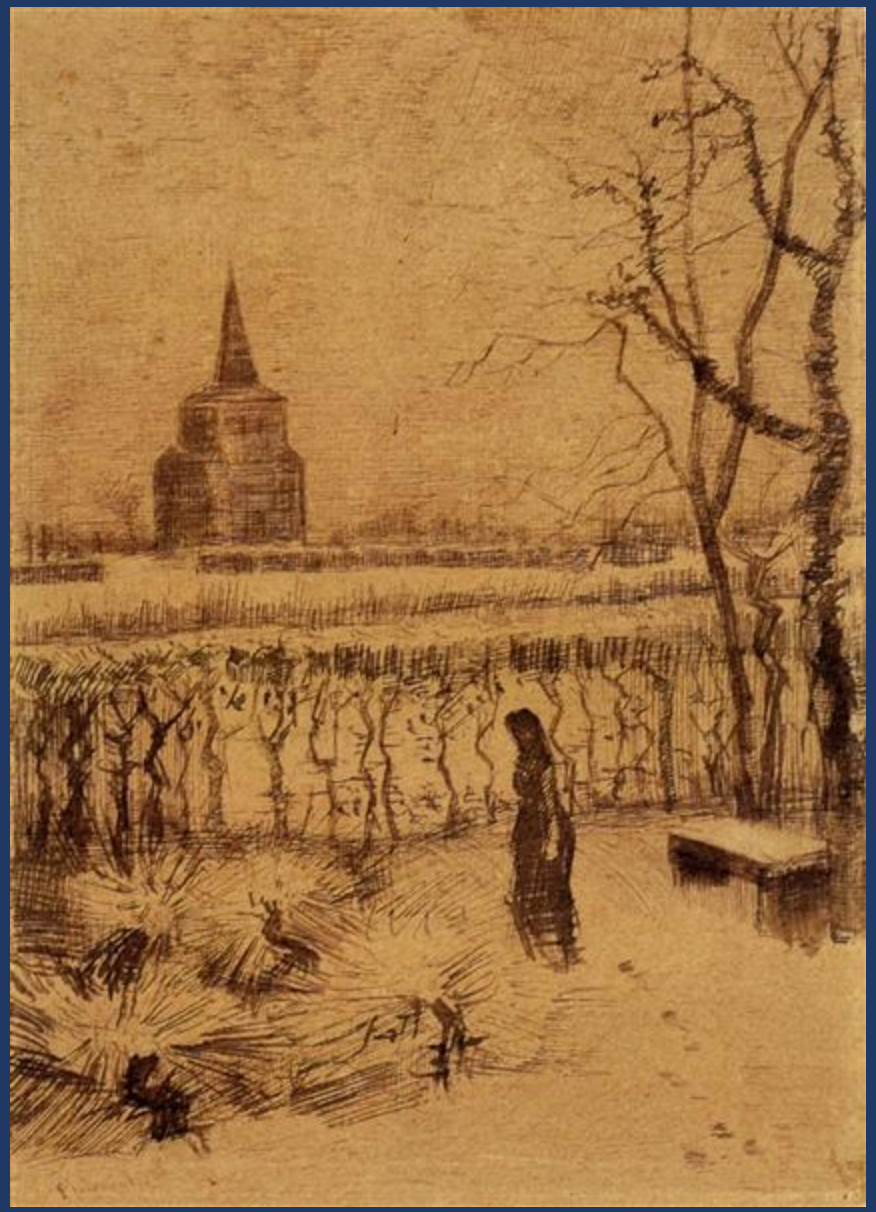
- More than 1.3 million people live with depression
- That is 5.9% of the national population (WHO, 2017)

The proportion of patients with Major Depressive Disorder (MDD) who achieve remission decreases significantly after each treatment failure (Rush, A.J, et al 2006):

- 31% with a second treatment
- 14% with a third
- 13% with a fourth treatment

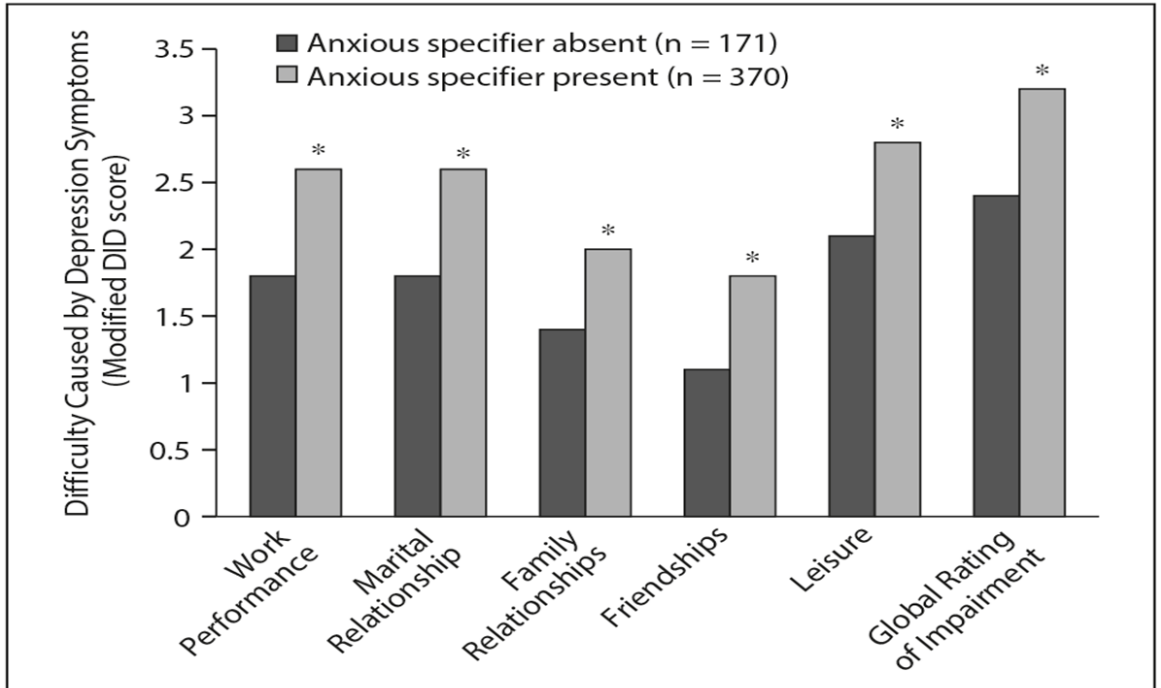
Ramsay Health Care

THE UNIVERSITY OF MELBOURNE Australia



Impact on Functioning

Figure 2. Psychosocial Functioning in MDD Patients Who Did and Did Not Meet the *DSM-5* Anxious Distress Specifier[a]



[a]Data from Zimmerman et al.[8] Scores reflect a modification of the Diagnostic Inventory for Depression (DID) on which patients rated how much difficulty they were having in 6 areas; items were rated from 0 = no difficulty to 4 = extreme difficulty.
*$P < .001$.
Abbreviation: MDD = major depressive disorder.

Ramsay Health Care

THE UNIVERSITY OF MELBOURNE Australia

RANZCP Guidelines

ANZJP

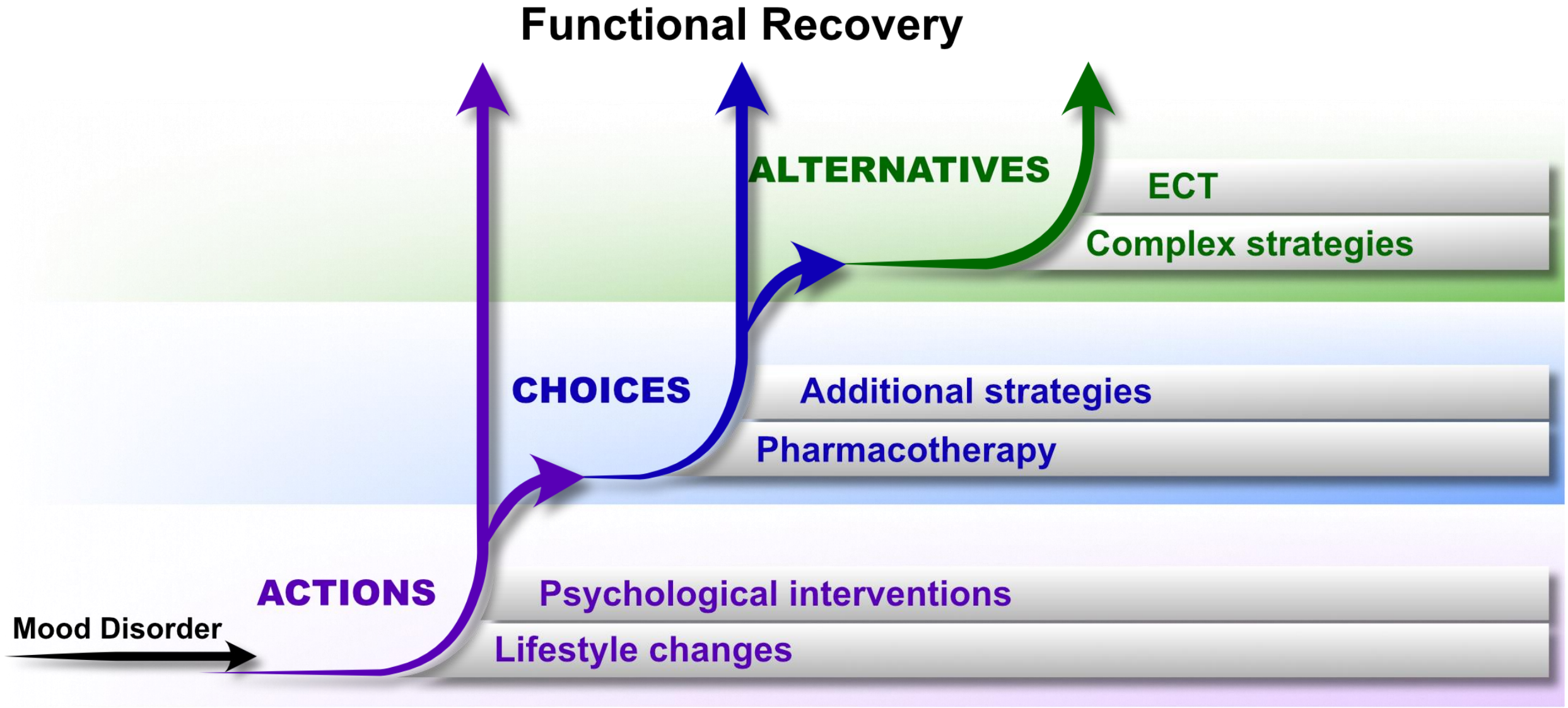
The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders

Australian & New Zealand Journal of Psychiatry
2021, Vol. 55(1) 7–117
DOI: 10.1177/0004867420979353

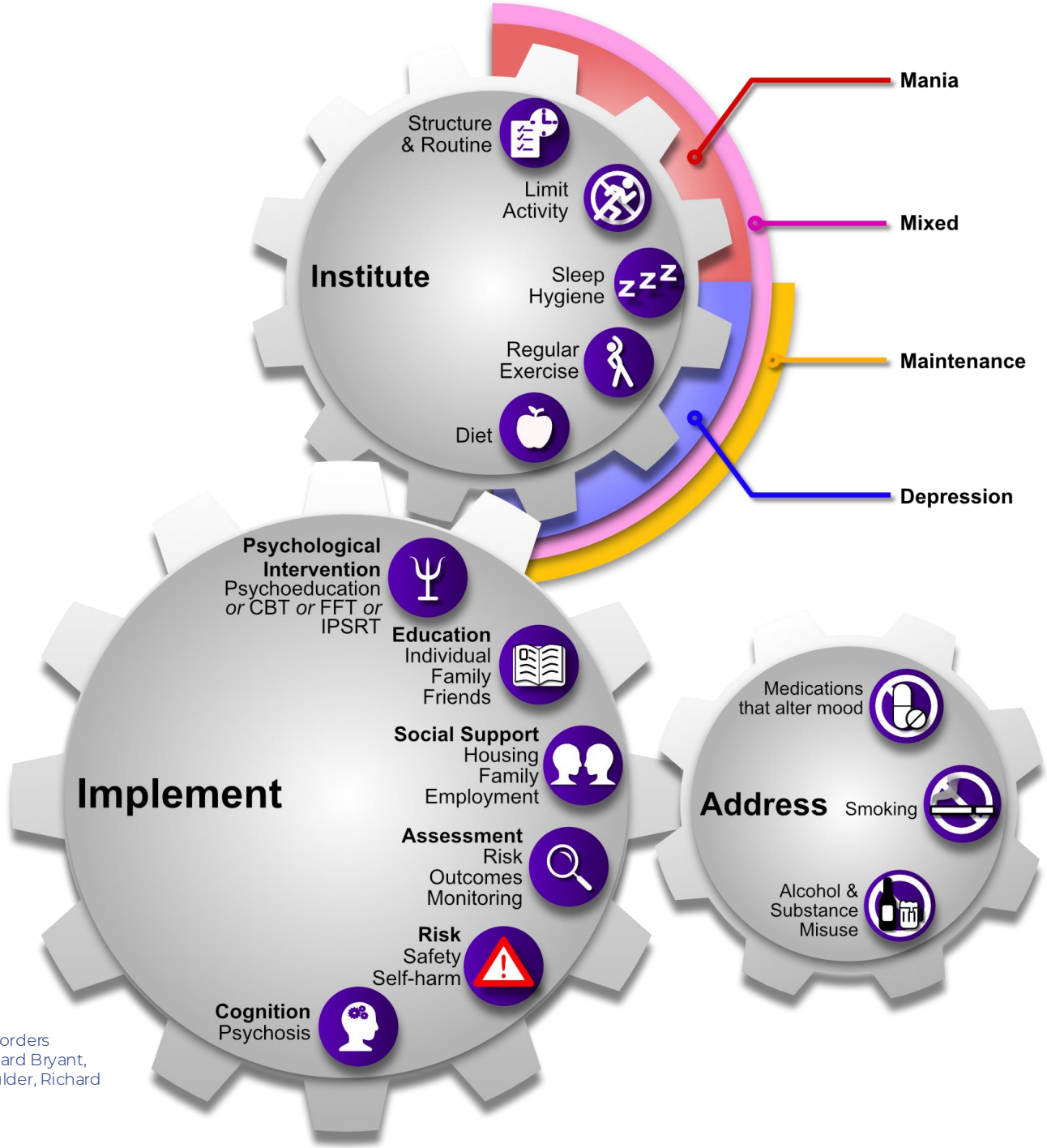
SAGE

Gin S Malhi[1,2,3], Erica Bell[1,2,3], Darryl Bassett[4], Philip Boyce[5,6], Richard Bryant[7], Philip Hazell[6], Malcolm Hopwood[8], Bill Lyndon[1], Roger Mulder[9], Richard Porter[9], Ajeet B Singh[10] and Greg Murray[11]

The Royal Australian & New Zealand College of Psychiatrists


Functional Recovery
ALTERNATIVES
ECT
Complex strategies
CHOICES
Additional strategies
Pharmacotherapy
ACTIONS
Psychological interventions
Lifestyle changes
Mood Disorder

Actions

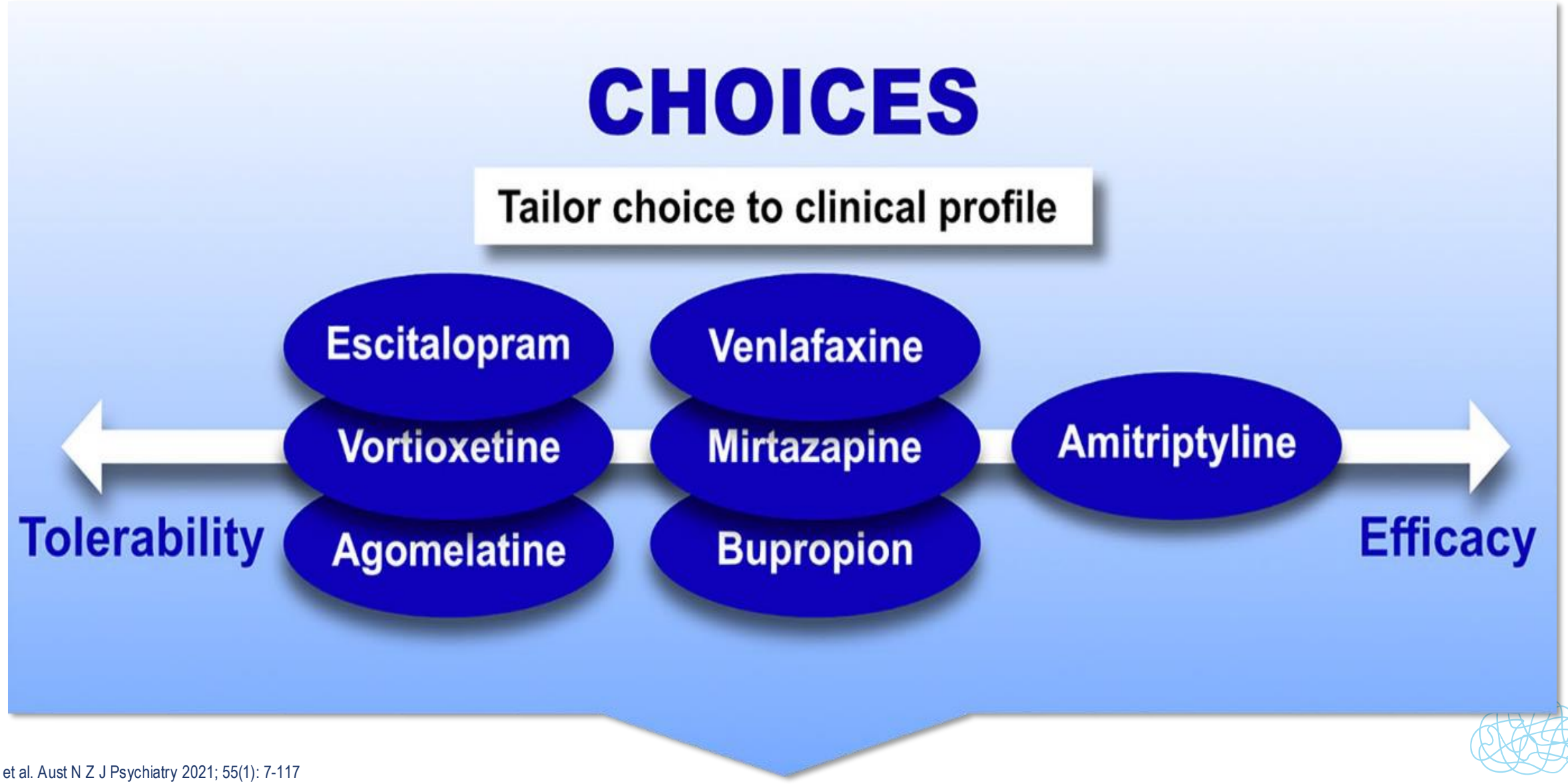


2020 RANZCP Clinical Practice Guidelines for Mood Disorders
Gin S Malhi, Erica Bell, Darryl Bassett, Philip Boyce, Richard Bryant, Philip Hazell, Malcolm Hopwood, Bill Lyndon, Roger Mulder, Richard Porter, Ajeet B Singh & Greg Murray

Combined Psychological and Pharmacological Treatments for Major Depressive Disorder

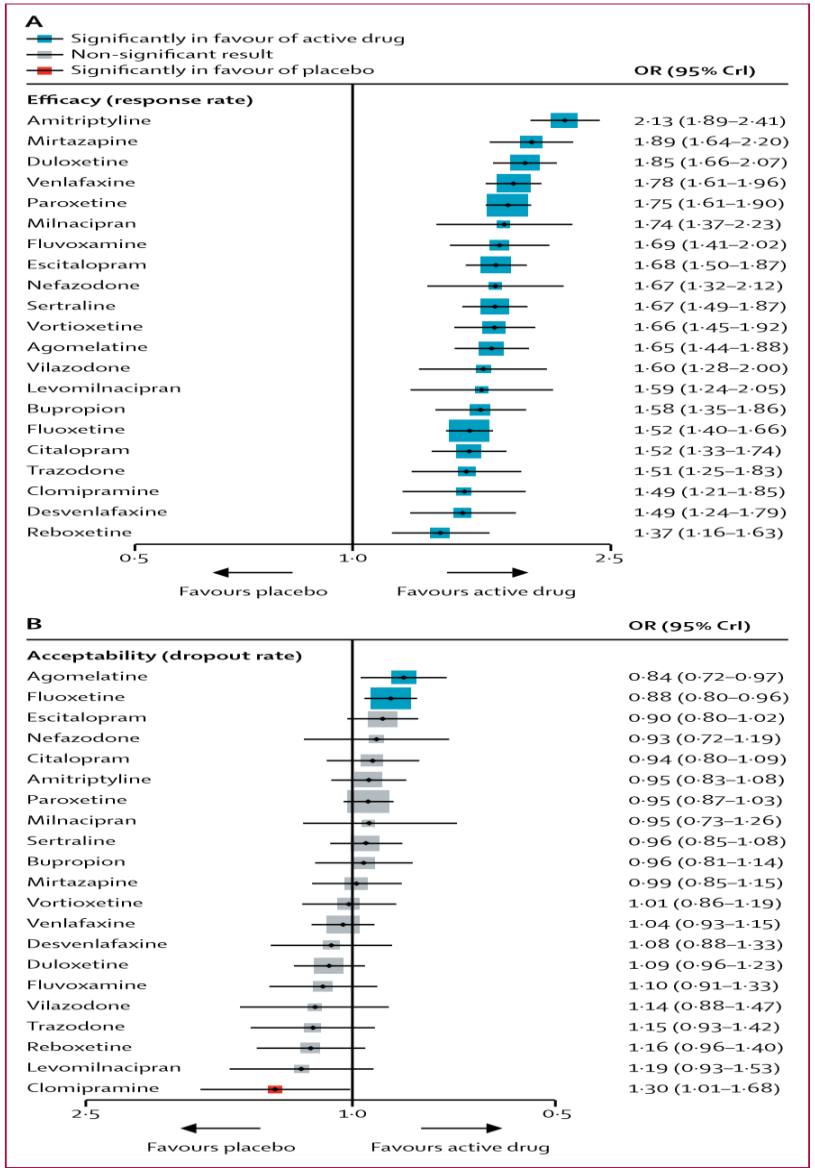
- Consistent evidence that the combination is the most effective strategy
- Adding psychotherapy to antidepressants and antidepressant therapy to psychological therapy in patients who did not achieve remission with either alone

Ramsay Health Care



Malhi G et al. Aust N Z J Psychiatry 2021; 55(1): 7-117

Network Meta-Analysis Cipriani Lancet 2018



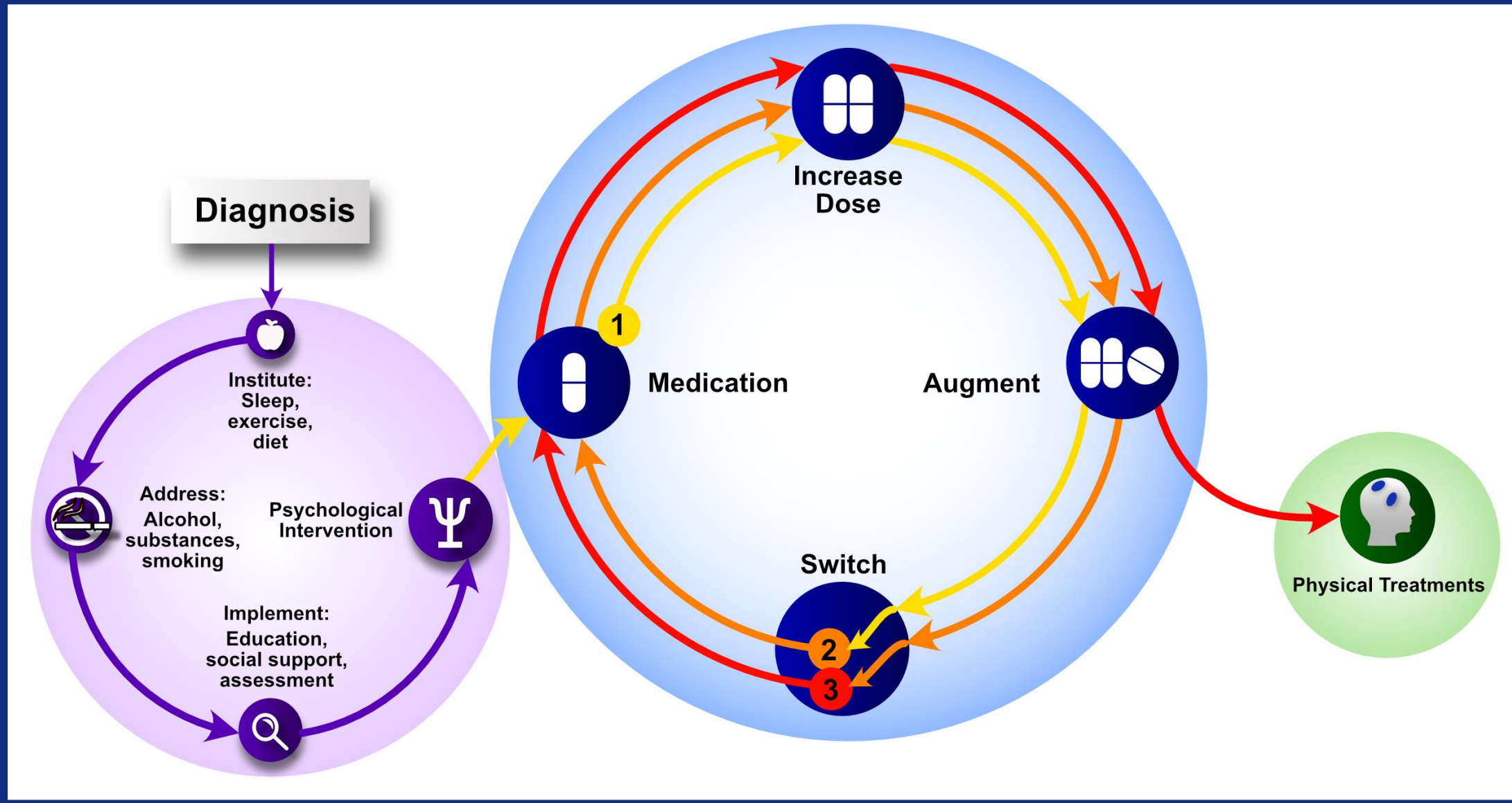
Major Depression – STAR*D Trial

Acute Treatment Outcome

- Remission rates based on QIDS-SR_{16} < 5:
  - Step 1 36.8%
  - Step 2 30.6%
  - Step 3 13.7%
  - Step 4 13.0%

  - Total Remission rate 67%

Rush et al. *Am J Psychiatry* 2006; 163:1905-1917.


Diagnosis
Institute:
Sleep,
exercise,
diet
Address:
Alcohol,
substances,
smoking
Psychological
Intervention
Implement:
Education,
social support,
assessment
Increase
Dose
1
Medication
Augment
Switch
2
3
Physical Treatments

Increasing the Dose?

- What is an ‘adequate dose’ of antidepressant?
- There is little evidence to guide dose rates other than dose ranges recommended in each medicine’s Approved Product Information: randomised controlled trials have not fully explored the dose ranges required in routine clinical practice.

•*Keks et al, 2007*

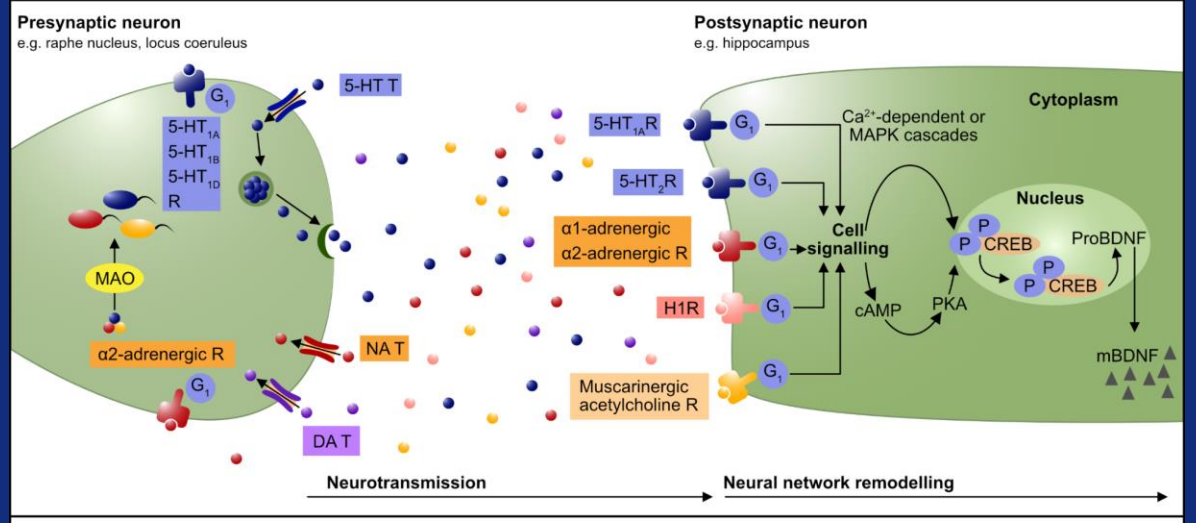
Increasing the duration?

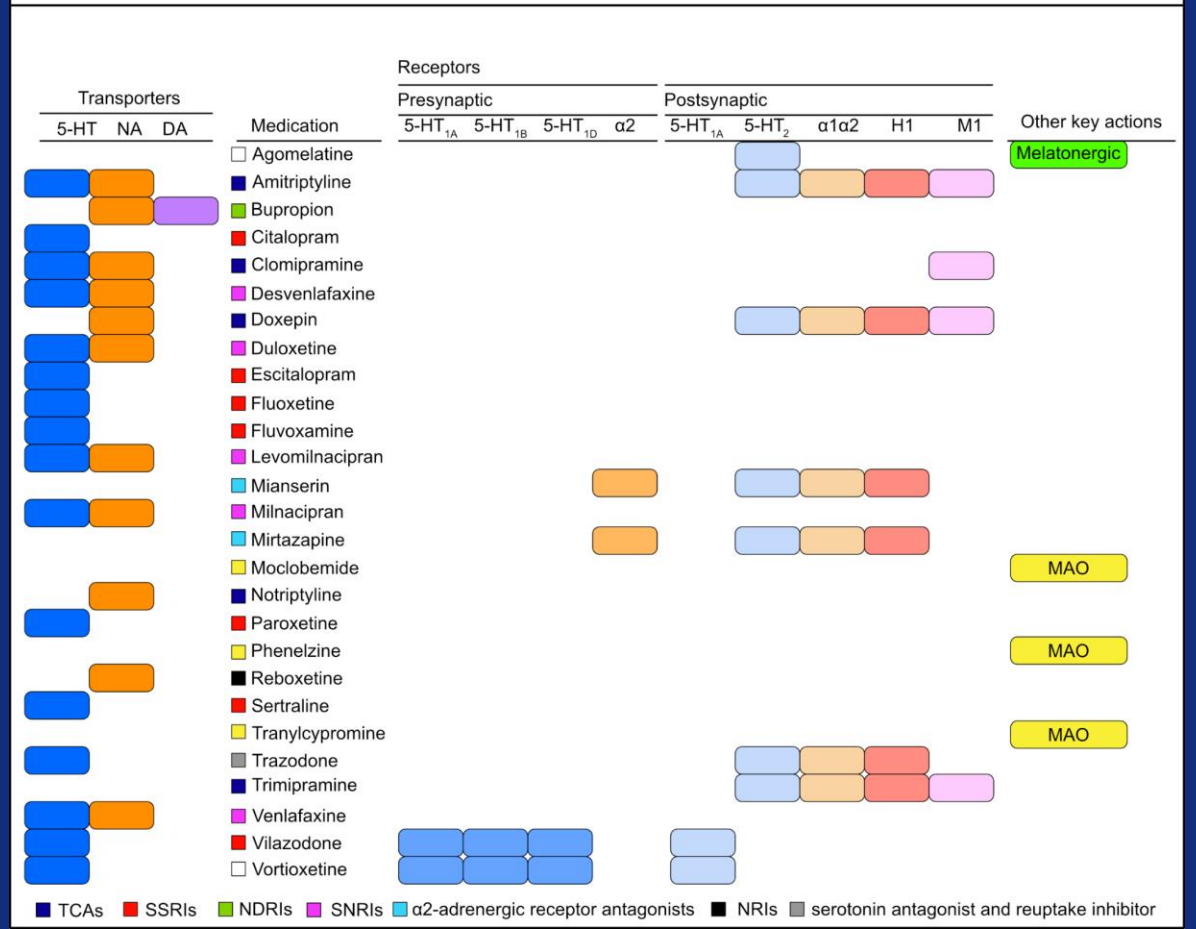
- When can an initial response to an antidepressant be assessed?
  - Malhi et al, 2009: “Usually 2-6 weeks...sometimes longer”
  - Lam et al, 2009 (CANMAT guidelines):
    - Clinical lore suggests a lag time of 2-4 weeks.
    - Recent studies suggest onset can occur in 1-2 weeks.
- But…in STAR*D, a minor improvement observed in the first 4-6 weeks may increase in the subsequent 2-4 weeks.

Switching Antidepressants?

- A common practice, and intuitively seems reasonable. Malhi et al, 2009:
  - Alter antidepressant class if possible.
  - Consider dual-acting agents (eg venlafaxine or duloxetine) if response to an SSRI is insufficient.

- Lam et al, 2009 (CANMAT guidelines):
  - Good response and remission rates in open label studies…but inconsistent evidence from RCTs: “Overall, there is no conclusive evidence to support switching out of class over switching within the class, for SSRI non-responders.”


Presynaptic neuron
e.g. raphe nucleus, locus coeruleus
Postsynaptic neuron
e.g. hippocampus
Cytoplasm
Nucleus
5-HT T
5-HT1A 5-HT1B 5-HT1D R
MAO
α2-adrenergic R
NA T
DA T
5-HT1AR
5-HT2R
α1-adrenergic α2-adrenergic R
H1R
Muscarinergic acetylcholine R
Ca2+-dependent or MAPK cascades
Cell signalling
cAMP
PKA
P CREB
ProBDNF
mBDNF
Neurotransmission
Neural network remodelling

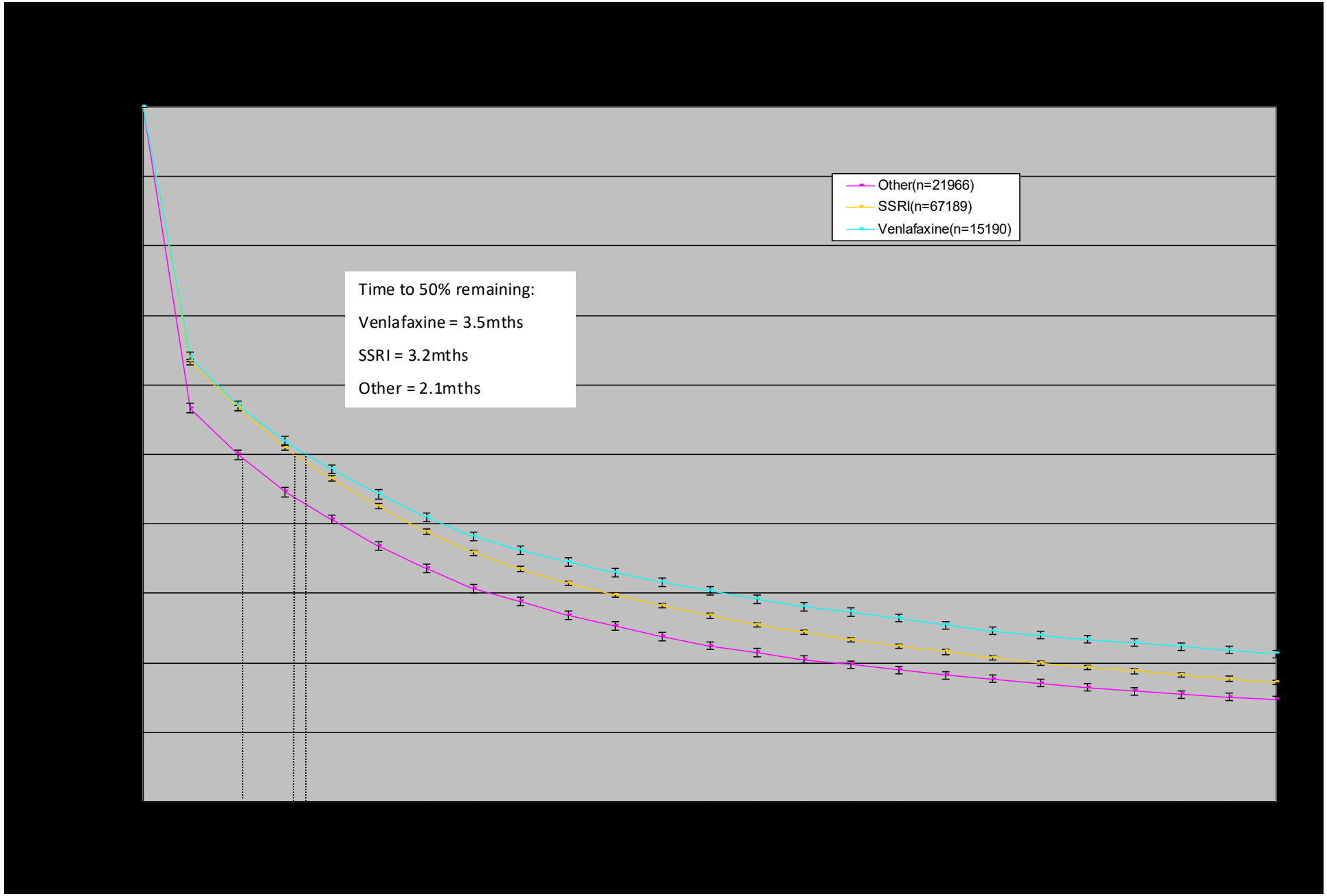

Transporters
5-HT NA DA
Medication
Receptors
Presynaptic
5-HT1A 5-HT1B 5-HT1D α2
Postsynaptic
5-HT1A 5-HT2 α1α2 H1 M1
Other key actions
Agomelatine
Amitriptyline
Bupropion
Citalopram
Clomipramine
Desvenlafaxine
Doxepin
Duloxetine
Escitalopram
Fluoxetine
Fluvoxamine
Levomilnacipran
Mianserin
Milnacipran
Mirtazapine
Moclobemide
Notriptyline
Paroxetine
Phenelzine
Reboxetine
Sertraline
Tranylcypromine
Trazodone
Trimipramine
Venlafaxine
Vilazodone
Vortioxetine
Melatonergic
MAO
MAO
MAO
TCAs
SSRIs
NDRIs
SNRIs
α2-adrenergic receptor antagonists
NRIs
serotonin antagonist and reuptake inhibitor

Combining Antidepressants

- Common, but controversial.
- “The effectiveness of combinations has not been tested against augmentation strategies, and long-term safety has not been established.”

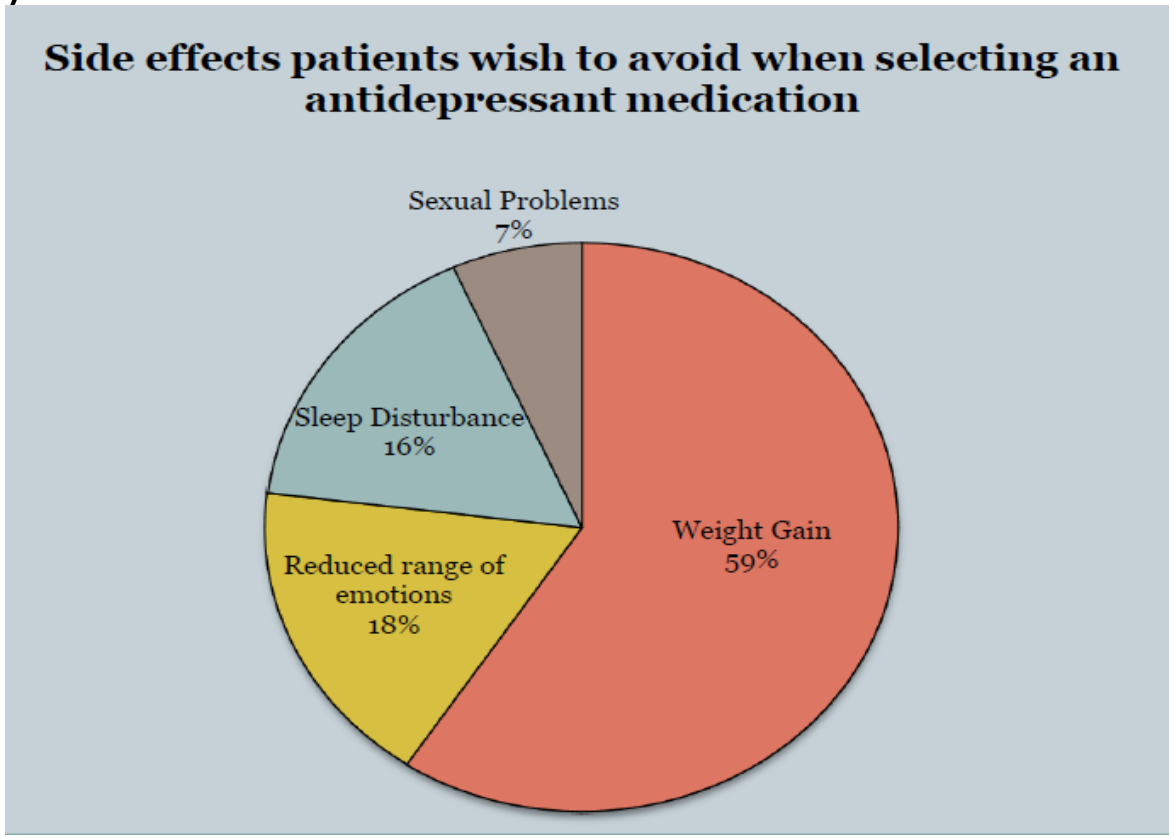
  Keks et al, 2007
- “There is only Level 2 evidence [non-randomised, cohort or case-control studies] to support efficacy of antidepressant combinations in non-responders to monotherapy.”

  Lam et al, 2009 (CANMAT guidelines)


Other(n=21966)
SSRI(n=67189)
Venlafaxine(n=15190)
Time to 50% remaining:
Venlafaxine = 3.5mths
SSRI = 3.2mths
Other = 2.1mths

Results-Patient Preferences

- Most people wanted to avoid weight gain when selecting an ADM (59%).

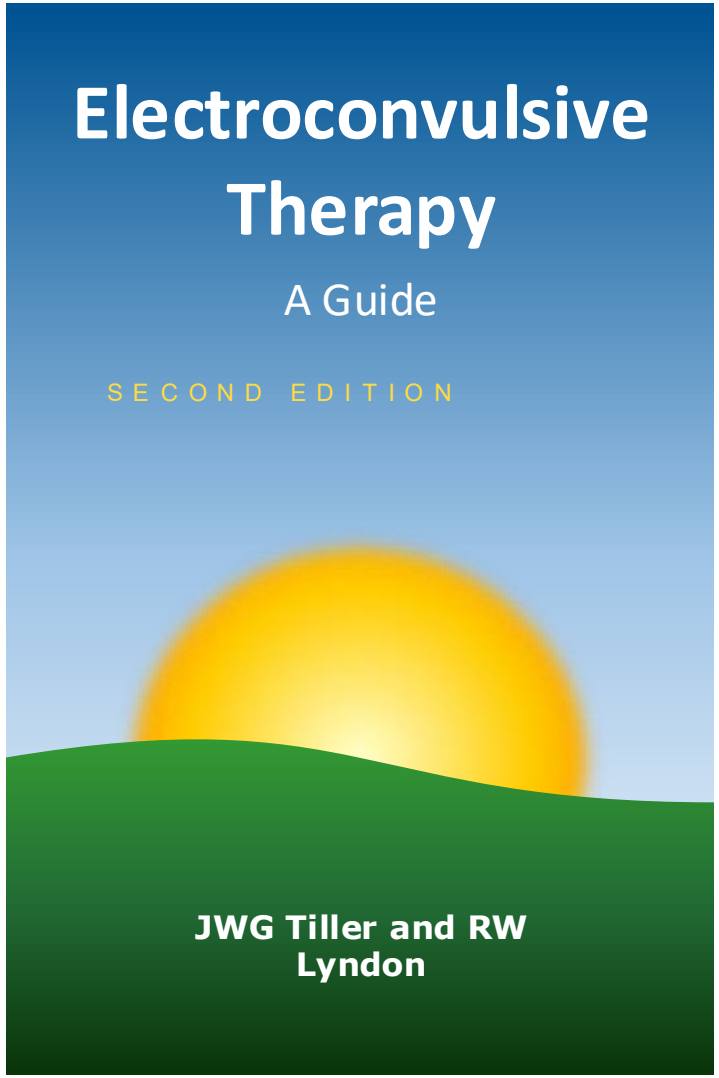


https://thinkgp.com.au/education/clinical-audit-tailor-target-antidepressant-initiation-choice-unlock-positive-patient (accessed 10/01/2018)

Augmenting Antidepressants

- In patients with an inadequate response to antidepressants and psychological therapy, clinical trials support the efficacy of augmenting antidepressants with the agents listed below.
- Evidenced for the treatment of major depressive disorder
  - Lithium
  - Thyroid supplementation (rare in Australia)
  - 2nd-generation antipsychotics:
    - Aripiprazole
    - Brexpiprazole
    - Olanzapine
    - Quetiapine XR
    - Risperidone
    - Ziprasidone


MANAGEMENT OF
MALIGNANT
HYPERTHERMIA
YOU'VE ONLY GOT A FEW MINUTES...
DOSAGE CHECKING
Basic Life Support Flow Chart
READY
35%

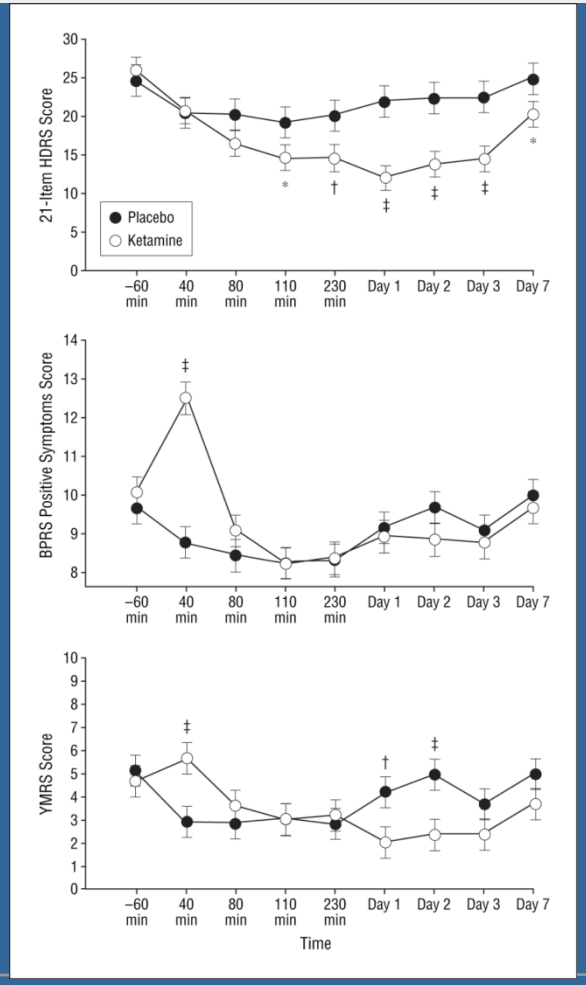


THE UNIVERSITY OF MELBOURNE

ALBERT ROAD CLINIC

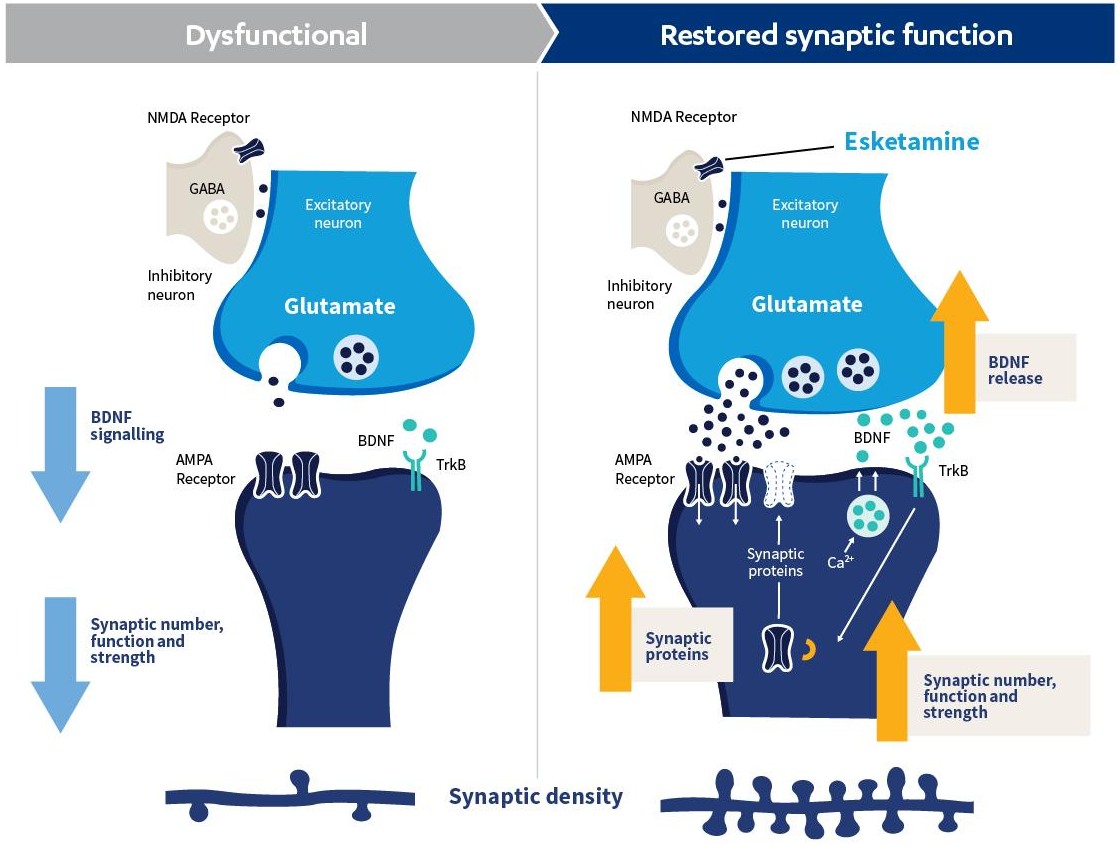
From: **A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression**

Arch Gen Psychiatry. 2006;63(8):856-864. doi:10.1001/archpsyc.63.8.856



Esketamine: A new mechanism of action in MDD

Modulation of glutamate neurotransmission to restore synaptic function[1-5]



Proposed esketamine mechanism of action[1-5]

Evidence suggests that through NMDA receptor blockade, esketamine produces a surge in glutamate release

This surge in glutamate transmission leads to increased AMPA receptor stimulation

AMPA receptor stimulation leads to a release of BDNF, activating downstream neurotrophic signalling to increase synaptic protein synthesis synaptogenesis

Restoring synaptic function

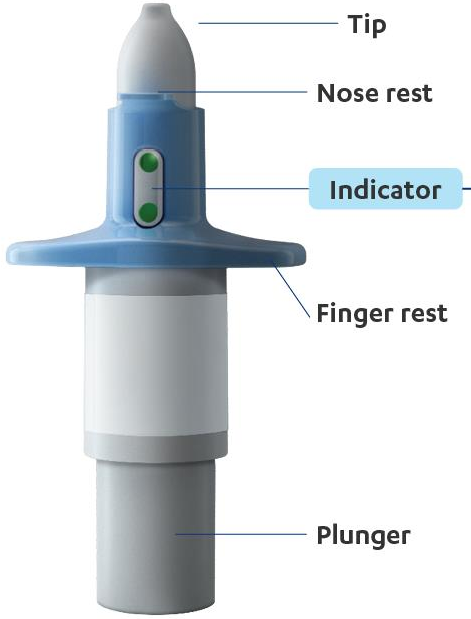
Adapted from Duman RS *et al.* 2016.[4]

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF: brain-derived neurotrophic factor; GABA: gamma-aminobutyric acid; MDD: major depressive disorder; NMDA: N-methyl-D-aspartate; TrkB: tropomyosin receptor kinase B.

References: 1. Murrough JW *et al. Nat Rev Drug Discov* 2017;16:472–486. **2.** Sanacora G *et al. Neuropharmacology* 2012;62:63–77. **3.** Duman RS. *Dialogues Clin Neurosci* 2014;16:11–27. **4.** Duman RS *et al. Nat Med* 2016;22:238–249.**5.** Dale E. *Biochem Pharmacol* 2015;95:81–97.

What does the esketamine nasal spray device look like?[1,2]

Nasal Spray Device

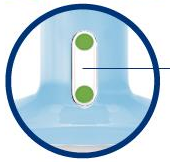


Each device delivers two sprays containing a total of 28 mg of medication.

Indicator

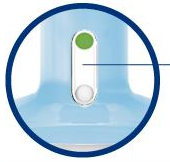
One device contains 2 sprays. (1 spray for each nostril)

2 green dots



Device full

1 green dot



One spray delivered

No green dots
Two sprays (28 mg) delivered

Device empty

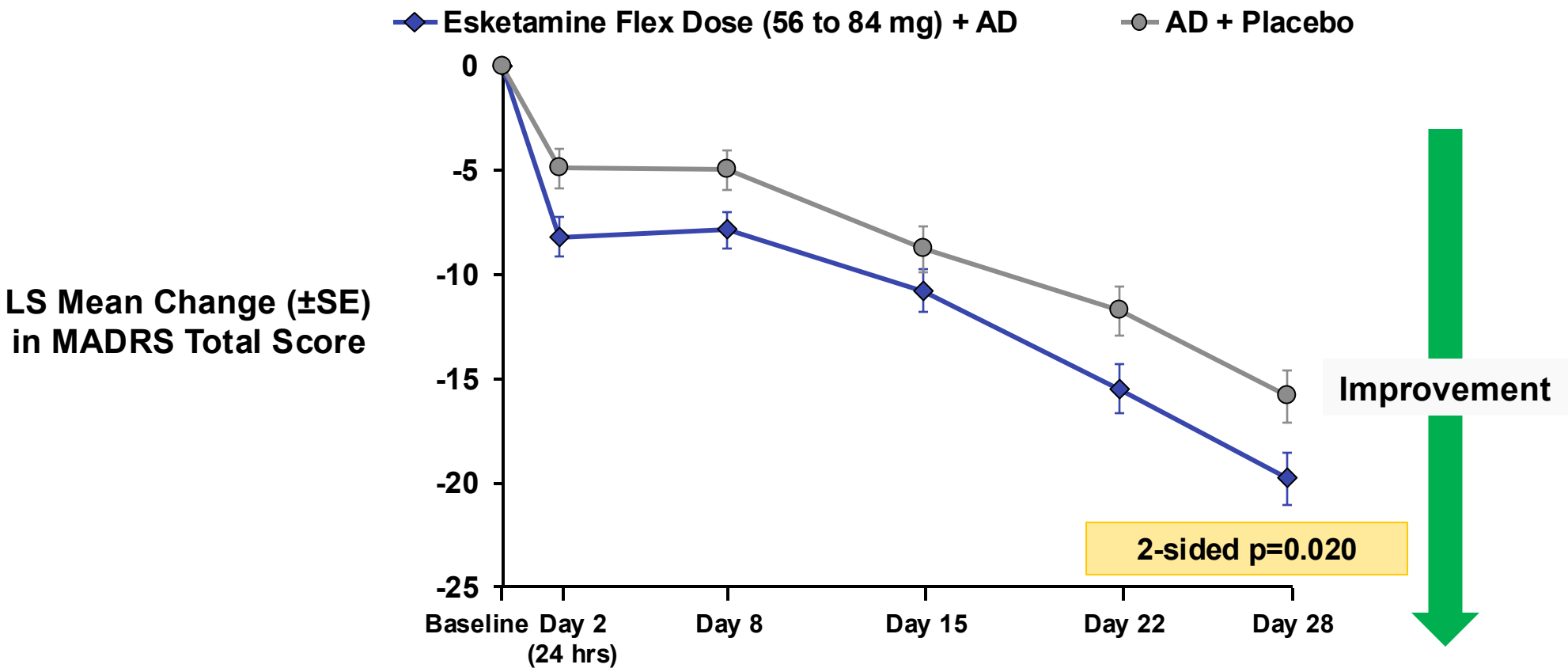
28 mg	=	1 esketamine nasal spray device
56 mg	=	2 esketamine nasal spray devices
84 mg	=	3 esketamine nasal spray devices

AD: antidepressant.

References: 1. Esketamine hydrochloride Approved Product Information. **2.** Esketamine hydrochloride Consumer Medicine Information.

Primary Endpoint: Least Squares Mean Changes in MADRS Total Score Over Time MMRM

TRANSFORM-2 (3002)



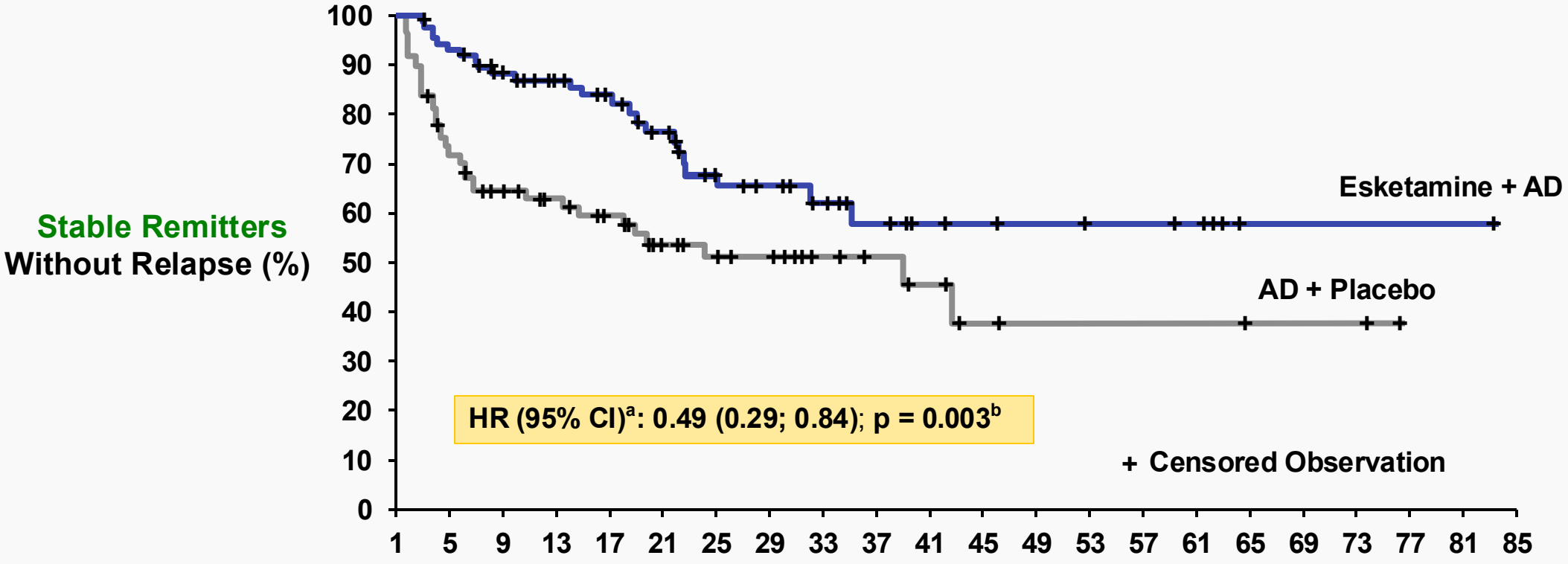
No. of Patients						
Esketamine + AD	114	109	109	107	103	101
AD + Placebo	109	102	105	102	104	100

Most Common Adverse Events (≥5%)
Short-term Phase 3 Studies

	Pooled TRANSFORM-1/2 (Age 18-64)	
	Esk + AD N=346 %	AD + Placebo N=222 %
Total percent of patients with TEAE	87.0	64.4
Nausea	28.3	8.6
Dissociation	26.6	3.6
Dizziness	23.7	6.8
Vertigo	22.5	2.3
Headache	20.2	17.1
Dysgeusia	18.8	13.5
Somnolence	17.3	9.0
Paresthesia	12.4	1.8
Hypoesthesia	11.0	1.4
Hypoesthesia oral	10.7	1.4
Vomiting	9.2	1.8
Vision blurred	9.0	1.4
Anxiety	9.0	5.4
Blood pressure increased	8.7	2.3
Insomnia	8.4	7.2
Fatigue	7.2	5.0

Janssen data on file 2024

Stable Remitters who Remained Relapse Free
SUSTAIN-1 (3003)



Patients at risk																						
Esketamine + AD	89	83	68	56	47	38	28	23	18	14	10	8	7	6	6	5	1	1	1	1	1	0
AD + Placebo	86	62	47	39	32	24	21	19	11	9	7	4	3	3	3	3	2	2	2	0	0	0

a. Hazard ratio and CI are weighted estimates based on Wassmer (2006) and calculated using R
b. Two-sided P-value is based on the final test statistic, which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters

Daly et al. (2019). Efficacy of esketamine nasal spray plus oral antidepressant treatment for Relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA psychiatry*, *76*(9), 893-903.

Improving Treatment – Esketamine

Results at Albert Road:

- 40 patients in total accepted into the EAP (as of Sep 2022)
- 39 (67.5% female; mean age: 44.5yrs) recruited into the QoL study
- referral source: internal (62.5%), external (15.0%), self (22.5%)
- Of the 39, 4 withdrew from treatment before week 16, 27 completed 16 weeks of treatment and 8 are still continuing treatment.

	Baseline score (T1)	Week 16 score (T2)	*p* value
HAM-D	23.3 (± 5.0)	16.0 (±7.2)	<.001

- **28% responders (T1 score reduced by ≥50% at T2)**
- **19% remitters (T2 score <10)**

Ramsay Health Care

THE UNIVERSITY OF MELBOURNE Australia

Key capabilities required to become an approved **SPRAVATO** Treatment Centre

SPRAVATO is a Schedule 8 medicine and is different from other pharmacological therapies currently used to manage treatment-resistant depression.

The key requirements needed to establish an approved SPRAVATO Treatment Centre include:

1 Pharmacy requirements

- An onsite pharmacy or an external pharmacy arrangement that is willing to complete the SPRAVATO Readiness Program
- Ability to dispense direct to the treatment room at time of treatment OR to store SPRAVATO securely in the treatment room*
  - SPRAVATO cannot be dispensed to the patient outside of the treatment room setting
- Locked safe and/or locked cabinet and/or locked drawer (in accordance with Schedule 8 drug regulations) in pharmacy or treatment room to hold SPRAVATO*

2 Facility requirements

- Blood pressure monitoring facilities
  - The patient must have their blood pressure checked prior to the self-administration of SPRAVATO and blood pressure must be reassessed during the post-administration period
- Room/space with chair/bed where patient can recline head to support self-administration of SPRAVATO
- Quiet room for patient to recover post self-administration of SPRAVATO. This can be the same room as above. Patient will need to remain in the clinic until deemed clinically stable to leave

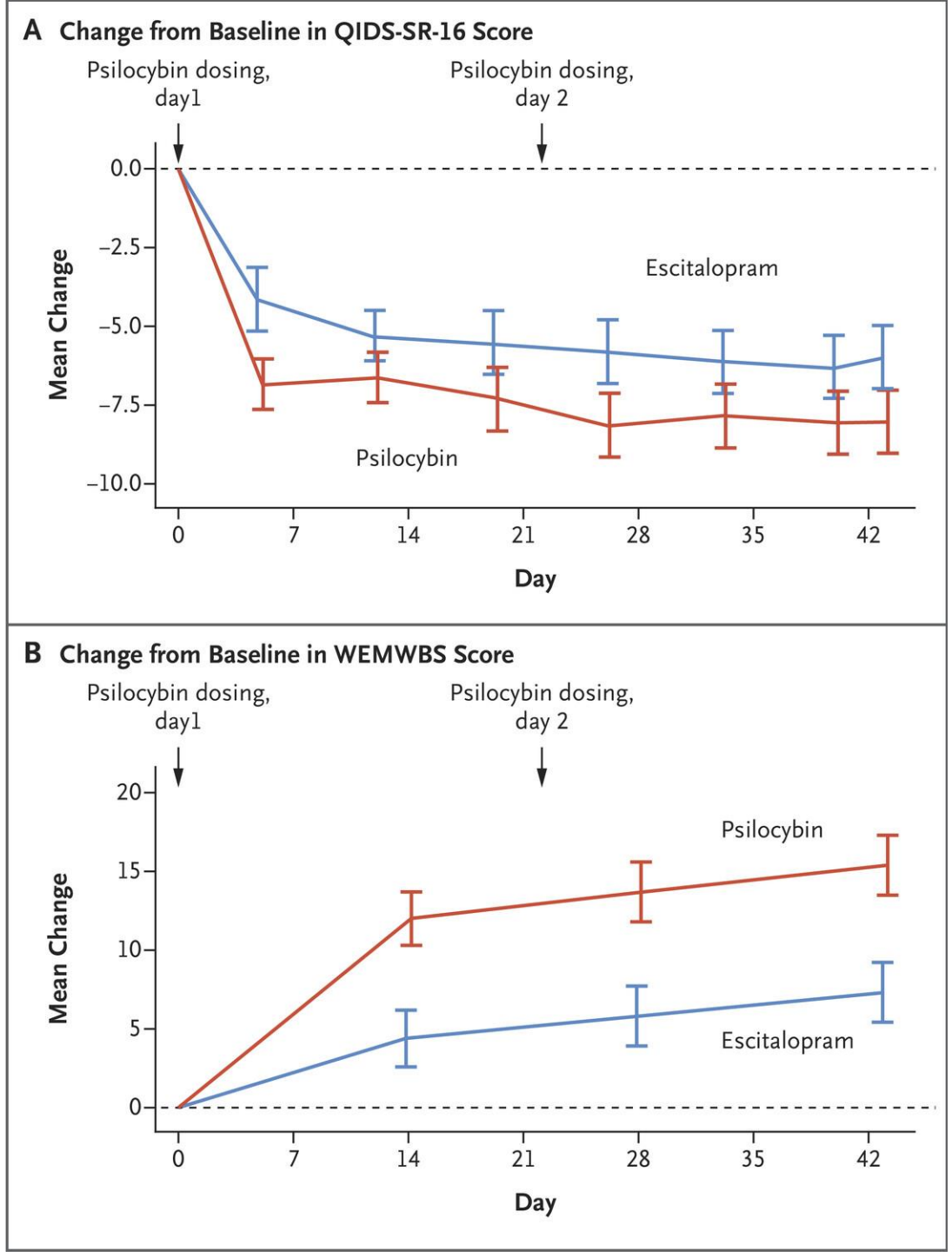
3 Healthcare professionals/ staffing requirements

- In compliance with state health department requirements, SPRAVATO can only be prescribed by a psychiatrist with appropriate credentials† and who has completed the SPRAVATO Readiness Program
- The treatment centre must also have a healthcare professional(s) who can assess the patient's blood pressure, oversee self-administration of SPRAVATO, perform the post-administration monitoring and use their clinical judgement to determine the patient's readiness to leave the clinic

*SPRAVATO is a Schedule 8 medicine and must be stored in accordance with your state regulations. In general this requires storage in an appropriate locked safe/cupboard with pharmacist-controlled access. Expired stock and/or used devices should be disposed of in accordance with your local state and institutional policies. †Local state health departments may have prescribing restrictions/requirements with respect to Schedule 8 medications.

1. SPRAVATO (esketamine hydrochloride) HCP Guide

Spravato® (esketamine) nasal spray



Cathart-Harris et al
NEJM 2021

Evidence for Cannabis/Cannabidiol in Major Depression

-129 patients were identified for inclusion.
-Median PHQ-9 at baseline was 16.0 (IQR: 9.0–21.0).
-There were reductions in PHQ-9 at 1-month (median: 8.0; IQR: 4.0–14.0; $p < 0.001$), 3-months (7.0; 2.3–12.8; $p < 0.001$), and 6-months (7.0; 2.0–9.5; $p < 0.001$).
-Improvements were also observed in GAD-7, SQS, and EQ-5D-5L Index Value at 1, 3, and 6 months ($p < 0.050$).
-153 (118.6%) adverse events were recorded by 14.0% (n = 18) of participants, 87% (n = 133) of which were mild or moderate

Mangoo, S., Erridge, S., Holvey, C., et al. (2022). Assessment of clinical outcomes of medicinal cannabis therapy for depression: analysis from the UK Medical Cannabis Registry. *Expert Review of Neurotherapeutics*, *22*(11–12), 995–1008. https://doi.org/10.1080/14737175.2022.2161894

Conclusions

- Major Depression Must be viewed as a Major Public Health Challenge
- Thoughtfully Guided Treatment is Critical
- Evidence Level is only Adequate for first steps
- Comparative data is lacking
- New Modalities are Needed and Promising but…
  - Evidence base is lower than existing treatments
  - Development is taking a range of pathways
  - Regulatory Bodies and Funders Challenged whilst…
- Patient driven demand escalates

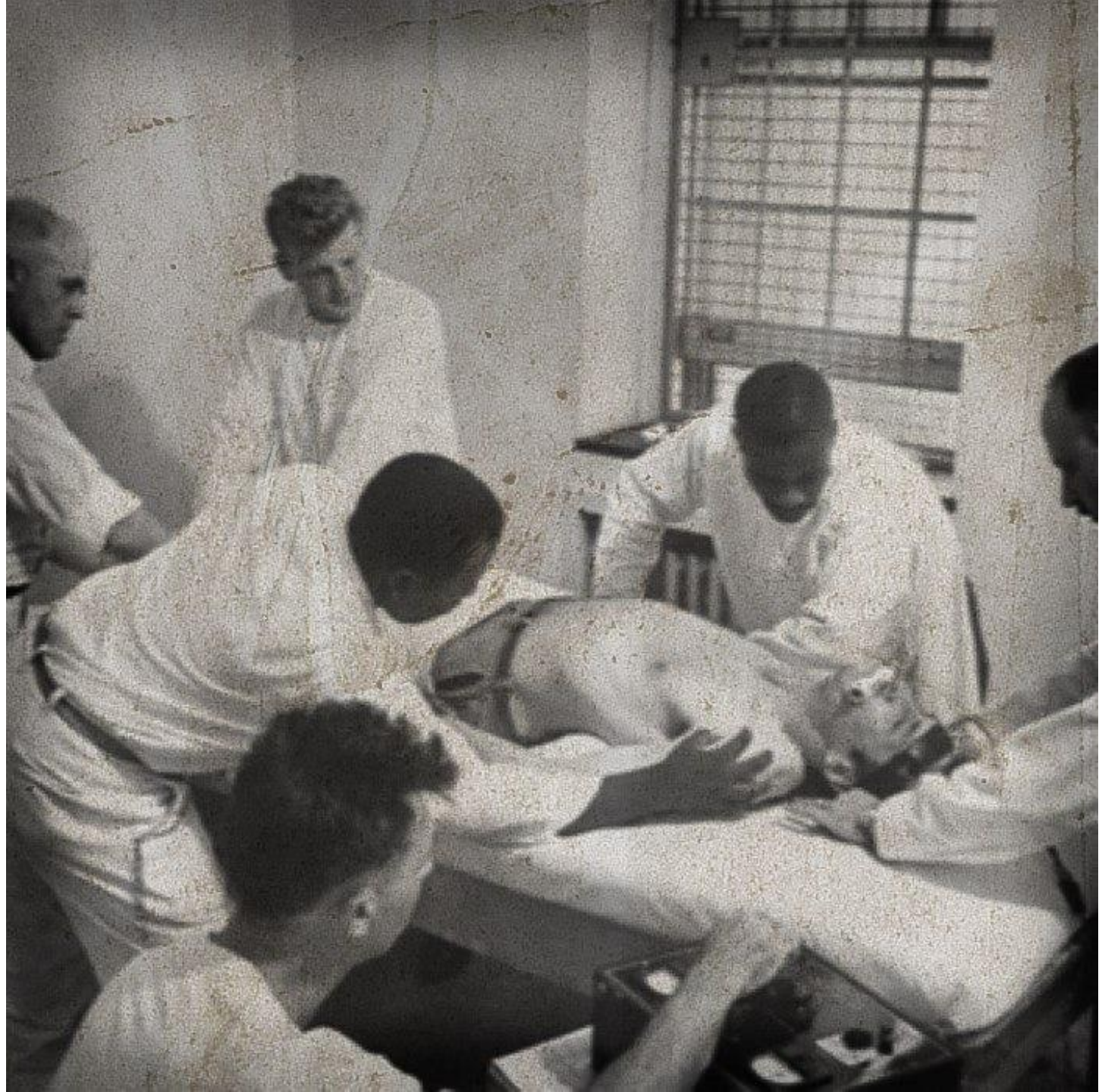
Presenter:

Prof. Saxby Pridmore

Transcranial magnetic stimulation (TMS) – an introduction

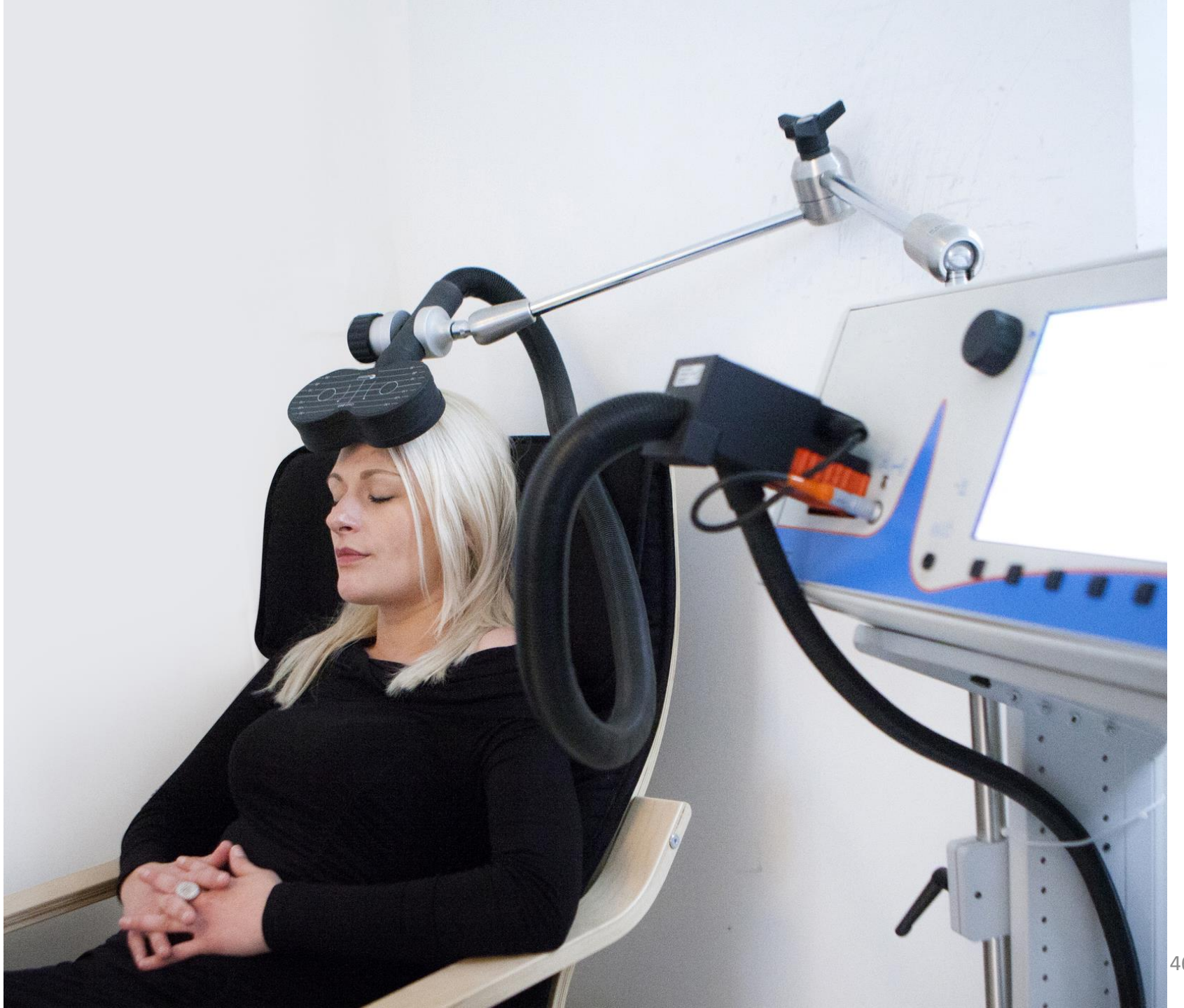
S Pridmore, Y Turnier-Shea, M Rybak

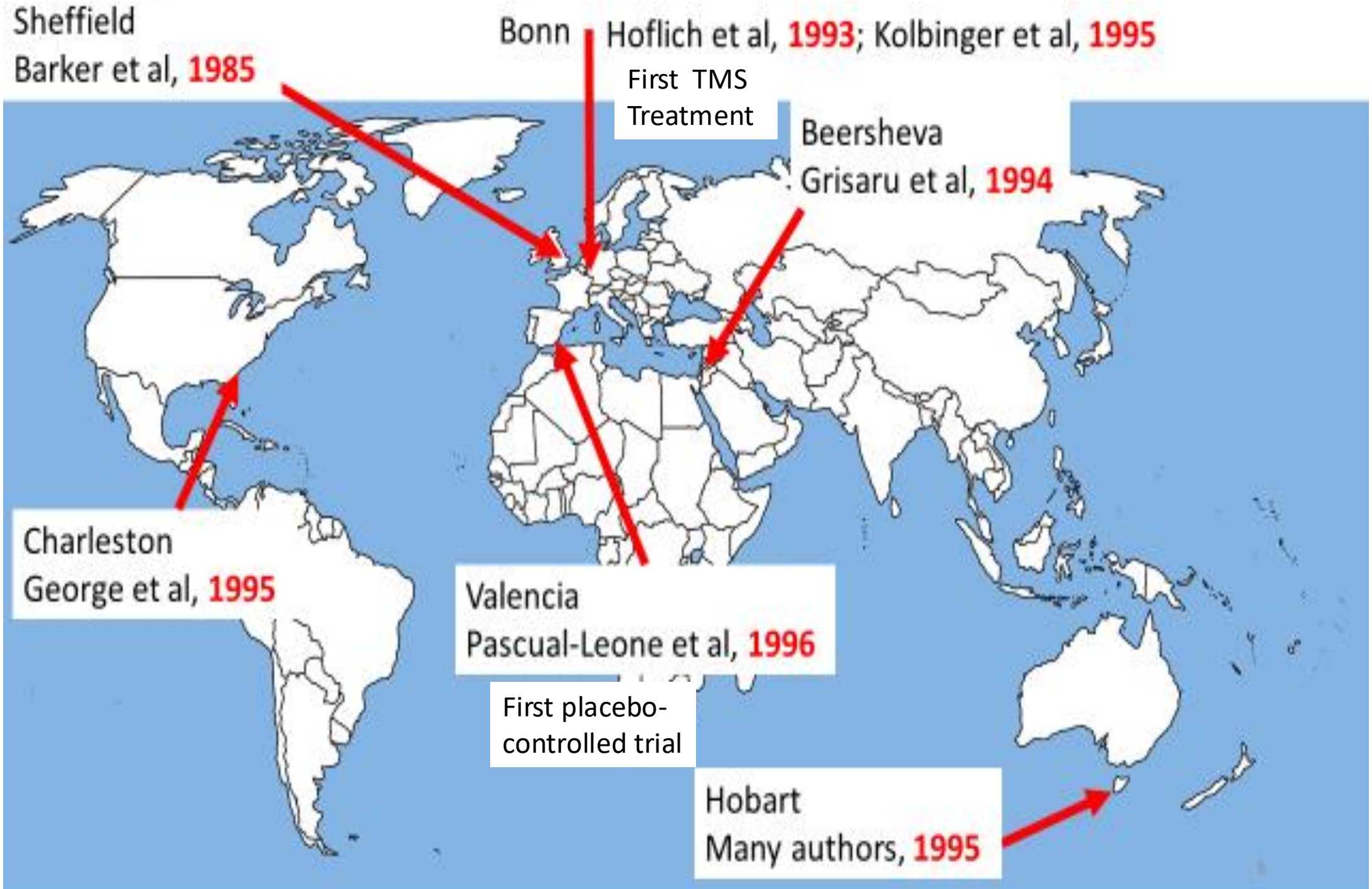
University of Tasmania
and
Hobart TMS (Bellerive)



Transcranial magnetic Stimulation

(TMS)




Sheffield
Barker et al, 1985
Bonn
Hoflich et al, 1993; Kolbinger et al, 1995
First TMS Treatment
Beersheva
Grisaru et al, 1994
Charleston
George et al, 1995
Valencia
Pascual-Leone et al, 1996
First placebo-controlled trial
Hobart
Many authors, 1995

Pioneers

Gottingen, Germany, 1998

German Journal of Psychiatry 1999;2:46-59

Update on psychotropic medication used concurrently with transcranial magnetic stimulation

Yvonne Turnier-Shea, Marzena Rybak, Phil Reid, Saxby Pridmore

Results. 82 patients received 986 treatments. 14 patients were receiving both an antidepressant and an antipsychotic medication. There were no seizures. 24% experienced headache on some occasion during treatment, and 10% took a mild analgesic for headache on some occasion during treatment.

Conclusion. While caution is still necessary, this study shows that it is possible to provide rTMS to patients receiving antidepressants and antipsychotic medications without causing seizure.

German J Psychiatry 2005;8:59-65

An Attempt to Increase the Rate and Magnitude of the Antidepressant Effect of Transcranial Magnetic Stimulation (TMS). A Pilot Study

M. Rybak, R. Bruno, Y. Turnier-Shea, S. Pridmore

An attempt to increase the rate and magnitude of the antidepressant effect of rTMS by providing
- fast frequency rTMS to the left prefrontal cortex (LPFC)
- followed by slow frequency TMS to the right (R)PFC at each treatment session.

10 treatments of 25 trains of 20Hz rTMS for 2 secs. to the LPFC
followed by 200 1Hz rTMS to the RPFC

- not clinically superior to the 10 treatments of 30 trains of 20Hz rTMS for 2 secs. to the LPFC
followed by 200 placebo 1Hz to the RPFC.

Rate of acute remission and probability of sustained benefit at each level of STAR*D

Sackheim H. Brain Stimulation 2016; 9: 313-319.

	Acute remission rate	Probability of sustained benefit
Level 1	36.8%	25.7%
Level 2	30.6%	13.7%
Level 3	13.7%	4.9%
Level 4	13.0%	3.8%

Sequenced Treatment Alternatives to Relieve Depression

Journal of Affective Disorders 277 (2020) 65–74

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation

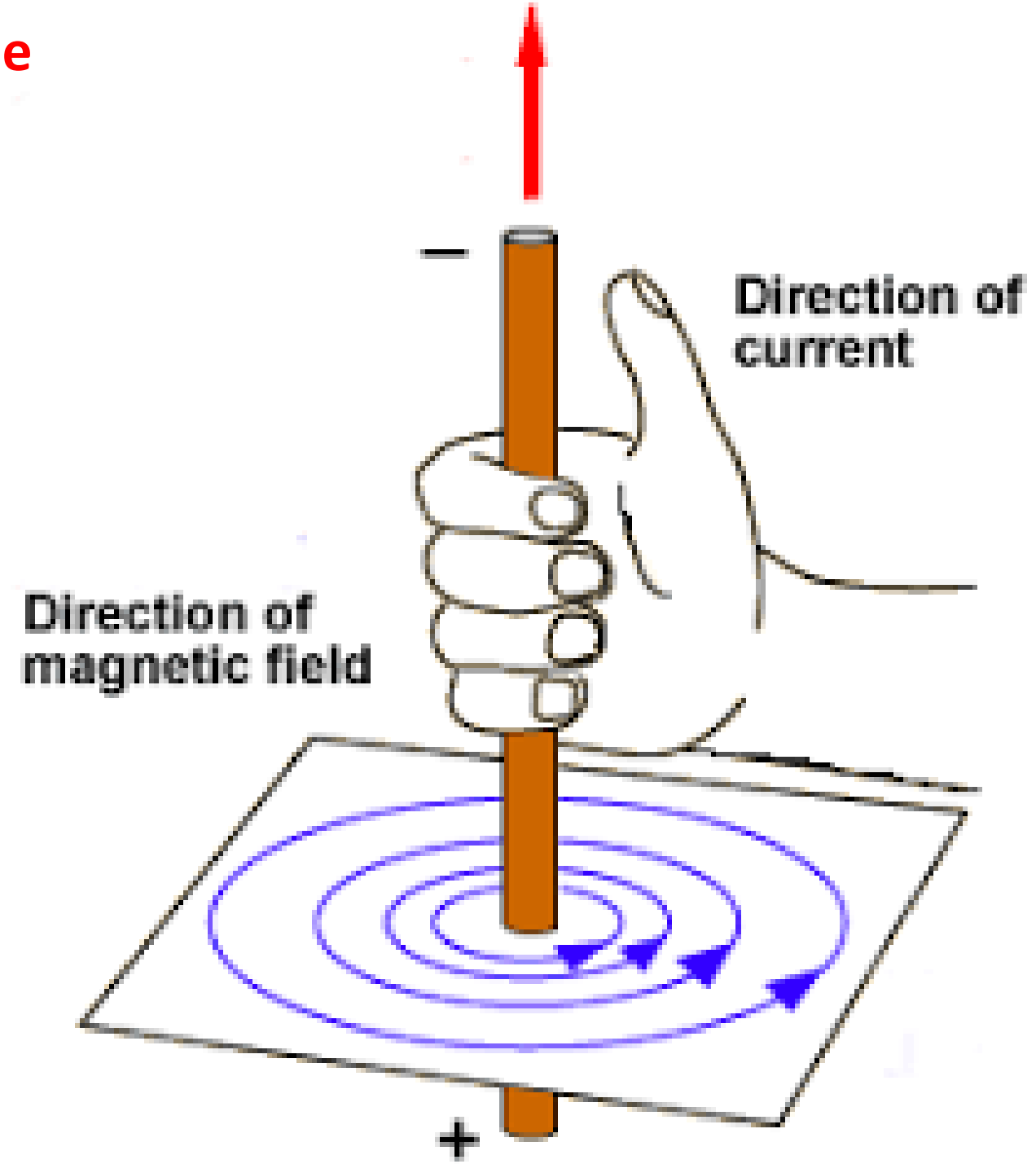
Harold A. Sackeim[a,*], Scott T. Aaronson[b], Linda L. Carpenter[c], Todd M. Hutton[d], Miriam Mina[e], Kenneth Pages[f], Sarah Verdoliva[g], W. Scott West[h]

Clinical outcomes

Response: 58-83%

Remission: 28-62%

The Right-Hand Rule



THE TRANSFORMER

The transformer, as most commonly used, is a simple device for changing the voltage in alternating current circuits. A **step-down** transformer reduces the voltage, while a **step-up** transformer increases it.

In principle, the transformer consists of two coils wound side by side on a soft-iron core, and insulated from one another (see fig. 37.23).

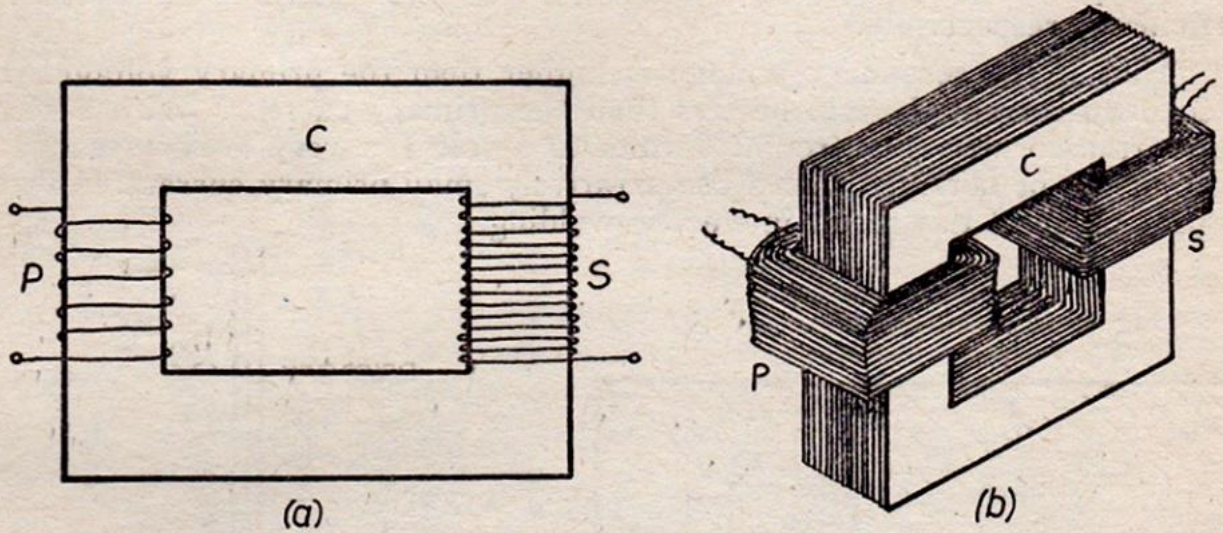


Fig. 37.23. A simple transformer.

The coil, P, which is connected to the supply of A.C., is called the **primary coil.** The other coil, S, from which an alternating current at a different voltage may be drawn, is called the **secondary.** Since the current flowing in both the primary and secondary coils is alternating, the iron core, C, must be laminated to reduce eddy current losses.

As the alternating current flows in the primary coil, it sets up a magnetic field. This field strongly magnetises the iron [illegible] through the secondary coil, S, and as the [illegible] magnetic field vary with the primary current, an alternating E.M.F. is induced in the secondary.

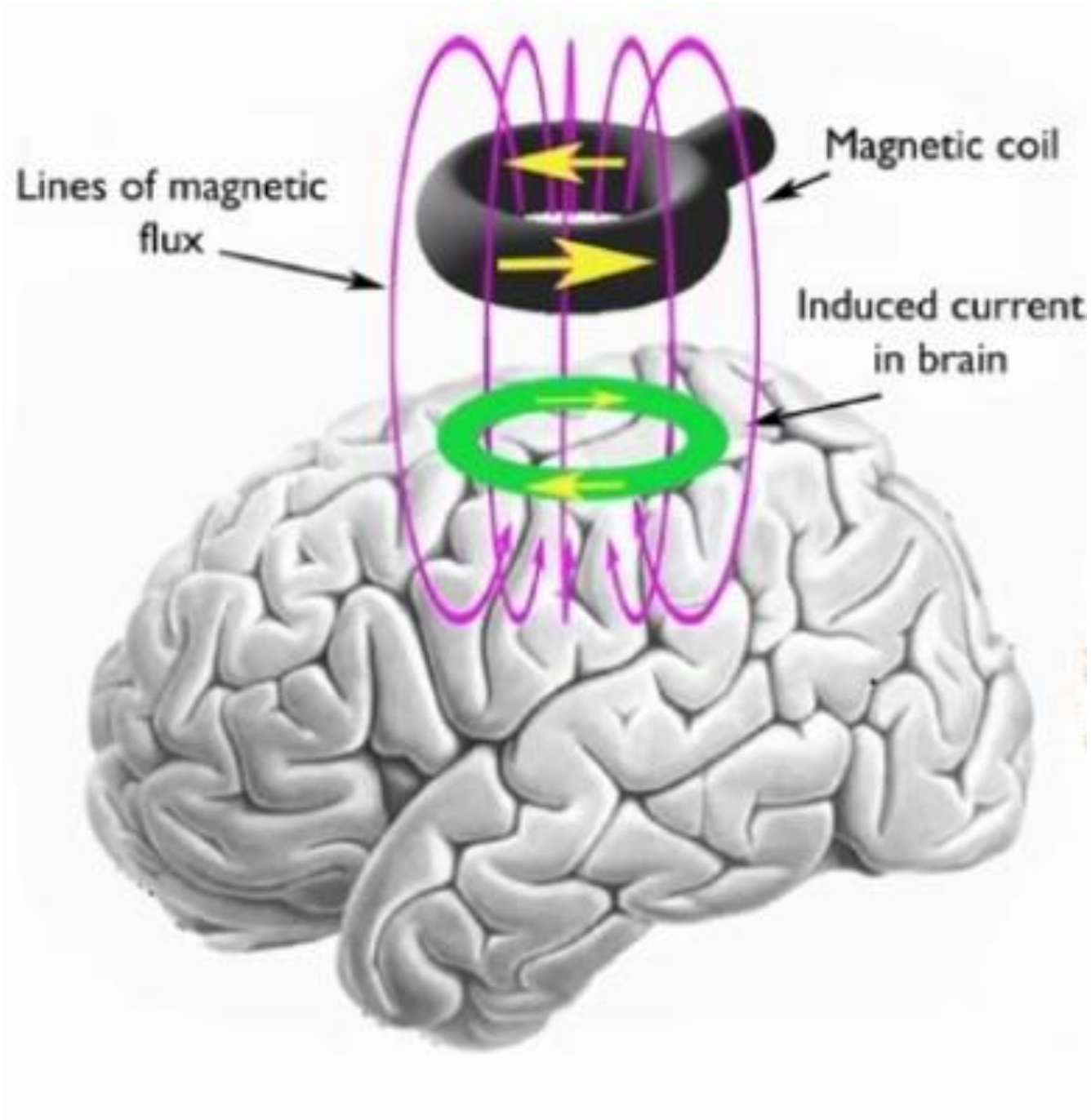
It is found that the change in voltage produced by the transformer is determined by the ratio of the numbers of turns of wire in the two coils.

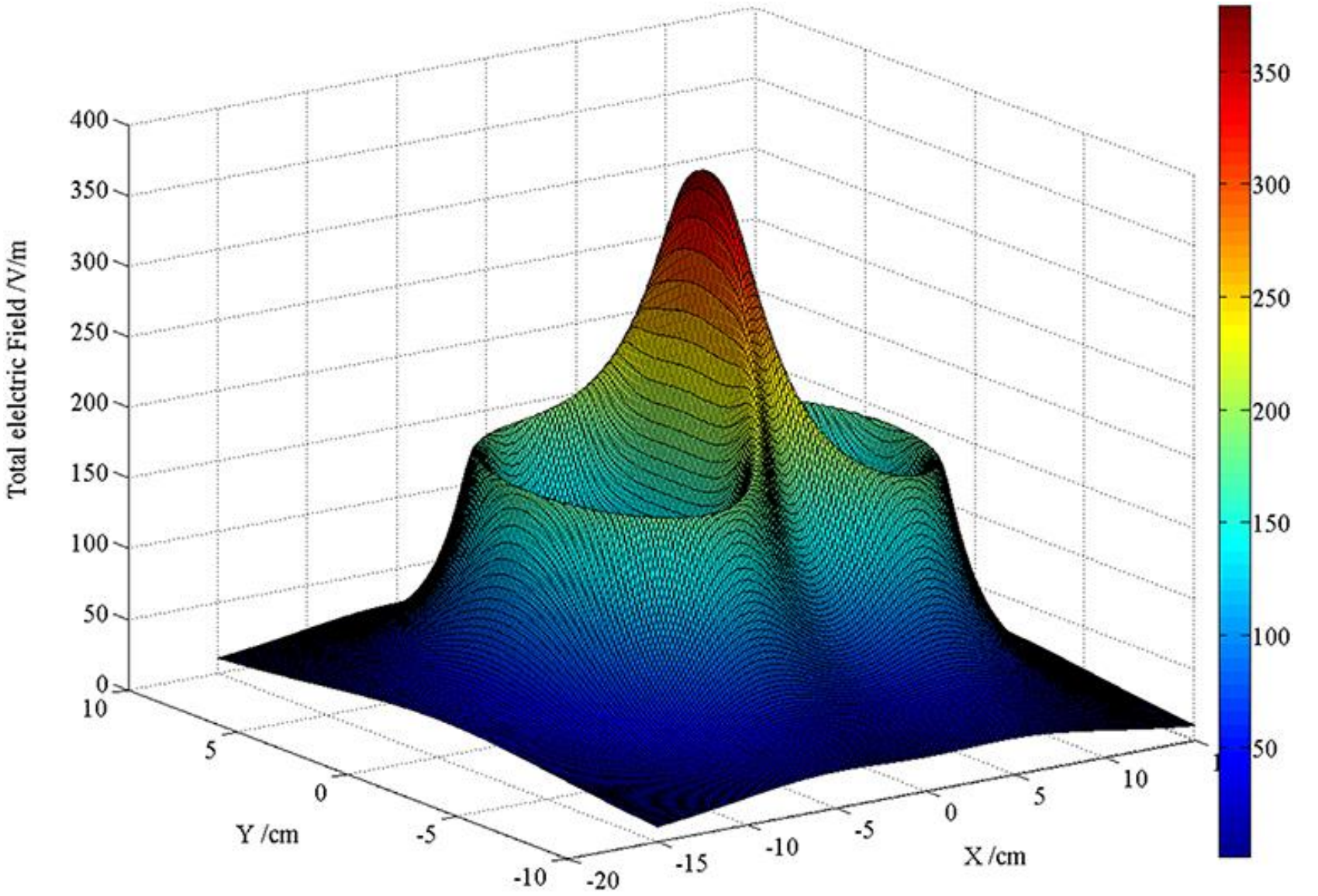
Thus

$$\frac{\text{Voltage in secondary}}{\text{Voltage in primary}} = \frac{\text{no. of secondary turns}}{\text{no. of primary turns}}$$

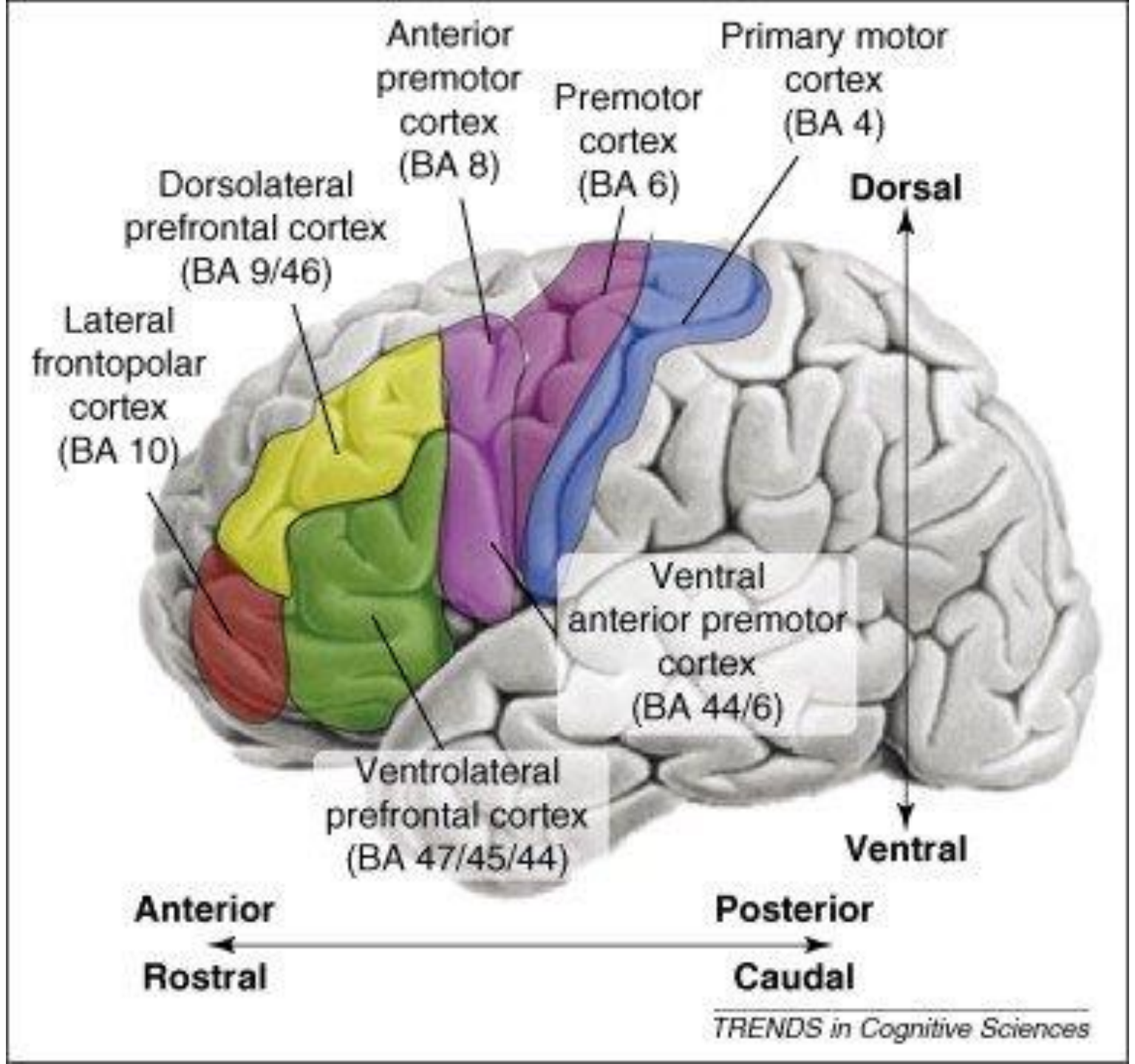
UNIVERSITY of TASMANIA
AUSTRALIA

TMS jumps electricity across the skull to the brain.


Lines of magnetic flux
Magnetic coil
Induced current in brain



Electric field projecting from the center of the figure-of-eight coil.


Anterior premotor cortex (BA 8)
Premotor cortex (BA 6)
Primary motor cortex (BA 4)
Dorsolateral prefrontal cortex (BA 9/46)
Lateral frontopolar cortex (BA 10)
Dorsal
Ventral anterior premotor cortex (BA 44/6)
Ventrolateral prefrontal cortex (BA 47/45/44)
Ventral
Anterior
Rostral
Posterior
Caudal
TRENDS in Cognitive Sciences

Treatment Variables

1 . Site of Stimulation – DLPFC –

Left and Right dorsolateral prefrontal cortex

2. Pulse Frequency – 1 Hz – inhibits neural tissue

>1Hz – activates neural tissue

3. Pulse Strength - % Resting Motor Threshold (RMT)

80-120% RMT

Side Effects

1 . Seizure – less risk than with antidepression medication.
Not available where there is a history of seizures

2. Scalp discomfort during treatment

3. Mild headache post treatment – Panadol

4. Intracranial metal and electronic objects – treatment may be possible – with special precautions

Psychiatric Clinics of North America
Volume 46, Issue 2, June 2023, Pages 307-329

Noninvasive Brain Stimulation Techniques for Treatment-Resistant Depression: Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

Andrea Boscutti MD [a b 1], Juliana Mendonca De Figueiredo MD [a 1], Dana Razouq MD [a],

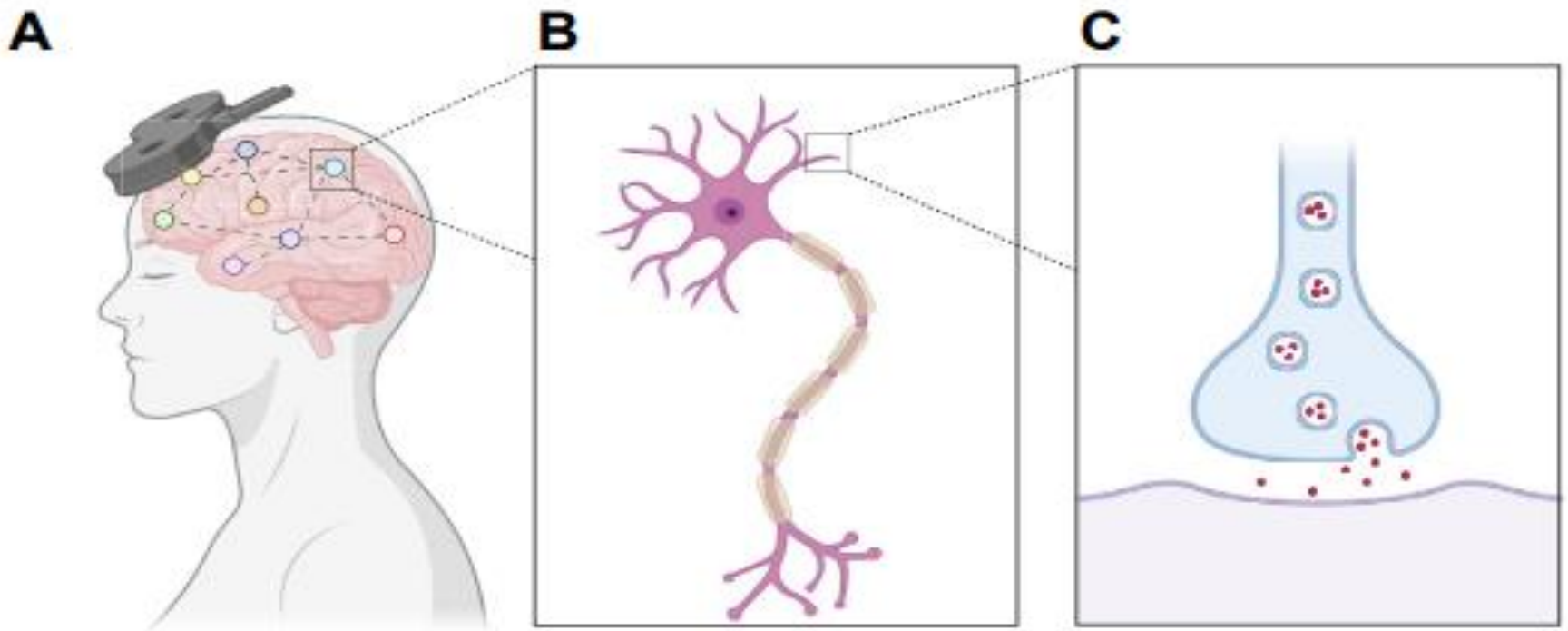
Key points

- Transcranial magnetic stimulation is a noninvasive neurostimulation technique approved for treatment-resistant depression (TRD)....
- The main advantage over pharmacologic treatments is the low incidence of side effects....

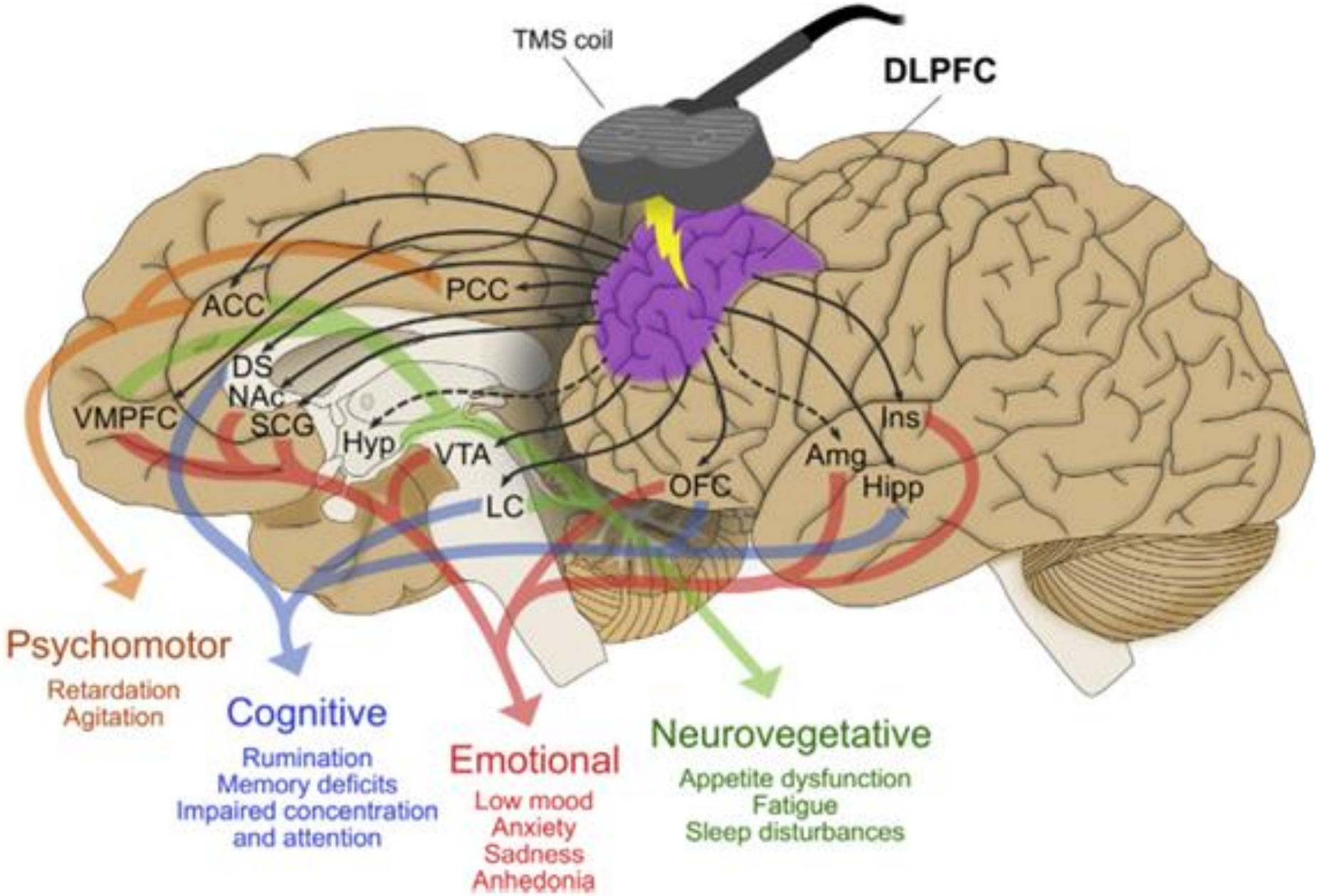
Repetitive Transcranial Magnetic Stimulation–Induced Neuroplasticity and the Treatment of Psychiatric Disorders: State of the Evidence and Future Opportunities

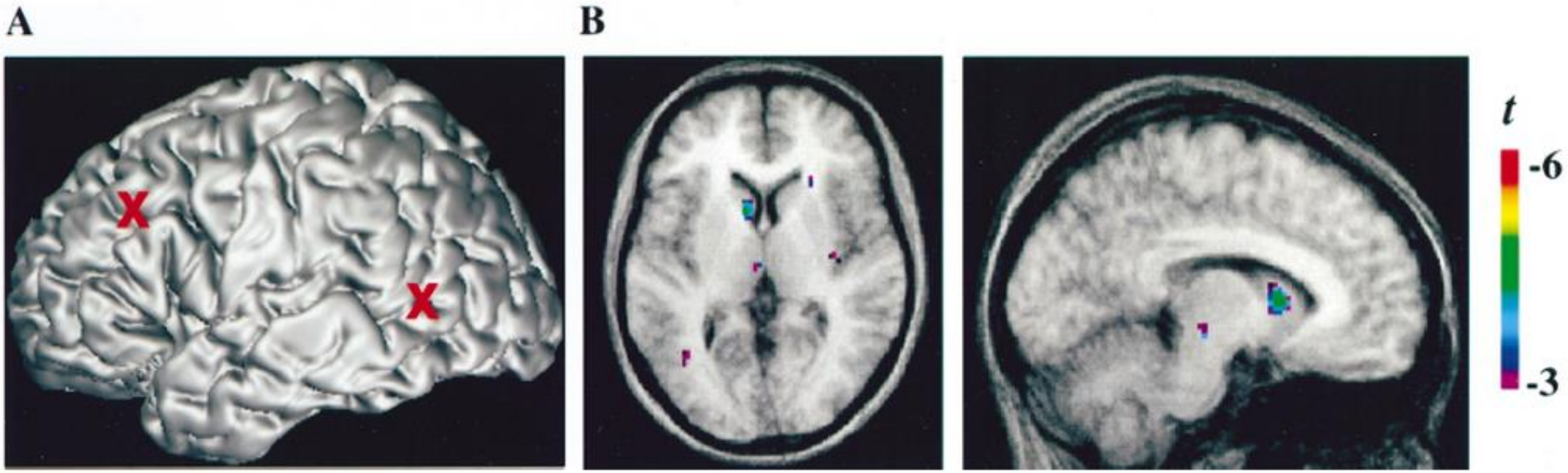
Sophie M.D.D. Fitzsimmons, Eva Oostra, Tjardo S. Postma, Ysbrand D. van der Werf, and Odile A. van den Heuvel

Biological Psychiatry 2023; 95: 592-600



Circuit	Neural	Synapse
• Altered activity • Altered functional connectivity • Altered white matter integrity and connectivity • Increased gray matter thickness and volume	• HF rTMS/iTBS: ↑ excitability / ↓ inhibition	• Increased BDNF release • Altered DA release • Altered 5-HT synthesis • Altered 5-HT receptor availability • Altered GABA and glutamate


TMS coil
DLPFC
ACC
PCC
DS
NAc
VMPFC
SCG
Hyp
VTA
LC
OFC
Amg
Hipp
Ins
Psychomotor
Retardation
Agitation
Cognitive
Rumination
Memory deficits
Impaired concentration
and attention
Emotional
Low mood
Anxiety
Sadness
Anhedonia
Neurovegetative
Appetite dysfunction
Fatigue
Sleep disturbances



TMS stimulation – Left DLPFC

Left caudate – [^{11}C]raclopride binding reduced significantly.

Indicating: TMS to Left DLPFC induced (via corticostriatal projections) endogenous dopamine release in the ipsilateral caudate.

Strafella A et al. J Neurosci 2001; 21: RC157.

A PET study

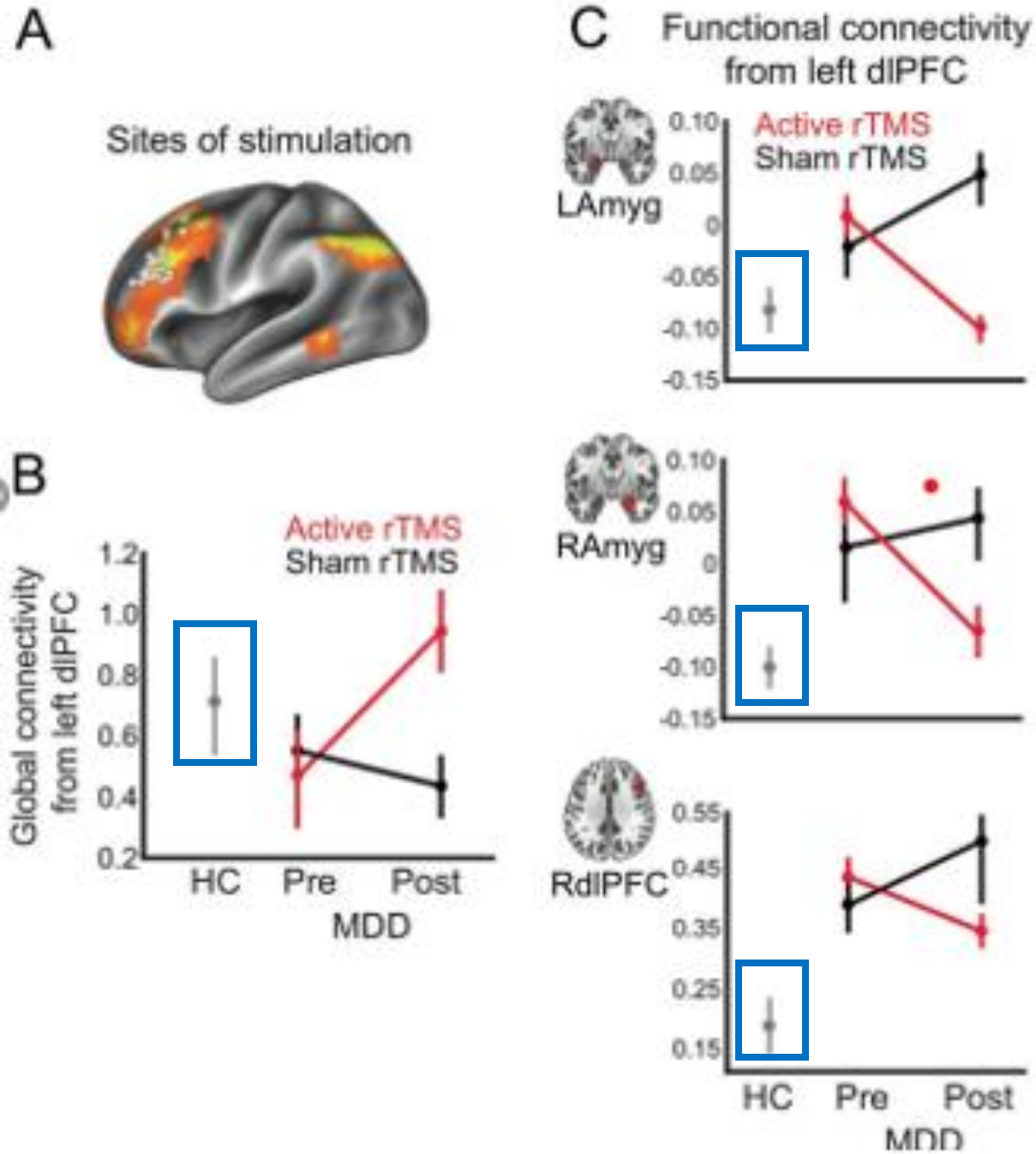
Connectivity is concerned with the amount and ease (speed) with which brain nodes communicate with each other.

Functional connectivity (FC)

Nothing looks broken, but something isn't working.

FC problems are often present in psychiatric disorders.

Can be assessed using brain imaging – also, using non-imaging EEG.



Global connectivity and local excitability associated with antidepressant effects of TMS

TMS increases global connectivity

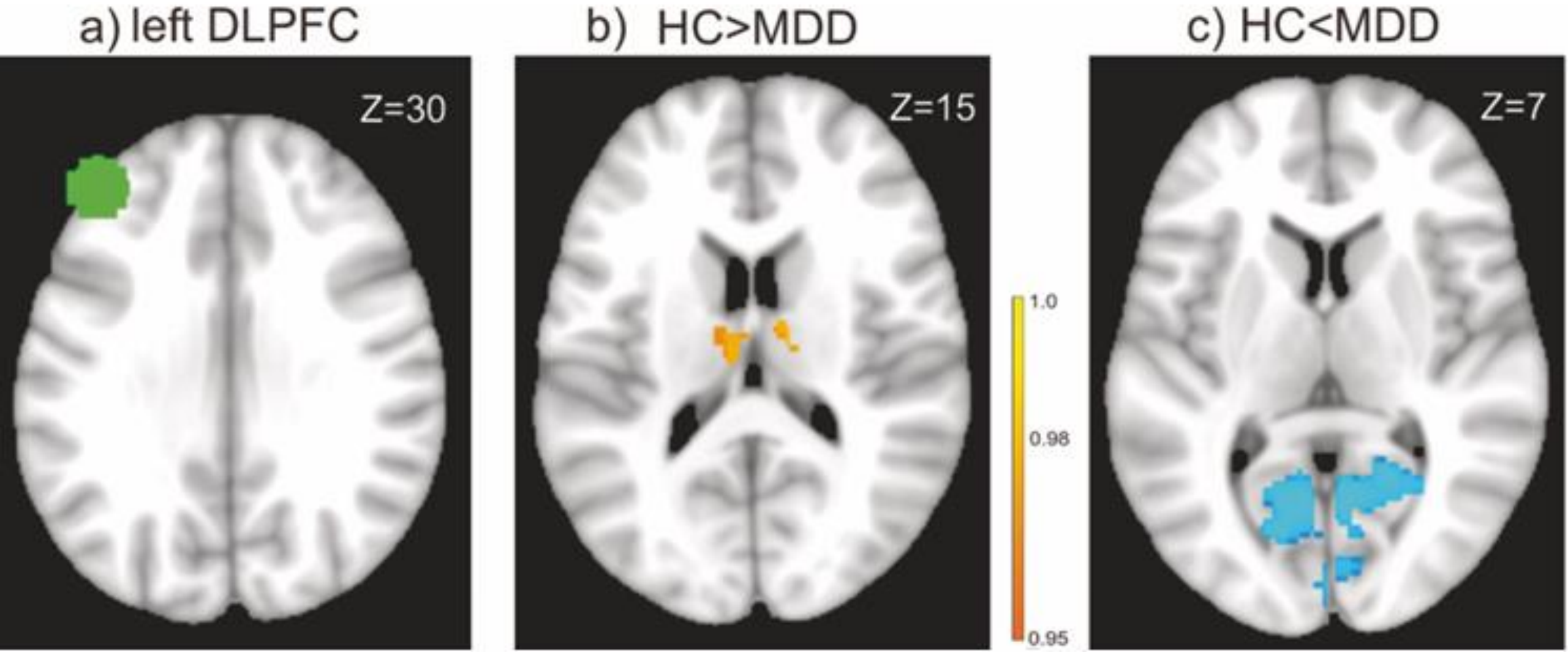
and decreases amygdala connectivity

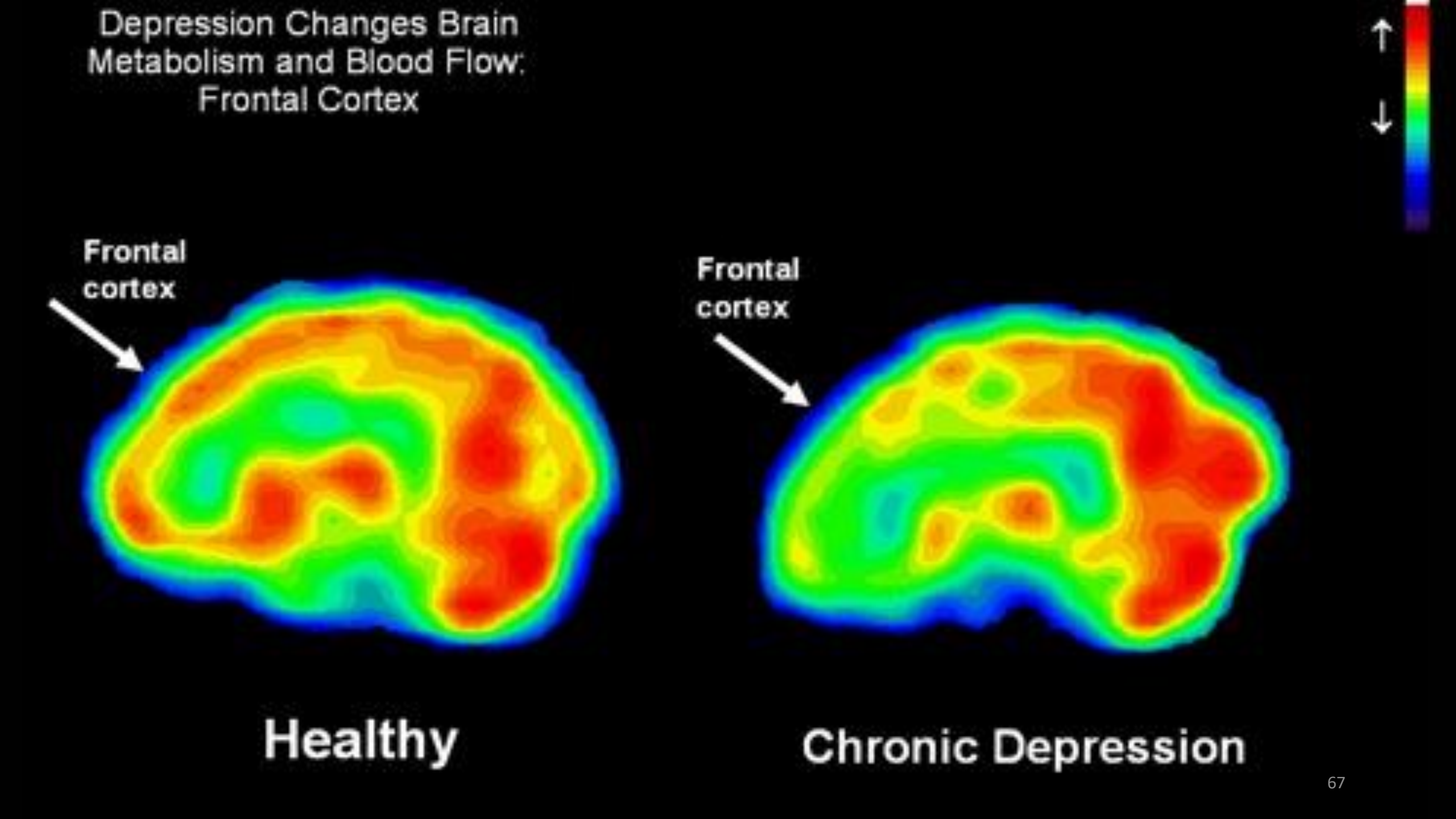
Eshel N, et al.
Neuropsychopharmacology
2020; 45: 1018-1025

Exploring the capabilities of repetitive transcranial magnetic stimulation in major depressive disorder: Dynamic causal modeling of the neural network

A. Kita et al.

Translational Psychiatry 2025




Depression Changes Brain Metabolism and Blood Flow: Frontal Cortex
↑
↓
Frontal cortex
Frontal cortex
Healthy
Chronic Depression

rTMS Therapy Reduces Hypofrontality in Patients With Depression as Measured by fNIRS

Kowabata Y, Imazu S, Matsumoto K, et al.

Frontiers in Psychiatry 2022; 13: 814611

Altered blood parameters in “major depression” patients receiving repetitive transcranial magnetic stimulation (rTMS) therapy: a randomized case-control study

Beyza Nur Ozkan[1,2,9]✉, Kubra Bozali[1,2,9]✉, Muhammed Emin Boylu[3,4], Halil Aziz Velioglu[5,6]✉, Selman Aktas[7], Ismet Kirpinar[3] and Eray Metin Guler[1,8]

Translational Psychiatry (2024) 14:264

European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-023-01704-9

ORIGINAL PAPER

Changes in neuroactive steroids, neurotrophins and immunological biomarkers after monotherapy 8-week rTMS treatment and their relationship with neurocognitive functions in depression

Muhammed Emin Boylu[1,5] · Şenol Turan[2] · Eray Metin Güler[3] · Fatma Betül Boylu[4] · Özge Kılıç[1] · Abdurrahim Koçyiğit[3] · İsmet Kırpınar[1]

Received: 1 July 2023 / Accepted: 15 October 2023

Brain connectivity and transcriptional changes induced by rTMS in first-episode major depressive disorder

Guan M, et al. Translational Psychiatry (2025) 15:159 ; https://doi.org/10.1038/s41398-025-03376-6

10 Hz stimulation to the Left DLPFC – Patients suffering MMD

Interested in the modulation of gene expression generated by TMS

Connectivity and gene expression quantified before and after treatment

A strong antidepressant result was achieved.

Genes SCN1A, SNAP25 and PVALB – increased expression (in response to TMS)

SCN1A – encodes a voltage-gated sodium channel – upregulation restores healthy connectivity

SNAP25 – involved in vesicle fusion in synapses enabling neurotransmitter release and synapse function

PVALB – critical modulator of calcium signalling within neurons – restoration improves neuroplasticity and connectivity.

Practical Matters

TMS devices are expensive.
A nurse or TMS Operator needs to be present throughout each treatment
.Using current methods, one treatment takes about 30 minutes
Treatments are administered daily [week days] for up to 7 weeks
(A course is frequently up to 35 treatments)
Big undertaking for both patients and staff.

Item rebates are unsatisfactory at this stage
in so far, they cover the cost of only 50 treatments over an individual's lifetime.

Those who come to TMS have treatment resistant depression [TRD] – which is frequently not only treatment resistant, but also relapsing – thus more than 50 treatments will probably be required over a lifetime.

Cost-effectiveness analysis comparing repetitive transcranial magnetic stimulation therapy with antidepressant treatment in patients with treatment-resistant depression in Japan

Noda Y, Miyashita C, Komatsu Y.
Psychiatry Research 2023; 330: 115573

"rTMS therapy for TRD can be a cost-effective treatment strategy compared to antidepressant medication under the NHI system in Japan."

COST effectiveness

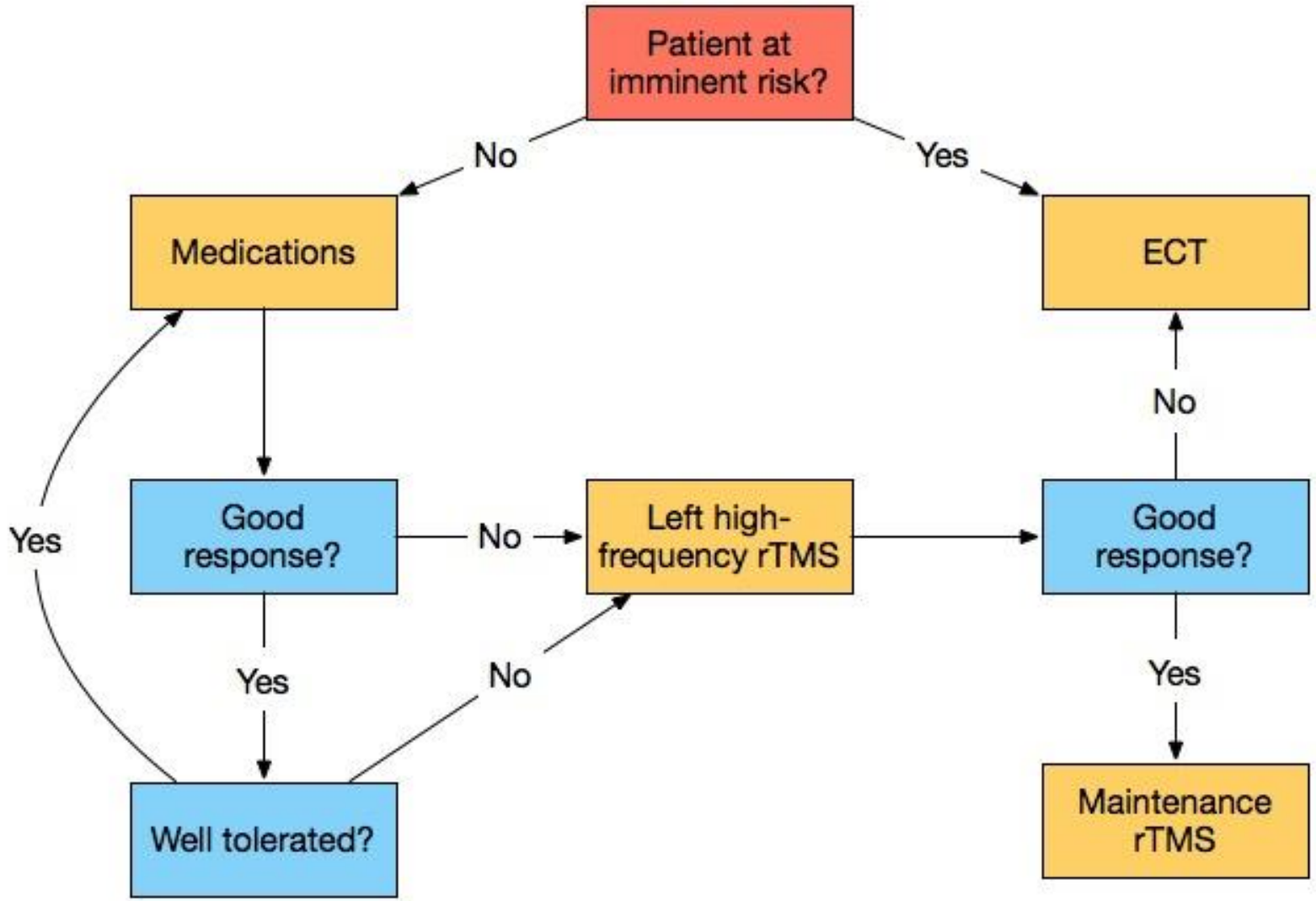
In spite of the costs being considerable
TMS is more cost effective than medication and ECT

Resource utilization and economic outcomes following repetitive transcranial magnetic stimulation for treatment-resistant depression: a retrospective observational analysis

Journal of Comparative Effectiveness Research

Taylor J, et al.
J. Comp. Eff. Res. (2025) e250019

"This study suggests that patients who receive rTMS for treatment-resistant depression required fewer high acuity hospital visits and incurred less expensive episode-of-care costs compared with patients who do not receive rTMS. From this perspective, rTMS is an investment that returns health and economic dividends through fewer high acuity hospital visits."



W. Pridmore 2020

Q&A Panel

Dr. Arnob Chakraborti, Dr. Marzena Rybek and Dr. Yvonne Turnier-Shea

Some final words

- After this webinar end, your browser will open a link to an evaluation survey.
- Statements of attendance will be emailed to participants.
- For event queries, please contact events@primaryhealthtas.com.au

Thank you

Disclaimer

- Information presented in webinars organised by Primary Health Tasmania can come from a number of sources, and does not necessarily reflect the views of Primary Health Tasmania. Every reasonable effort is taken to ensure the information is accurate and current.
- The content is general in nature – please refer to any referenced guidelines or standards for further information. Health professionals should rely on their own independent inquiries and professional judgement when making any decisions.
- Primary Health Tasmania and the Australian Government are not responsible for any injury, loss or damage however arising from the use of or reliance on the information provided in this webinar.

Stay informed

www.primaryhealthtas.com.au

www.facebook.com/primaryhealthtas

www.twitter.com/TasPHN
@TasPHN