Emerging Evidence and Clinical Translation of Transmagnetic Stimulation in Pediatric Populations

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- Grant Support (Past):
  - NIMH, Ketamine vs. Midazolam Trial (Co-I)
  - AFSP Inflammatory Profiles & Suicidality (Co-I)
- Clinical Trials (Past):
  - Janssen – Esketamine TRD Trial (Sub-I)
  - NIMH – Tele-Behavioral Activation (Clinician)

Objectives

Current evidence and clinical guidance to TMS in children and adolescents with psychiatric disorders.

Age-appropriate TMS protocols, dosing parameters, safety monitoring, and outcome evaluation in pediatric populations.

Evaluate safety and tolerability considerations, including consent/assent and family-centered care.

Recognize evolving research, regulatory considerations, and future directions impacting the use of TMS in child and adolescent psychiatry

A Growing Mental Health Burden in Youth

- Mental disorders remained among the top 10 leading causes of disease burden worldwide, with no evidence of reduction since 1990
- ~9.2% of the global mental disorder burden occurred in people under 16
- Of 2,516 million individuals aged 5–24 globally, 293 million had at least one mental disorder (11.63% mean prevalence); 31 million had a substance use disorder (1.22%)

GBD 2019 Mental Disorders Collaborators. (2022). *The Lancet Psychiatry*, *9*(2), 137-150.
Kieling, C. et al (2024). *JAMA psychiatry*, *81*(4), 347-356.

A Growing Mental Health Burden in Youth

- Prevalence rose steadily with age
  - Ages 5–9: 6.80% (95% UI, 5.58–8.03)
  - Ages 10–14: 12.40% (95% UI, 10.62–14.59)
  - Ages 15–19: 13.96% (95% UI, 12.36–15.78)
  - Ages 20–24: 13.63% (95% UI, 11.90–15.53)
- 24.85% of all mental-disorder YLDs across the entire human lifespan occur before age 25
- Diagnosed mental/behavioral health conditions among U.S. adolescents (12–17) rose 35% from 2016 to 2023 (15.0% → 20.3%)

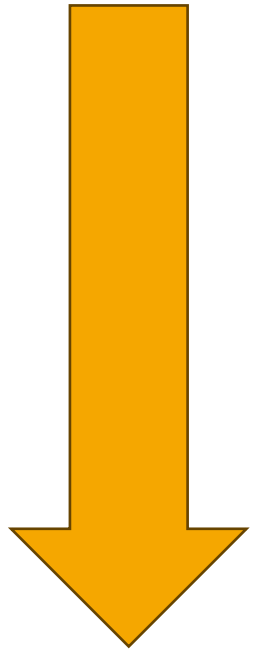
Burnett, A. L et al. (2026). *JAMA pediatrics*, *180*(4), 451-453..
Kieling, C. et al (2024). *JAMA psychiatry*, *81*(4), 347-356.

Innovative Treatment Options

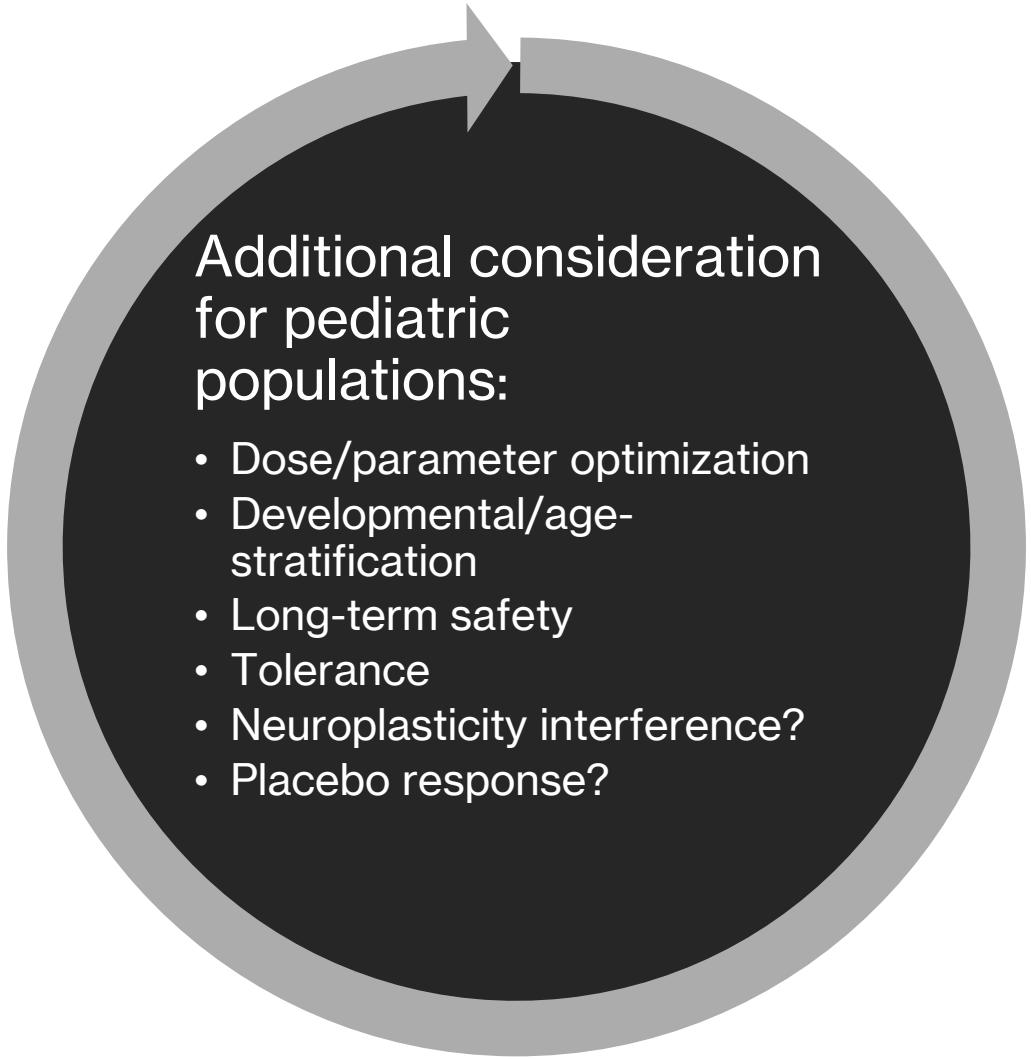
- TMS is an emerging, non-invasive neuromodulation therapy
- Uses magnetic fields to modulate cortical excitability
- High- and low-frequency stimulation produce different effects on brain activity
- First demonstrated in 1985 by Barker et al. in Sheffield, England
- Commonly used for depressive illness, but also other psychiatric conditions such as OCD, Substance Use, ASD, Tics etc in clinical and research settings

Before moving into pediatric TMS landscape

- Feasibility
- Safety and Tolerability
- Effectiveness
- Large/multisite research studies
- Clinical guidelines



Before moving into pediatric TMS landscape



A Definitional Problem in context of TRD

- No consensus definition of "treatment-resistant" exists across pediatric psychiatric diagnoses, unlike adults, where TRD in MDD has semi-standardized criteria
- Dwyer et al. (2020) proposes a staging model for adolescent TRD, but notes the evidence base rests on just four large trials (TADS, TORDIA, ADAPT, IMPACT), and evidence gets thin fast after two failed medication trials + one adequate psychotherapy trial
- Roughly 1 in 3 depressed adolescents fail first-line treatment, but "failure" is doing a lot of definitional work here

Ayvaci, E. R., & Croarkin, P. E. (2023). Special populations

10 Proposed stages of treatment resistance in pediatric depression		Treatment modalities				
Stage	**Definition (substantial residual symptoms of depression despite …)**	Therapy	SSRI	Alternative antidepressants	Augmentation	Interventional techniques
0	No previous treatment for depression					
1	Previous counseling for depression of unclear modality or efficacy	?				
2	Previous evidence-based psychotherapy for depression	Y				
3	1 prior pharmalogical trial of FDA approved antidepressant for depression (fluoxetine, escitalopram, sertraline) of adequate duration and at the ***minimally*** recommended dose	Y*	?			
4	1 prior pharmalogical trial of FDA approved antidepressant for depression (fluoxetine, escitalopram, sertraline) of adequate duration and at the ***maximally*** tolerated dose *Treatment Resistant Depression* (see Box 1)	Y*	1			
5	Two trials of adeqaute dose and duration with SSRI medications *Treatment Refractory Depression* (see Box 1)	Y*	2-2+			
6	≥2 trials of SSRI medications (adeqaute dose and duration) **AND [**≥ 1 trial with an alternative antidepressant (SNRI, bupropion, or mirtazapine) **OR** evidence-based augmentation strategy in adults (antipsychotics, lithium, bupropion, mirtazapine, stimulant)]	Y*	2-2+	1		
7	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults	Y*	2-2+	2		
8	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 1 trial with an alternative antidepressant agent (SNRI, bupropion or mirtazapine) **AND** ≥ 2 augmentation strategies with evidence of efficacy in adults	Y*	2-2+	1	2	
9	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults **AND** an interventional treatment (rtms or ketamine)	Y*	2-2+	1	2	rtms or Ketamine**
10	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults **AND** electroconvulsive therapy	Y*	2-2+	1	2	ECT**

Dwyer, J.B., Stringaris, A., Brent, D.A. and Bloch, M.H. (2020), Annual Research Review: Defining and treating pediatric treatment-resistant depression. J Child Psychol Psychiatr, 61: 312-332.

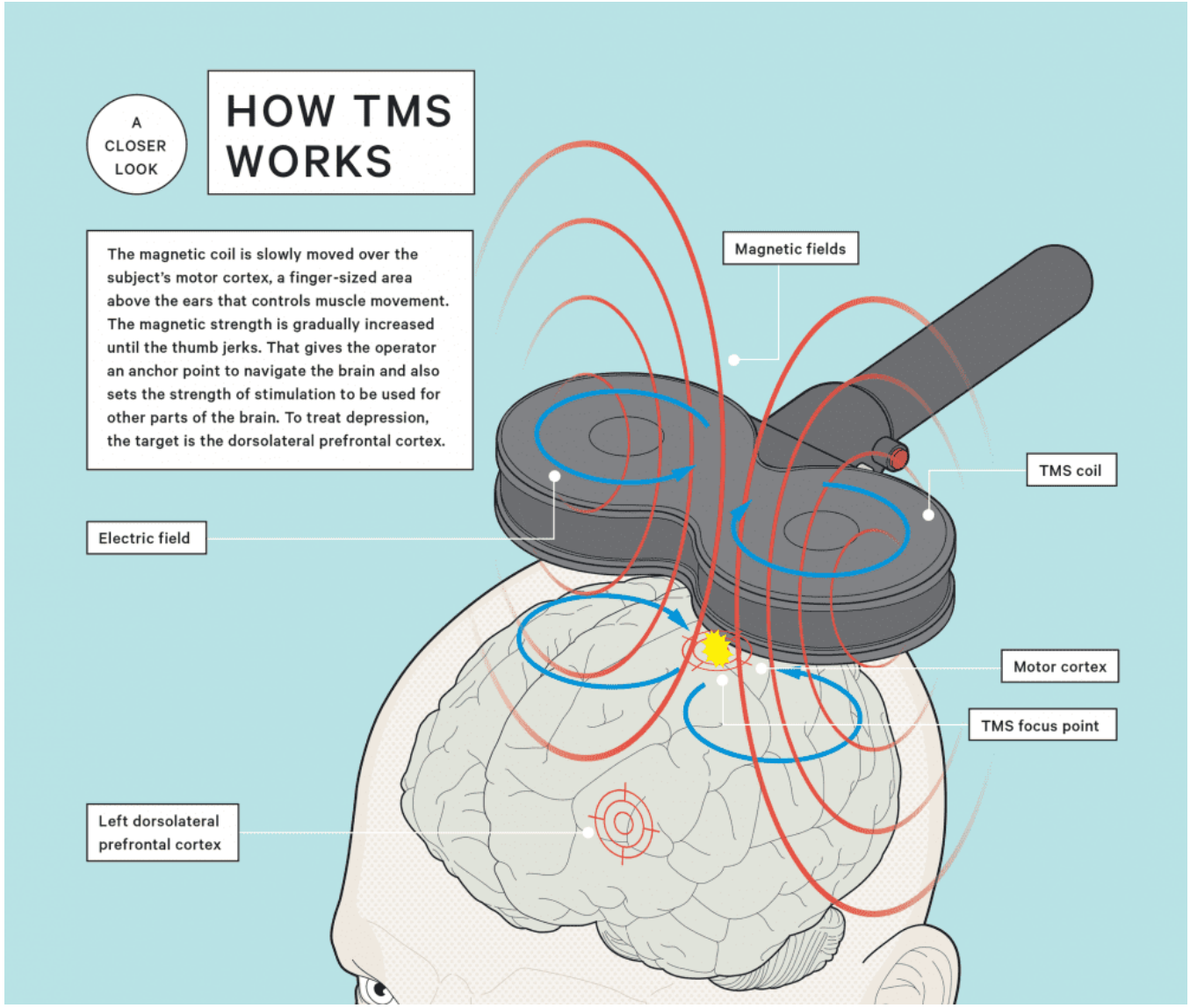
Clinical Dilemma: Definitional

- Treatment resistance, or a treatment-adequacy problem?
  - Was the medication dose actually adequate? (e.g., equivalent to 40mg fluoxetine)
  - Was the psychotherapy actually evidence-based and dosed correctly (8–16 sessions)?
  - Was there a diagnostic reassessment for comorbidity, misdiagnosis, or non-adherence?

Clinical Dilemma: When and how

- Where does TMS fit?
- Which patients? (confirmed TRD only, or broader?)
- Which stage? (after 1 failed trial? 2? only after psychotherapy + meds both fail?)
- Standalone vs. augmentation?

Transmagnetic Stimulation



Brief History

1985

Barker et al. demonstrate first non-invasive human cortical stimulation using TMS

1990s

Repetitive TMS protocols developed for psychiatric research

2008

First FDA approval for adjunctive treatment for adult MDD

2024

FDA approval for teens 15 and above

Types of TMS

- Single-pulse TMS (sTMS)
- Paired-pulse TMS
- Paired associative stimulation (PAS)
- Repetitive TMS (rTMS)
- Theta-burst stimulation (TBS)
- Deep TMS
- Sequential bilateral approaches
- Accelerated TMS

Single-pulse TMS (sTMS)

- Delivering a single magnetic pulse to a specific brain region
- Most commonly used for neurophysiological mapping and measuring cortical excitability.
- Critical for determining the resting motor threshold (RMT): the minimum stimulation intensity needed to elicit a motor-evoked potential (MEP)
- Important for establishing individualized treatment parameters, particularly in therapeutic rTMS and TBS protocols
- Accurate determination of RMT is essential for safe and effective especially for pediatric populations

Rossi S, Antal A, Bestmann S, et al. (2021)

Paired-Pulse Transcranial Magnetic Stimulation (ppTMS)

- Delivers two magnetic pulses in rapid succession to the same brain region (typically the primary motor cortex
- Subthreshold conditioning stimulus (S1) is followed by a suprathreshold test stimulus (S2)
- Varying the interstimulus interval (ISI) probes different intracortical inhibitory and excitatory circuits
- ppTMS + EEG measures cortical reactivity and functional connectivity
- Primarily a research tool, with potential to identify biomarkers of neurodevelopmental disorders by quantifying excitation/inhibition imbalance

Tremblay S, Rogasch NC, Premoli I, et al. (2019)

Repetitive TMS (rTMS)

- Delivers trains of magnetic pulses to targeted brain regions
- Low frequency (≤1 Hz): decreases cortical excitability (inhibitory)
- High frequency (≥10 Hz): increases cortical excitability (excitatory)
- Longer stimulation produces longer-lasting after-effects
- Thought to induce long-term potentiation (LTP) and long-term depression (LTD), promoting neuroplasticity

Repetitive TMS (rTMS)

- rTMS' antidepressant potential was first reported over 20 years ago[1]
- A randomized sham-controlled trial over 300 participants demonstrated active rTMS' efficacy over sham stimulation[2]
- rTMS received FDA approval in 2008 for treatment resistant depression
- In clinical studies of treatment-resistant MDD, rTMS' response rates have been reported at 40–60% and remission rates at 30–40% in adult populations[3]

George M, Wassermann E, Williams W, et al. 1995
O'Reardon J, Solvason H, Janicak P.. Biol Psychiatry 2007
Fitzgerald PB, Hoy KE, Anderson RJ, et al. Depress Anxiety 2016

rTMS

- In clinical practice, rTMS is applied over the left or right dorsolateral prefrontal cortex (DLPFC).
- A standard treatment course involves 20–30 daily stimulation sessions applied over 4–6 weeks.
- rTMS session is typically under 45-min duration with stimulation intensity set at 120% of resting MT
- High-frequency 10 Hz rTMS applied to the left DLPFC remains the most studied rTMS protocol
- There are other protocols such as low-frequency 1 Hz rTMS applied to the right DLPFC, and sequential bilateral rTMS, where 1 Hz right- followed by 10 Hz left-sided DLPFC stimulation

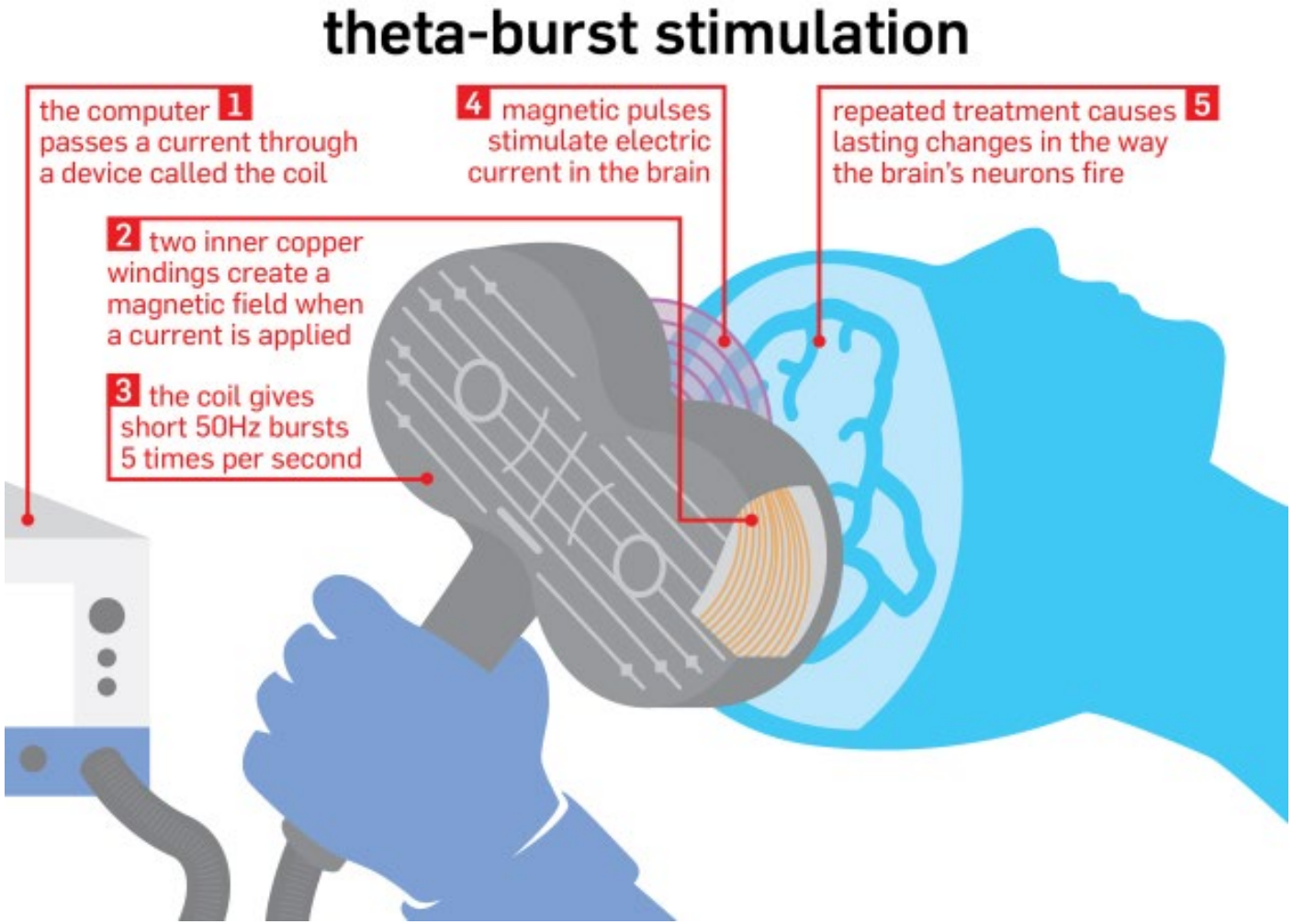
Theta Burst Stimulation

- TBS is a specific form of rTMS, refers to stimulation applied at 3–4 gamma frequency pulses repeated at theta frequency intervals.
- In typical TBS dosing 3 pulse 50 Hz bursts are delivered at 5 Hz which is every 200 milliseconds (ms) mimicking theta rhythm of brain
- TBS was first introduced by Huang et al in 2005, showed TBS-induced motor cortical conditioning effects lasting 60 min after stimulation[1]
- Types of TBS:
    - Intermittent TBS (iTBS) - enhances cortical excitability and changes LTP
    - Continuous TBS (cTBS) - suppresses cortical excitability (explained by its LTD of synaptic activity[1]

Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., and Rothwell, J. C. (2005).

TBS - FDA approval

- The approval of iTBS was granted in 2018 following the THREE-D trial
- FDA approved iTBS treatment protocol
  - Stimulation Intensity: 120% MT
  - Repetition rate: 50 Hz (5 pulses pr sec)
  - Train duration: 2 sec
  - Interval between Trains: 8 secs
  - Burst pulses: 3 Bursts : 200
  - Inter pulse interval: 20 msec
  - Number of trains : 20
  - Numbers of pulses/session: 600
  - Total duration: 3 min and 9 sec



Accelerated TMS

- Compresses the total number of TMS treatments into days rather than weeks
- Delivers multiple sessions per day while maintaining or increasing the cumulative treatment dose
  - Traditional TMS
  - 1 session/day, 5 days/week
  - 30–36 sessions over 4–6 weeks
  - Accelerated TMS
  - 5–10 sessions/day over several days to 1–2 weeks
  - Sessions separated by ~50 minutes to allow cortical recovery

Stanford Neuromodulation Therapy (SNT/SAINT)

- Most studied accelerated TMS protocol
- Combines three innovations:
  - Accelerated schedule: 10 sessions/day × 5 days (50 total sessions)
  - High-dose iTBS: intermittent theta-burst stimulation with increased cumulative stimulation dose
  - Personalized targeting: resting-state fMRI-guided targeting of DLPFC based on connectivity with subgenual ACC
- Original open-label trial in treatment-resistant depression19/21 participants (90%) achieved remission
- No significant negative cognitive effects observed

Williams NR, Sudheimer KD, Cole EJ, et al. (2020).

Accelerated TMS in Adolescents

- Pediatric evidence remains limited
- Potential benefits for adolescents
  - Minimizes school disruption
  - Improves treatment accessibility and adherence
- Key unanswered questions
  - Optimal dose and schedule
  - Long-term safety and cognitive effects
  - Efficacy compared with standard TMS protocols

Use of TBS for adult depression

	Sample	Treatment	Dur	Outcome
Cole, 2021 (SNT)	14/15	Ten sessions of active or sham iTBS were delivered daily, for a total of 18,000 pulses per day, on 5 consecutive days (10 session/day) 90% of RMT, adjusted for depth of the identified fcMRI target (individualized left DLPFC target)	5 week	Primary outcome was MADRS score 4 weeks after the end of the 5-day tx. After 5 days of treatment, 79% in the active group (11/14) achieved remission from their depressive episodes at some point during the 4-week follow-up, compared with 13% (2/15) in sham
Li 2019	105	TBS, rTMS and sham groups. Daily treatment for 10 days. MRI guided targeting vs 5-cm rule	2 weeks	The TBS group exhibited significantly greater decreases in depression scores than the sham group at week 2
Blumberger 2018 (THREE-D)	205/209	rTMS vs iTBS over left DLPFC – 5d/week for 4-6 weeks. Used MRI guided neuronavigation. rTMS- 120% RMT stimulation intensity; 10 Hz frequency; 4 s on and 26 s off; 3000 pulses per session; total duration of 37·5 min iTBS- 120% RMT, triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session. total duration of 3 min 9 s	12 weeks	iTBS was non-inferior to standard 10 Hz rTMS in reducing depressive symptoms at week 4 and 12. iTBS response rate was 49% and remission rate was 32%.
Caeyenberghs 2018	46	TBS stimulation pattern of 50 Hz frequency with a 2 s on 8 s. off cycling. 110% RMT. Between 5 session daily for 4 days (3 iTBS session each day). pause was 15 min each. Total 20 session vs.; Sham crossover trial	1 week	Network changes did not correspond directly with clinical improvements. Reduction in depressive symptoms was unrelated to active or sham stimulation
Christyakov 2015	15/14	cTBS over right DLPFC active vs sham for 10 days (on session/day) TBS: triple-pulse 50 Hz bursts given at a rate of 5 Hz at an intensity of 100% of patient's RMT vs.; Sham	2 weeks	No significant difference between cTBS vs sham
Desmyter 2016	50	Randomized sham controlled cross over design iTBS: 5 sessions per day for 4 days (total 20 sessions), 110% of patient's RMT. vs.; Sham Used fMRI neuronavigation, 15 min pause between sessions	2 weeks	No statistically different suicide risk in active vs sham
Duprat 2016	50	Sham controlled cross over design. Total of 20 iTBS sessions spread over 4 days (5 sessions per day) intensity of 110% RMT with 15-min pause vs.; Sham	2 weeks	No statistically significant differential effects between sham and real stimulation on depression severity symptoms.

Table 1. Comparative Overview of Various Types of Transcranial Magnetic Stimulation (TMS).

TMS Modality	Stimulation Frequency	Intensity (% of Motor Threshold)	Typical Session Duration	Number of Sessions	Total Treatment Duration	Primary Clinical Applications
Repetitive TMS (rTMS)-a [18]	High-Frequency rTMS (Left DLPFC): 10 Hz	80–120% RMT	~20–37.5 min	10–30 sessions	2–6 weeks	Major Depressive Disorder (treatment-resistant), Anxiety, ASD (modest evidence), ADHD
Repetitive TMS (rTMS)-b [18]	Low-Frequency rTMS (Right DLPFC/SMA/LTPC): 1 Hz	90–110% RMT	~15–30 min	10–30 sessions	2–6 weeks	OCD, Tourette Syndrome, Schizophrenia (auditory hallucinations), Depression with irritability
Theta Burst Stimulation (TBS) [18]	Bursts at 50 Hz, repeated at 5 Hz	~80% of Active Motor Threshold	iTBS: ~3 min cTBS: 20–40 s	Typically 8–30 sessions	4 days to 6 weeks	Depression, ASD, Tourette Syndrome (limited studies; ongoing trials)
Deep TMS (H1 Coil) [19]	18 Hz	Up to 120% of MT	55 trains × 2 s, 20-s intertrain interval (1980 pulses)	~20–30 sessions planned	~4–6 weeks	Treatment-Resistant Depression (adolescent trial phase)
Low-Intensity TMS (LI-TMS) [20]	10 Hz	Subthreshold	10 min/session	Standard: 1×/day for 10 days Accelerated: 3×/day for 5 days	1–2 weeks	Preclinical model of adolescent depression; informs future clinical use
Magnetic Seizure Therapy (MST) [21]	100 Hz	100% (train duration titrated)	2–10 s train duration (seizure induced)	Acute: 18 sessions Continuation: 9 sessions	Acute: 6 weeks Continuation: 6 months	Refractory Bipolar Depression (Adolescent case study)
Single pulse TMS (sTMS) [22]	1 pulse per stimulus (not repeated)	Variable (usually suprathreshold, e.g., 120%)	Milliseconds (used for motor evoked potentials or silent periods)	1	N/A (Research use only)	Neurophysiological assessment: cortical excitability, inhibition (e.g., CSP, MEP), biomarker research
Paired Pulse TMS (ppTMS) [22]	Two pulses: Conditioning + Test (1–200 ms ISI)	Conditioning: subthreshold; Test: suprathreshold (e.g., 80–120%)	~30–60 min (research session)	1 (research setting)	N/A (used as assessment)	Assessment of cortical excitability and inhibition (e.g., SICI, ICF, LICI); research in ADHD, ASD, depression

Abbreviations: RMT: resting motor threshold; MT: motor threshold; iTBS: intermittent theta-burst stimulation; cTBS: continuous theta-burst stimulation; OCD: obsessive–compulsive disorder; ASD: autism spectrum disorder; ADHD: attention-deficit/hyperactivity disorder.

El-Shahawy et al. (2024). Exploring Applications of Transcranial Magnetic Stimulation in Child and Adolescent Psychiatry: A Narrative Review. Brain Sciences.

rTMS/TBS for adolescent depression

	Sample	Age	Treatment	Dur	Outcome
Pan et al 2020	21/21	13-45	Daily rTMS for 7 days, Each session comprised 120 trains of 5 seconds duration at 10 Hz with inter-train intervals of 15 seconds with %100 RMT vs sham Used Fmri neuronavigation	1 week	SI was significantly decreased in the active vs sham. The reduction in depression severity was significant in rTMS group.
Croarkin et al 2021	48/55	12-21	10Hz rTMS at 120% over LDLPFC (5 cm targeted) vs sham 30 treatment total	4-6 week	Active arm -Response rate of 41.7%; remission rate of 29.2%; Sham arm-Response rate of 36.4%; remission rate of 29.0%
Dhami et al. 2019	20	16-24	Bilateral theta burst stimulation**: iTBS** on LDLPFC and cTBS on RDLPFC at 80% RMT (structural-MRI targeted) Daily 10 treatment sessions over 2 weeks	2 weeks	4/20 had more than 50% reduction in depressive symptoms, 2/20 achieved remission.
Zhang et al 2019	42	10-18	10Hz rTMS at 120% MT over LDLPFC (5 cm targeted) ,5 sessions per week for 2 weeks. Add-on treatment	2 weeks	2-week response rate 50% 2-week remission rate 54.3%
Macmaster 2019	32	13-21	10Hz rTMS at 120% RMT over LDLPFC (structural-MRI targeted). 15 treatment over 3 weeks. MRI neuronavigation.	3 weeks	Response rate of 56%, remission rate of 44%
Roselinch 2019	15	17-25	Either unilateral low-freq TMS over RDLPFC or bilateral intermittent high freq rTMS over LDLPFC followed by low freq RDLPFC. %110 RMT. 3 days/week for 6 weeks	6 weeks	Response rate 40% and remission %13. No difference between unilateral and bilateral TMS.
Wall et al 2016	10	12-18	30 rTMS sessions (10 Hz, 120% motor threshold, left 3000 pulses applied to the dorsolateral prefrontal cortex) over 6–8 weeks. MRI neuronavigation.	6-8 weeks	6/10 responded to rTMS. CDRS-R scores improved from tx 10 to tx 30 and at 6-month follow-up
Bloch et al 2008	9	16-18	10Hz rTMS at 80% RMT over LDLPFC (5 cm targeted); daily treatment for total 14 days	2 weeks	33% response

Other psychiatric disorders

Authors	Type of Study	Sample Size	Psychiatric Disorder	Stimulation Target/Site	Protocol	Key Findings
Cao et al., 2018	RCT	64	ADHD	Right DLPFC	10 Hz, 4 s on/26 s off, 100% RMT, 2000 pulses/session, 25 min/session, 5 days/week for 6 weeks (30 sessions total)	All three arms (rTMS, atomoxetine, and combined) improved; the combination group showed the largest gains in attention, hyperactivity/impulsivity, oppositional behavior, and executive function (digit span, arithmetic, coding, CPT, IGT); well tolerated
Croarkin et al., 2018	Open-label	19	Suicidal ideation (with MDD)	Left DLPFC	30 sessions, 10 Hz, 120% motor threshold, 4 s trains/26 s intertrain interval, 3000 pulses/session	Suicidal ideation (C-SSRS, CDRS-R Item 13) decreased significantly over treatment, but the effect lost significance after adjusting for overall depression severity; well tolerated
Sokhadze et al., 2018	Randomized, comparative-effectiveness (dose-comparison)	124	Autism spectrum disorder	DLPFC	1 Hz, 90% MT, 180 pulses/session (9 trains of 20 pulses, 20–30 s inter-train interval)	Improved error-monitoring performance (fewer commission errors, restored post-error slowing) with ERP changes (larger/faster ERN, altered P3a/P3b); parent ratings showed reduced ritualistic behavior, stereotypy, irritability, hyperactivity, and lethargy
Rosenich et al., 2019	Retrospective, naturalistic study	15	Treatment-resistant MDD (with various psychiatric comorbidities)	Right DLPFC (unilateral protocols); bilateral DLPFC (bilateral protocols)	Unilateral or bilateral rTMS, 6-week protocol	Significant improvement in depression scores (HAM-D, MADRS); 40% response rate, 13% remission rate, 87% at least partial response; well tolerated in real-world clinical care
Zhang et al., 2019	Naturalistic, observational study	117 (42 teens, 75 adults)	Depression and anxiety disorders (with bipolar II, dysthymia, GAD, eating disorder, OCD comorbidities in some patients)	Left DLPFC	10 Hz, 120% motor threshold, 10–20 sessions	All age groups improved significantly in depressive symptoms; adolescents showed a greater reduction in depression scores and higher response/remission rates than adults
Ameis et al., 2020	RCT, blinded, parallel, sham-controlled	40	Autism spectrum disorder (with ADHD comorbidity in some patients)	Left DLPFC	4-week course of 20 Hz rTMS, 90% RMT, vs. sham	No significant overall improvement in executive function vs. sham; exploratory analysis found greater benefit among participants with lower baseline adaptive functioning; safe and feasible in ASD youth/young adults

Adapted from El-Shahawy et al. (2024)

Other psychiatric disorders

Authors	Type of Study	Sample Size	Psychiatric Disorder	Stimulation Target/Site	Protocol	Key Findings
Croarkin et al., 2021	RCT, sham-controlled, multicenter	112	Major depressive disorder	Left DLPFC	10 Hz, 30 sessions over 6 weeks, no more than 2 days between sessions	Clinically meaningful reduction in depression (HAM-D-24), but no significant difference between active and sham; response rates 41.7% (active) vs. 36.4% (sham); remission ~29% in both arms; pooled meta-analysis with adult trials showed a small, non-significant effect
Kahl et al., 2021	Open-label trial	10	Tourette syndrome (with ADHD, anxiety, social phobia, OCD, epilepsy comorbidities in some patients)	Bilateral SMA	15 sessions, 1 Hz, 100% RMT, 900 pulses per hemisphere (each hemisphere stimulated separately)	Tic severity fell markedly (YGTSS 64.4→26.4, p=0.005); motor/phonic tic subscores, impairment, anxiety (MASC-2), and depression (CDRS-R) also improved; cortical silent period lengthened and intracortical facilitation increased; well tolerated, though some MRS data were inconclusive
Wang et al., 2024	Case-control observational study	116	Tourette syndrome	Left SMA (identified via functional connectivity, no stimulation delivered)	3T MRI acquisition; resting-state functional connectivity analysis (imaging study, not an interventional trial)	TS children showed significantly lower left GPi–left SMA functional connectivity than controls reduced connectivity correlated with greater tic severity (YGTSS, p=0.01); supports using an individualized SMA connectivity peak as a candidate rTMS target
Garzon et al., 2025	Open-label study	41	Treatment-resistant depression	Left DLPFC	Retreatment sessions upon partial relapse (mean 22.5 sessions)	Maintenance TMS was feasible, safe, and clinically effective; 43% of participants required retreatment; higher baseline depression severity (HAMD-24) predicted greater relapse risk (HR=1.11, p≤0.001); treatment-resistance level (ATR) did not predict relapse
Wang et al., 2025	Randomized longitudinal study	54	Tourette syndrome	Function-specific SMA (left or right, via GPi-based peak functional connectivity) vs. conventional scalp-localized SMA	cTBS: 600 pulses/train (3 pulses/burst at 5 Hz), 3 trains/day for 5 days	Left-SMA fMRI-guided target produced ≥30% YGTSS reduction in 4/19 patients by week 1; GPi–SMA connectivity changes correlated with tic reduction (r=0.638, p=0.026); YGTSS improved significantly at 1 week (p<0.0001) and 2 weeks (p=0.005); supports added value of function-specific over conventional scalp-based targeting

Adapted from El-Shahawy et al. (2024)

rTMS in Adolescents

- Challenges for adolescent rTMS studies
  - high placebo rate
  - 5-cm rule, scalp-based measurements
  - Lack of neurodevelopmentally informed targets
  - Standard protocols can be burdensome
- The rTMS protocol, targeting strategy, frequency of stimulation, and dosage influence effect size in rTMS trials.

FDA Clears NeuroStar TMS for Treatment of MDD in Adolescents

March 27, 2024

By Erin O'Brien

News *Article*

This treatment is now the first and only TMS treatment that is FDA-cleared for this patient population.

NeuroStar Advanced Therapy has received clearance from the US Food and Drug Administration (FDA) as an adjunct in the treatment of major depressive disorder (MDD) in adolescent patients aged 15 to 21 years.

This clearance marks NeuroStar as the first and only transcranial magnetic stimulation (TMS) treatment that is FDA-cleared for this age group. MDD in adolescent patients is also the fourth FDA-cleared indication for NeuroStar,[1] along with treatment of MDD in adults,

FDA clearance

- March 25, 2024: FDA cleared NeuroStar Advanced Therapy as an adjunct treatment for MDD in patients aged 15–21
- 4th FDA-cleared indication for NeuroStar overall (alongside adult MDD, adult OCD, and anxious depression in adults)
- Cleared under 510(k) pathway (K231926), based on equivalence to prior predicate devices
- Evidence base: a large retrospective real-world dataset (TrakStar registry)
  - 1,169 adolescent patients (ages 12–21) across 347 U.S. TMS centers

Youth Protocols May Differ From Adult Protocols

- “Neurodevelopmental considerations for TMS trials in youth” (Neuropsychopharmacology, 2025) is the core reference for pediatric dosing
- Developmental changes in cortical anatomy, skull thickness, and scalp-to-cortex distance affect appropriate TMS parameter selection
- Electric-field modeling studies show age-related differences in induced electric fields — youth are not simply “small adults”
- Modeling work has been used to optimize coil placement over the DLPFC specifically in depressed adolescents

Safety Considerations

- Safety data for pediatric rTMS remain limited compared with adults
- Available studies suggest that rTMS is generally well tolerated in children and adolescents.
- Most adverse effects are:
  - Mild
  - Transient
  - Similar to those reported in adults

Safety Considerations

- Guidelines have historically focused on adults
- Requires careful evaluation when applying protocols to youth
- Key areas of concern:
  - Seizure risk
  - Neurodevelopmental effects
  - Long-term safety

Common Adverse Effects Reported With Pediatric rTMS

- Most frequently reported side effects:

  scalp discomfort or pain, headache, dizziness, fatigue or restlessness, neck discomfort, stiffness, or musculoskeletal pain, twitching: facial muscles, eye muscles, jaw muscles, tinnitus, nausea or gastrointestinal symptoms

- Clinical course
  - Symptoms are typically mild and resolve spontaneously.
  - Rates and severity appear comparable to adult rTMS studies.

Serious Adverse Events and Rare Risks

- Seizure risk
  - Seizure is the most serious potential complication of rTMS
  - Incidence is very low and usually occurs in individuals with additional risk factors:
    - History of epilepsy
    - Neurological disorders
    - Stroke or brain injury
    - Medication/substance-related risk factors

Rossi et al. (2021), *Clin Neurophysiol* 132:269–306

Serious Adverse Events and Rare Risks

- Reported rare events
  - Seizures reported in isolated cases.
  - New-onset hypomanic episodes that resolved after treatment.
  - Transient complex visual hallucinations following low-frequency rTMS:
    - Occurred after six sessions of right DLPFC stimulation
    - Resolved approximately one week after stopping treatment without medication.

Rossi et al. (2021); Bejenaru & Malhi (2022), *Innov Clin Neurosci* 19(4–6):11–22

Evidence From Pediatric Safety Studies

- Hong et al. pediatric safety study (ages 6–18 years)
  - Compared standard/paired-pulse TMS and theta burst stimulation.
  - Participants included healthy controls and youth with neuropsychiatric disorders.
  - Findings: No seizures reported
  - No serious adverse events
  - Adverse events were mild/minimal

Hong et al. (2015), *Front Hum Neurosci* 9:29

Evidence From Pediatric Safety Studies

- Systematic Review: Elmaghraby et al., *Neuromodulation* (2022)
- 20 studies; ~176 youth participants (≤21 years)
- TBS was generally well tolerated
- Most common adverse event: headache
- Other mild effects: scalp discomfort, fatigue, dizziness
- One seizure case report associated with TBS
- Limited long-term safety data remain a major gap

Ethical Questions

- Minors have diminished capacity to consent, a legal guardian consents on their behalf.
- IRBs and FDA determine whether assent is additionally required for a given study or treatment context.
- Assent gives the minor autonomy to dissent once they understand what participation/treatment involves.

Ethical Questions

- *“An Ethics Perspective on TMS and Human Neuromodulation” (2006, Behav Neurol)* argues safety and informed consent are paramount, but personal values and sociocultural context also matter in evaluating TMS applications.
- Practical implication: consent conversations should go beyond a checklist, they should account for the family's values and circumstances, not just the clinical facts.

Illes et al. (2006), *Behav Neurol* 17(3–4):149–157

What Families Think & What Consent Should Cover

- “The Fewer Pills the Better” (Croarkin & Cabrera et al.)
- Semi-structured interviews with adolescents and parents
- Most had low baseline awareness of TMS as a treatment option
- No strong pre-existing ethical objections once informed
- Practical implication: family-centered care should prioritize clear education over persuasion against resistance that may not exist.

Henegan, Croarkin, Kodavatiganti & Cabrera (2025), *Advances in Neuroethics*

Future Directions

- Emerging trial infrastructure: CBIT + TMS combination trial for pediatric chronic tics, TMS paired with behavioral therapy
- Continued expansion of indications beyond MDD (OCD, tics)
- Electric-field modeling and neuronavigation have potential for personalized, developmentally-tailored targeting
- No dedicated AACAP practice parameter for pediatric TMS exists yet

Summary

- Youth mental illness carries a substantial and rising global burden, with a persistent gap between need and adequate treatment response.
- “Treatment-resistant” remains poorly defined in pediatric psychiatry, ruling out an adequacy or access problem should precede escalation to interventional options.
- rTMS and TBS are mechanistically well-characterized in adults (FDA-cleared for MDD in 2008, OCD in 2018); the adolescent evidence base is smaller and still maturing.
- Real-world safety data are reassuring, but consent, assent, and family-centered communication remain essential, not optional
- Regulatory clearance and insurance coverage are expanding rapidly (2024–2025), though a dedicated pediatric practice parameter is still missing.


Questions?