

INTRODUCTION

- There are limited treatment options for tinnitus, and there is a lack of consensus on treatment guidelines.^{1,2}
- Functional brain imaging studies have suggested atypical hyperactivity in the brains of individuals with tinnitus.^{3,4}
- Neuromodulation for the treatment of tinnitus has been tested as early as 1886 and aims to suppress hyperactive neuronal activity with targeted stimuli.⁵
- Common modalities of neuromodulation include repetitive transcranial magnetic stimulation (rTMS), transcranial direct electric stimulation (tDCS), theta-burst stimulation (TBS), and transcutaneous electric nerve stimulation (TENS).⁶
- TBS and rTMS deliver electromagnetic energy through a coil while tDCS and TENS deliver electrical current through electrodes.⁶
- The efficacy of active neuromodulation versus sham has conflicting evidence.

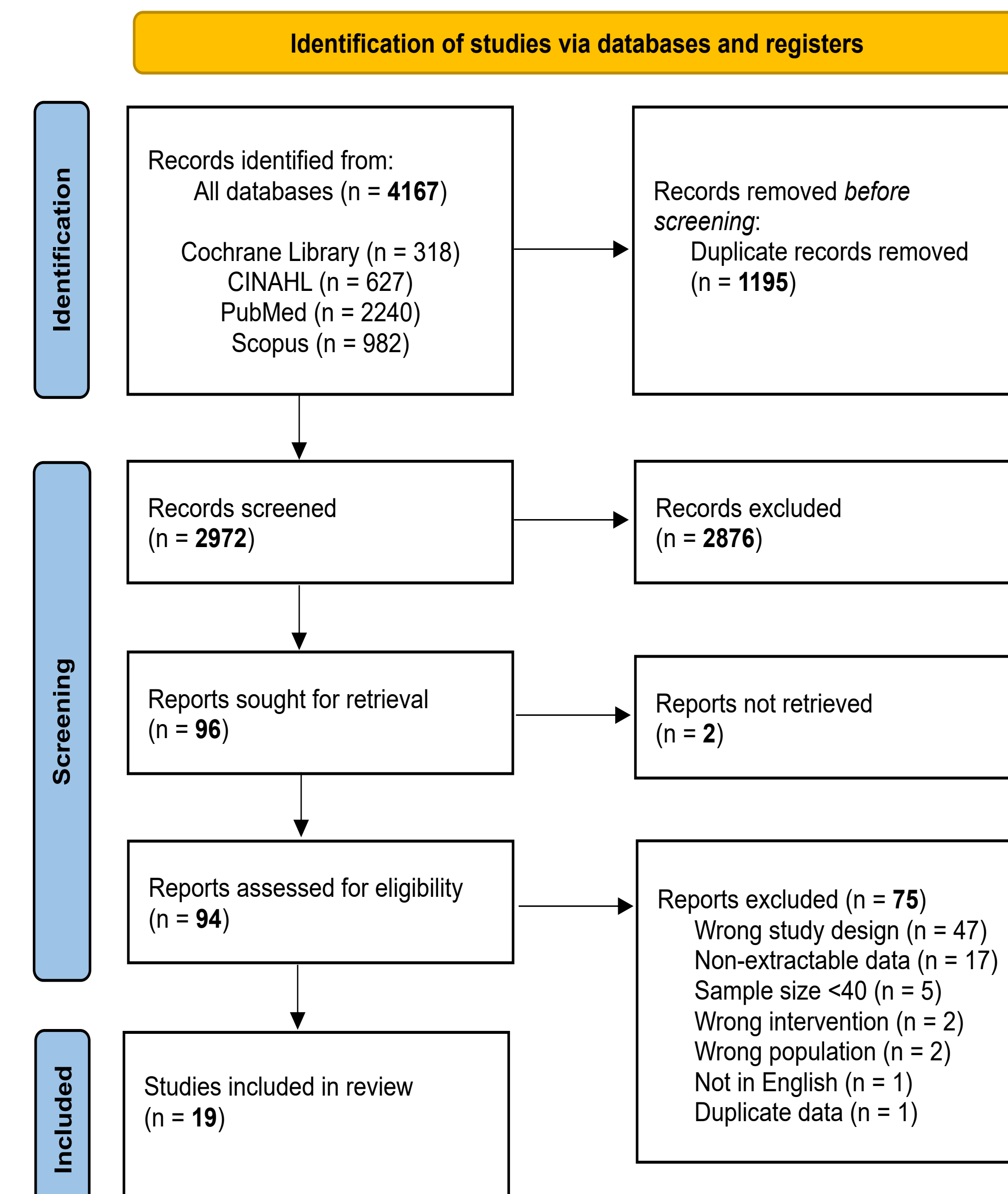


Figure 1. PRISMA systematic review flow diagram.

Study Characteristics

- After full-text review, 19 articles were selected after meeting inclusion criteria.⁷⁻²⁶

Patient Characteristics

- A total of 1186 patients were included with a mean age of 48.4 ± 5.3 (range: 19-74) and 61% [56.2 to 65.7] were male.
- The mean duration of tinnitus was 3.8 ± 3.4 years with 55.7% [46 to 65] of patients having unilateral tinnitus.
- All patients had subjective tinnitus that was either idiopathic or secondary to hearing loss. No patients had tinnitus secondary to trauma, infection, Meniere's disease, or other associated conditions.

Table 1. THI Short Term Outcomes (≤1 month)

Treatment	Group	Total patients (N)	Meta-analysis of single means	95% CI	Comparison of means	95% CI	P value
rTMS	Active	382	-4.8	-6.8 to -2.8	4.9	1.7 to 8.1	p = 0.0028
	Sham	266	0.1	-2.4 to 2.6			
TENS	Active	108	-16.2	-23.1 to -9.3	13.5	4.4 to 22.6	p = 0.0039
	Sham	63	-2.7	-3.9 to -1.5			
tDCS	Active	66	-19	-30.1 to -7.8	16	3.4 to 28.6	p = 0.0132
	Sham	59	-3	-7.3 to 1.3			

- A comprehensive literature search of the Cochrane Library, CINAHL, PubMed, and Scopus was performed from inception through May 30, 2023.
- Two authors (L.D.H. and J.M.O.) independently screened articles based on title and abstract followed by full text to identify all articles that met inclusion criteria.
- Inclusion criteria were: 1) sham-controlled randomized control trials testing neuromodulation in patients with tinnitus, 2) sample size of 40 or more patients, 3) tinnitus outcome data.
- Exclusion criteria were: 1) non-English studies, 2) non-human studies, 3) any study design other than sham-controlled randomized control trials, 4) non-extractable data.
- Outcome data including Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Tinnitus Handicap Inventory (THI), Tinnitus Questionnaire (TQ), Visual Analogue Scale (VAS), and 12-Item Short Form Health Survey (SF-12) were collected.
- The risk of bias of all included studies was determined as “low”, “high”, or “some concerns” using the revised Cochrane risk of bias tool for randomized trials (ROB 2).²¹

RESULTS

Table 2. THI Long Term Outcomes (>1 month)

Treatment	Group	Total patients (N)	Meta-analysis of single means	95% CI	Comparison of means	95% CI	P value
rTMS	Active	192	-8.6	-11.5 to -5.7	6.5	2.0 to 11.0	p = 0.0048
	Sham	150	-2.1	-5.6 to 1.4			

Table 3. TQ Short Term Outcomes (≤1 month)

Treatment	Group	Total patients (N)	Meta-analysis of single means	95% CI	Comparison of means	95% CI	P value
Neuromodulation	Active	219	-2.8	-9.7 to 4.1	1.5	-6.1 to 9.1	p = 0.6988
	Sham	200	-1.3	-3.7 to 1.2			
rTMS	Active	164	1.5	-0.1 to 3.1	-0.8	-3.0 to 1.4	p = 0.458
	Sham	161	0.7	-0.8 to 2.2			

Table 4. TQ Long Term Outcomes (>1 month)

Treatment	Group	Total patients (N)	Meta-analysis of single means	95% CI	Comparison of proportions (%)	95% CI	P value
rTMS	Active	110	-2.3	-6.7 to 2.1	4	-2.2 to 10.2	p = 0.2078
	Sham	106	1.7	-2.6 to 6.1			

Table 5. Patient Safety and Adverse Events

Adverse Events	Group	Proportion (%)	95% CI	Comparison of proportions (%)	95% CI	P value
Dropout	Active	9.4	6.1 to 13.9	1	-4.8 to 6.5	p = 0.72
	Sham	8.4	2.2 to 18.1			
Facial fasciculations	Active	15.3	7.6 to 26.4	9.7	-1.5 to 21.2	p = 0.08
	Sham	5.6	1.4 to 14.6			
Headache	Active	11.6	8.5 to 15.5	2.4	-3 to 7.4	p = 0.37
	Sham	9.3	5.9 to 13.7			
Dizziness	Active	6	2.1 to 12.9	2.7	-9.4 to 10.1	p = 0.54
	Sham	3.3	0.2 to 14.9			
Worsening of tinnitus	Active	5.7	3 to 10	1.6	-3.6 to 7	p = 0.53
	Sham	7.4	2.5 to 14.5			

Table 6. BDI Outcomes

Treatment	Group	Total patients (N)	Meta-analysis of single means	95% CI	Comparison of means	95% CI	P value
rTMS	Active	119	-0.5	-1.9 to 0.9	0.3	-1.7 to 2.3	p = 0.7655
	Sham	119	-0.2	-1.5 to 1.2			
tDCS	Active	46	-11.8	-13.3 to -10.3	9.9	7.7 to 12.1	p < 0.0001
	Sham	38	-1.9	-3.5 to -0.3			

CONCLUSIONS

- Neuromodulation is a safe treatment option for patients with tinnitus.
- This study found significant short-term benefit of TENS and tDCS as measured by the THI.
- Additionally, rTMS demonstrated long-term reduction in the THI.
- Based on the BDI, tDCS significantly reduces comorbid depression in patients with tinnitus.
- Relative to neuromodulation and across all outcomes meta-analyzed, sham treatment does not demonstrate significant improvement in tinnitus symptoms.

REFERENCES

- Tunkel DE, Bauer CA, Sun GH, et al. Clinical practice guideline: tinnitus executive summary. *Otolaryngol Head Neck Surg*. 2014;151(4):533-41. doi:10.1177/0194599814547475
- Cima RFF, Mazurek B, Haider H, et al. A multidisciplinary European guideline for tinnitus: diagnosis, assessment, and treatment. *Hno*. Mar 2019;67(Suppl 1):10-42. doi:10.1007/s00106-019-0633-7
- Weisz N, Müller S, Schlegel W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. *J Neurosci*. Feb 7 2007;27(6):1479-84. doi:10.1523/JNEUROSCI.3711-06.2007
- Vanneste S, Plazier M, Der Loof E, de Heyning PV, Congedo M, De Ridder D. The neural correlates of tinnitus-related distress. *Neuroimage*. Aug 15 2010;52(2):470-80. doi:10.1016/j.neuroimage.2010.04.029
- J.A. On tinnitus aurium and its treatment by electricity. *Lancet*. 1886;128:205-206.
- Peter N, Kleinjung T. Neuromodulation for tinnitus treatment: an overview of invasive and non-invasive techniques. *J Zhejiang Univ Sci B*. Feb. 2019;20(2):116-130. doi:10.1631/jzus.B1700117
- Sterne JAC, Savovic J, Page MJ, et al. ROB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Aug 29 2019;365:4498. doi:10.1136/bmj.n4498
- Anders M, Dvorakova J, Rathova L, et al. Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: a randomized, placebo controlled study. *Neuro Endocrinol Lett*. 2010;31(2):238-49.
- Aydin M, Erkan M, Gundogdu R, Vural A, Kokoglu K, Sahin M. Assessment of the Effectiveness of Transcranial Magnetic Stimulation in Subjective Tinnitus. *Int Arch Otorhinolaryngol*. Jul 2021;25(3):e453-e458. doi:10.1055/s-0040-1718530
- Silic S, Yigit O, Taskin LU, Cor AP, Yilmaz ED. Medium-term results of combined treatment with transcranial magnetic stimulation and antidepressant drug for chronic tinnitus. *Eur Arch Otorhinolaryngol*. Feb 2015;272(2):337-43. doi:10.1007/s00405-013-2851-2
- De Ridder D, Song JJ, Vanneste S. Frontal cortex TMS for tinnitus. *Brain Stimul*. May 2013;6(3):355-62. doi:10.1016/j.brs.2012.07.002
- Folmer RL, Theodoroff SM, Casiana L, Shi Y, Grest S, Vachhani J. Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg*. Aug 2015;141(8):716-22. doi:10.1001/jamaoto.2015.1219
- Formánek M, Migalová P, Krulová P, et al. Combined transcranial magnetic stimulation in the treatment of chronic tinnitus. *Ann Clin Transl Neurol*. Jul 2018;5(7):857-864. doi:10.1002/actn.3.587
- Hoekstra CE, Versnel H, Neggers SF, Niesten ME, van Zanen CA. Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: a randomized controlled trial. *Audiol Neurootol*. 2013;18(6):62-73. doi:10.1159/000354977
- Langguth B, Langguth B, Frank E, et al. Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. *World J Biol Psychiatry*. May 2014;15(4):276-85. doi:10.3109/15622975.2012.708438
- Lee SK, Chung H, Chung JH, Yeo SG, Park MS, Byun JY. Effectiveness of transcutaneous electrical stimulation for chronic tinnitus. *Acta Otolaryngol*. Feb 2014;134(2):159-67. doi:10.1097/oto.0000000000000375
- Li L, Shi H, Wang M. A Pilot Randomized Controlled Trial of Transcutaneous Electrical Nerve Stimulation for Patients With Acute Tinnitus. *Medicine (Baltimore)*. Jan 2019;98(1):e13793. doi:10.1097/MD.0000000000001375
- Li Y, Shen YQ, Galvin JJ, 3rd, Liu JS, Tao DD. Effect of Ipsilateral, Contralateral or Bilateral Repetitive Transcranial Magnetic Stimulation in Patients with Lateralized Tinnitus: A Placebo-Controlled Randomized Study. *Brain Sci*. Jun 2 2022;12(6):doi:10.3390/brainsci12060733
- Nikakhlagh S, Fatahiasi J, Saki Malehi A, Tabibzadeh SM. The Evaluation of Effects of Electrical Stimulation in Treatment of Patients with Chronic Tinnitus with Normal Hearing Sensitivity. *Indian J Otolaryngol Head Neck Surg*. Apr 2023;75(Suppl 1):409-15. doi:10.1007/s12070-023-03503-z
- Noth TS, Kyoung JS, Park MK, Lee JH, Oh SH, Suh MW. Dual-site TMS is More Effective than Single-site TMS in Tinnitus Patients: A Blinded Randomized Controlled Trial. *Brain Topogr*. Nov 2020;33(6):767-775. doi:10.1007/s10548-020-00797-y
- Pat N, Maire F, Stephan MA, Herrmann FR, Benninger DH. Transcranial Direct Current Stimulation for the Treatment of Chronic Tinnitus: A Randomized Controlled Study. *Brain Stimul*. Nov-Dec 2015;8(6):1101-7. doi:10.1016/j.brs.2015.06.014
- Plewinska G, Vonheim R, Wasserra B, et al. Treatment of chronic tinnitus with 90 burst stimulation: a randomized controlled trial. *Neurology*. May 22 2012;78(21):1628-34. doi:10.1212/WNL.0b013e3182574e9f
- Tutar B, Akar S, Berkler G, Usün O, Kumral TL, Uyar Y. The effect of transcutaneous electrical nerve stimulation (TENS) on chronic subjective tinnitus. *Am J Otolaryngol*. Jan-Feb 2020;41(1):102326. doi:10.1016/j.amjoto.2019.102326
- Yadollahpour A, Bayat A, Rashidi S, Saki N, Karimi M. Dataset of acute repeated sessions of bifrontal transcranial direct current stimulation for treatment of intractable tinnitus: A randomized controlled trial. *Data Brief*. Dec 2017;15:40-46. doi:10.1016/j.dib.2017.09.006
- Yilmaz M, Yener MH, Turgun NF, Aydin F, Altug T. Effectiveness of transcranial magnetic stimulation application in treatment of tinnitus. *J Craniofac Surg*. Jul 2014;25(4):1315-8. doi:10.1097/SCS.0000000000000782