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·论 著·

非侵入式脑刺激对帕金森病患者执行功能的影响：网状 meta 分析

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［摘要］ **目的** 探索非侵入式脑刺激措施改善帕金森病患者执行功能的有效性。**方法** 检索 Web of Science、PubMed、EMBASE、中国知网、万方数据 5 个数据库中关于经颅磁刺激、经颅交流电刺激、经颅直流电刺激 3 种非侵入式脑刺激干预措施治疗帕金森病且结局指标包括执行功能的随机对照试验，根据预先确定的标准筛选文献并提取数据。采用网状 meta 分析方法比较 3 种非侵入式脑刺激干预措施对帕金森病患者执行功能障碍的疗效，使用标准化均数差（*SMD*）及 95% 贝叶斯可信区间（*CrI*）汇总结果，通过累积排序曲线下面积（SUCRA）对各干预措施的疗效进行排序。**结果** 共纳入 20 项随机对照试验，包括 809 例帕金森病患者。与对照组相比，经颅磁刺激对帕金森病患者的执行功能有显著改善效果（*SMD*＝0.16，95% *CrI* 0.01～0.32）。各干预措施疗效的概率排序结果显示，对帕金森病患者执行功能障碍疗效最佳的干预措施排序为经颅磁刺激＞经颅交流电刺激＞经颅直流电刺激＞对照（SUCRA 分别为 0.72、0.61、0.41、0.25），经颅磁刺激最有可能是疗效最佳的干预措施。**结论** 目前的有限证据显示，经颅磁刺激对帕金森病患者的执行功能有直接的改善效果。受纳入研究的数量及质量影响，上述结论需进行更进一步的高质量研究验证。

［关键词］ 帕金森病；执行功能；非侵入式脑刺激；经颅磁刺激；网状 meta 分析
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Effects of non-invasive brain stimulation on executive functions in Parkinson's disease patients: a network meta-analysis

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［**Abstract**］ **Objective** To investigate the effectiveness of non-invasive brain stimulation in improving the executive functions of patients with Parkinson's disease (PD). **Methods** The randomized controlled trials (RCTs) about transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS) or transcranial direct current stimulation (tDCS) in treating PD patients with outcome indicators including executive functions were retrieved from 5 databases (Web of Science, PubMed, EMBASE, CNKI, and Wanfang data). The literatures were screened according to the predetermined criteria and the data were extracted. The effectiveness of 3 non-invasive brain stimulation interventions on executive dysfunction of PD patients was compared using network meta-analysis (NMA). The results were summarized by standardized mean difference (*SMD*) and 95% Bayesian credibility interval (*CrI*), and the effectiveness of each intervention was ranked by surface under the cumulative ranking curve (SUCRA). **Results** A total of 20 RCTs (809 PD patients) were included. Compared with the control group, TMS significantly improved the executive functions of PD patients (*SMD*＝0.16, 95% *CrI* 0.01-0.32). The probability ranking results of the effectiveness of the interventions on the executive functions of PD patients were TMS＞tACS＞tDCS＞

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control (SUCRA=0.72, 0.61, 0.41, 0.25, respectively). TMS was the most likely intervention with the best performance. **Conclusion** TMS has a direct improvement effect on executive functions of PD patients. Limited by the number and quality of the included studies, the above conclusion need to be further verified by high-quality studies.

[**Key words**] Parkinson's disease; executive functions; non-invasive brain stimulation; transcranial magnetic stimulation; network meta-analysis

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帕金森病以静止性震颤、僵直和运动迟缓等运动障碍为主要特征[1]，但在疾病进展过程中各种非运动特征并不少见，如认知功能下降和精神障碍等[2-3]。研究表明，帕金森病可能会影响到每个认知领域，包括注意、视觉空间功能、记忆和执行功能[3-4]，其中执行功能障碍可能是帕金森病患者的主要认知障碍。

非侵入式脑刺激治疗帕金森病因不良反应少、安全性高、易于操作、治疗效果好而受到广泛关注，目前用于帕金森病治疗的非侵入式脑刺激方案主要包括经颅磁刺激（transcranial magnetic stimulation，TMS）、经颅直流电刺激（transcranial direct current stimulation，tDCS）、经颅交流电刺激（transcranial alternating current stimulation，tACS）。前额叶皮质是执行功能的主要神经基础，虽然 TMS、tDCS、tACS 调节皮质兴奋性的机制不同，但三者均被证明可以诱导长时程增强或抑制突触可塑性[5-10]。目前非侵入式脑刺激对帕金森病患者执行功能障碍的疗效尚不明确。本研究采用网状 meta 分析（network meta-analysis，NMA）方法评价上述 3 种非侵入式脑刺激方式对帕金森病患者执行功能的改善效果，以期为临床实践提供参考。

1 资料和方法

1.1 纳入和排除标准　纳入标准：（1）研究类型为随机对照试验，其研究对象为根据诊断标准被判定为帕金森病患者，且无认知功能障碍；（2）研究的干预措施需至少包括 TMS、tDCS、tACS 其中一项，结局指标必须包括与执行功能相关的评分。排除标准：（1）无法获取全文及数据不全的研究；（2）相关结局指标仅用图片展示、无法获取确切数据的研究。

1.2 检索策略　利用计算机检索 5 个数据库（Web of Science、PubMed、EMBASE、中国知网、万方数据）中关于非侵入式脑刺激治疗帕金森病患者且结局指标包括执行功能的随机对照试验，检索的时间范围为建库至 2023 年 12 月。在检索电子数据库的同时，手工检索所收录文章的参考文献。检索词采用主题词与自由词结合，中文检索词包括帕金森病、经颅电刺激、经颅直流电刺激、经颅交流电刺激、经颅磁刺激，英文检索词包括 Parkinson disease、Parkinson's disease、transcranial alternating current stimulation、transcranial direct current stimulation、transcranial electrical stimulation、transcranial magnetic stimulation。中文检索式（以万方数据为例）为主题:("帕金森病") AND 题名或关键词:(经颅直流电刺激 OR 经颅磁刺激 OR 经颅交流电刺激 OR 经颅电刺激)，英文检索式（以 PubMed 为例）为 (Parkinson disease[MeSH] OR Parkinson's disease) AND (transcranial alternating current stimulation [Title/Abstract] OR transcranial direct current stimulation [Title/Abstract] OR transcranial electrical stimulation [Title/Abstract] OR transcranial magnetic stimulation [Title/Abstract])。

1.3 文献筛选、数据提取和质量评价　由 2 名研究者根据预先确定的纳入和排除标准独立进行文献筛选和数据提取。提取每项研究的样本量、分组、干预情况、执行功能量表评分。使用 Cochrane 5.4.0 版推荐的偏倚风险评估工具对所有纳入研究的偏倚风险进行评估，每种偏倚分为低风险、不明确或高风险 3 个等级。2 名研究者若遇到分歧，通过讨论解决；若讨论后分歧仍然存在，则咨询第 3 名研究者，然后做出最终决定。

1.4 统计学处理　采用 R 4.2.0 软件进行统计分析。构建网状关系图对不同干预措施之间的关系进行可视化。NMA 采用贝叶斯马尔科夫链-蒙特

卡罗算法（Markov chain Monte Carlo，MCMC），建立 4 条 MCMC 链，进行 20 000 次自适应迭代和 50 000 次仿真迭代。使用 Gelman-Rubin 方法诊断模型的收敛程度。纳入研究的总体异质性采用 χ^2 检验进行分析，若 $I^2>50\%$ 则认为异质性较大。使用节点分割法对闭环研究进行不一致性检验。考虑到纳入研究中执行功能评分存在广泛差异性，使用标准化均数差（standardized mean difference，*SMD*）汇总结果，并提供 95% 贝叶斯可信区间（Bayesian credibility interval，*CrI*）。计算每种干预措施疗效的排序概率，通过累积排序曲线下面积（surface under the cumulative ranking curve，SUCRA）来衡量综合优选排序和不确定性。采用逐一剔除法进行敏感性分析。使用漏斗图评估发表偏倚。检验水准（α）为 0.05。

2 结　果

2.1　文献筛选结果及基本信息　文献筛选流程和结果见图 1。共纳入 20 项随机对照试验[11-30]，包括 809 例帕金森病患者。各研究的基本信息见表 1，偏倚风险评估见图 2。

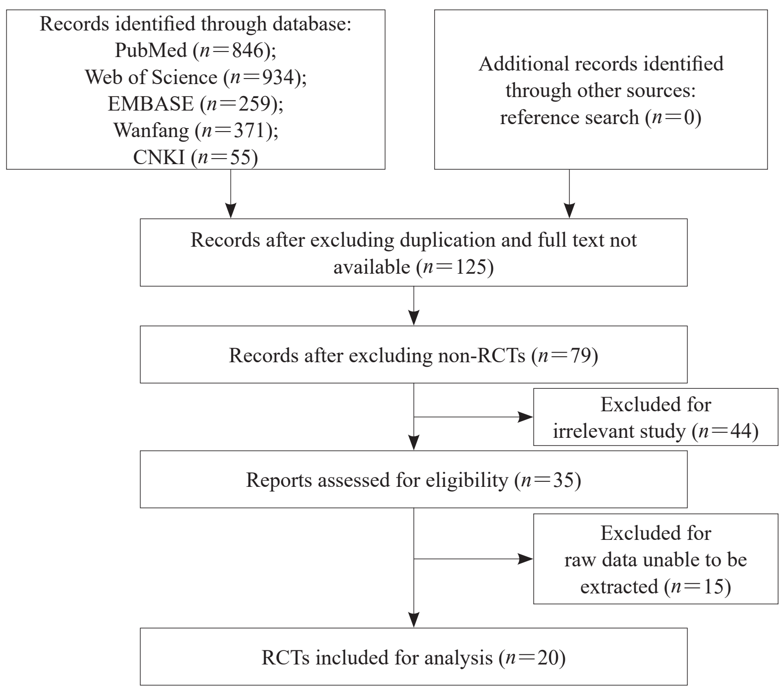

图 1　文献筛选流程图

Fig 1　Flow diagram of study selection

RCT: Randomized controlled trial.

2.2　纳入研究中不同干预措施的网状关系和一致性分析　纳入的 809 例帕金森病患者中，412 例接受积极非侵入式脑刺激治疗，不同干预措施的网状关系见图 3，直接比较和间接比较的异质性森林图见图 4。

2.3　不同非侵入式脑刺激方式对帕金森病患者执行功能的疗效比较　NMA 结果（表 2）显示，TMS 与对照组相比显示出显著的益处（*SMD*＝0.16，95% *CrI* 0.01～0.32），而 tACS 和 tDCS 与对照组相比并未显示疗效的改善（95% *CrI* 均包含 0，即无统计学意义）。在 3 种脑刺激方式的两两比较中，并未发现明显优于其他干预方法的干预措施。

根据 SUCRA 结果，TMS 最有可能是 3 种干预措施中治疗帕金森病患者执行功能障碍疗效最佳的干预措施（SUCRA＝0.72，排序最佳的概率为 37%），概率排序为 TMS＞tDCS＞tACS＞对照组（表 3）。

2.4　发表偏倚检验和敏感性分析　漏斗图呈现明显的不对称结构（图 5）。采用线性回归模型（Egger's 检验）检验漏斗图的对称性，结果显示有统计学意义（Egger's＝3.22，*P*＜0.05），提示可能存在发表偏倚。敏感性分析结果显示，剔除个别研究后结论无明显方向性改变（表 4）。

表 1　纳入研究的基本信息

Tab 1　Characteristics of included studies

Study	Observation group				Control group		Execution function rating scale
	n	Intervention	Stimulation plan	Stimulation parameter	*n*	Intervention	
Del Felice, 2019[11]	20	tACS+physical therapy	30 min per day, 5 d per week for 2 weeks	4 Hz, 30 Hz; 2 mA	10	Physical therapy	Digit symbol substitution test
Manenti, 2018[12]	11	tDCS+computerized cognitive training	25 min per day, 5 d per week for 2 weeks	2 mA	11	Computerized cognitive training	TMT, attentional performance test, Stroop test, FAB
Wei, 2022[13]	30	rTMS+cognitive training	1 200 pulses×2 sessions per day, 5 d per week for 2 weeks	5 Hz	30	Cognitive training	WCST
Srovnalova, 2012[14]	10	rTMS+cognitive training	600 pulses per day, 4 sessions with 1-2 d in between	25 Hz	10	Cognitive training	Tower of London test
Trung, 2019[15]	14	TMS	600 pulses twice a day for 3 d with 1-2 d in between	50 Hz	14	Usual care	Executive function
Bueno, 2019[16]	10	tDCS	20 min×1 session	2 mA	10	Sham stimulation	TMT, verbal fluency test, Stroop test
Buard, 2018[17]	22	rTMS	750 pulses once a day for 10 consecutive weekdays	20 Hz	24	Sham stimulation	TMT, Boston naming test
Srovnalova, 2011[18]	10	rTMS	600 pulses×1 session	25 Hz	10	Sham stimulation	Stroop test, FAB
He, 2021[19]	20	rTMS	600 pulses once a day for 10 consecutive weekdays	Resting motor threshold, 50 Hz	15	Sham stimulation	Repeatable battery for the assessment of neuropsychological status
Boggio, 2005[20]	13	rTMS	40 trains of 5 s each for 10 d over a 2-week period	15 Hz, 110% of motor threshold	12	Sham stimulation	Stroop test, WCST
Guerra, 2022[21]	6	tACS	6 min×2 session	20 Hz, 70 Hz, 1 mA	6	Sham stimulation	FAB
Deppermann, 2014[22]	22	rTMS	600 pulses once a day for 15 d over a 3-week period	80% of resting motor threshold	22	Sham stimulation	Verbal fluency task
Hill, 2020[23]	7	TMS	600 pulses once a day for 10 d	50 Hz	7	Sham stimulation	Berg's card sorting test
Qi, 2019[24]	47	Low-frequency rTMS	20 min, 5 times a week for 8 weeks	1 Hz, 80% of motor threshold	47	Usual care	Rapid verbal retrieve, clock drawing test, TMT
Zhang, 2023[25]	32	Virtual reality+rTMS	20 min, 5 times a week for 8 weeks	10 Hz, 90% of motor threshold	32	Cognitive training	Montreal cognitive assessment
Huang, 2021[26]	30	rTMS+rehabilitation training	800 pulses once a day, 6 times a week for 1 month	1 Hz/5 Hz, 80% of motor threshold	30	Rehabilitation training	Montreal cognitive assessment
Zhang, 2020[27]	37	rTMS+rehabilitation training	800 pulses once a day, 6 times a week for 3 months	10 Hz	37	Rehabilitation training	Montreal cognitive assessment
Liu, 2019[28]	30	Low-frequency rTMS	20 min per day for 20 d	1 Hz, 110% of resting motor threshold	30	Usual care	Montreal cognitive assessment
Li, 2018[29]	28	tDCS	20 min×1 session	2 mA	28	Sham stimulation	Montreal cognitive assessment
Sedláckova, 2009[30]	13	High-frequency rTMS	1 350 pulses×1 session	10 Hz,100% of resting motor threshold	12	Usual care	Letter verbal fluency test, TMT

tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; rTMS: Repetitive transcranial magnetic stimulation; TMS: Transcranial magnetic stimulation; TMT: Trail making test; FAB: Frontal assessment battery; WCST: Wisconsin card sorting test.

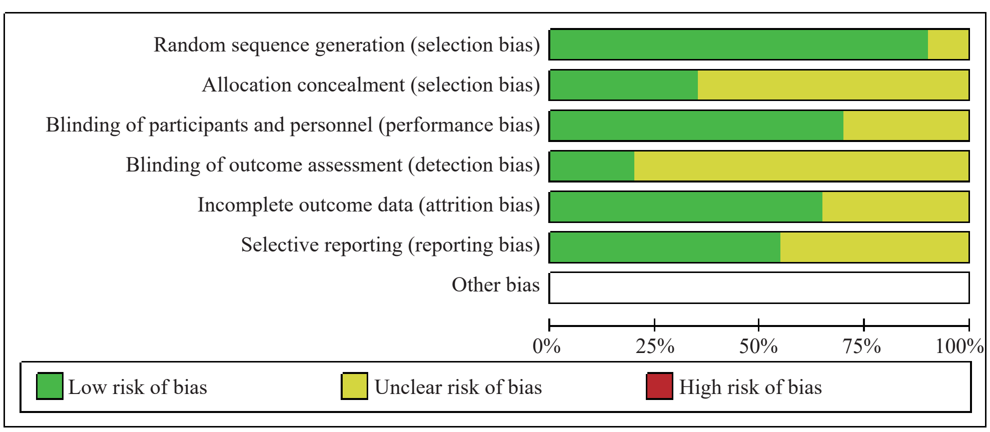

图 2　纳入研究的偏倚风险评估

Fig 2　Bias risk assessment of included studies

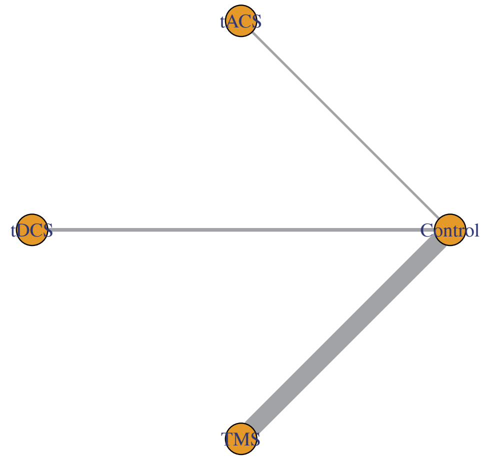

图 3　纳入研究中不同干预措施的网状关系图

Fig 3　Network diagram of different interventions in included studies

Lines represent treatments with direct comparisons. The thickness of edges represents the number of studies underlying each comparison. tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation.

3　讨　论

认知缺陷在帕金森病患者中很常见，多巴胺耗竭导致前额纹状体回路中断，进而导致认知能力下降[31-33]。帕金森病可能影响每个认知领域，包括记忆、语言、注意力、视觉空间和视觉建构能力及执行功能[31,34]。既往文献中报道的一部分更广泛的认知缺陷实际上是潜在的执行功能障碍的一种表现[4,34-35]。在帕金森病中观察到皮质-纹状体兴奋性和抑制性传递的改变[36-37]，依赖前额叶、运动皮质和纹状体之间联系的执行功能受损可能是多巴胺缺乏的结果[38-39]。

非侵入式脑刺激技术可能通过调节潜在皮质组织的兴奋性促使与帕金森病相关的异常神经生理学正常化。目前临床上对非侵入式脑刺激的选择往往根据临床经验，缺乏循证医学证据支持。本研究采用 NMA 方法评价 3 种非侵入式脑刺激方式对帕金森病执行功能恢复效果的优劣。

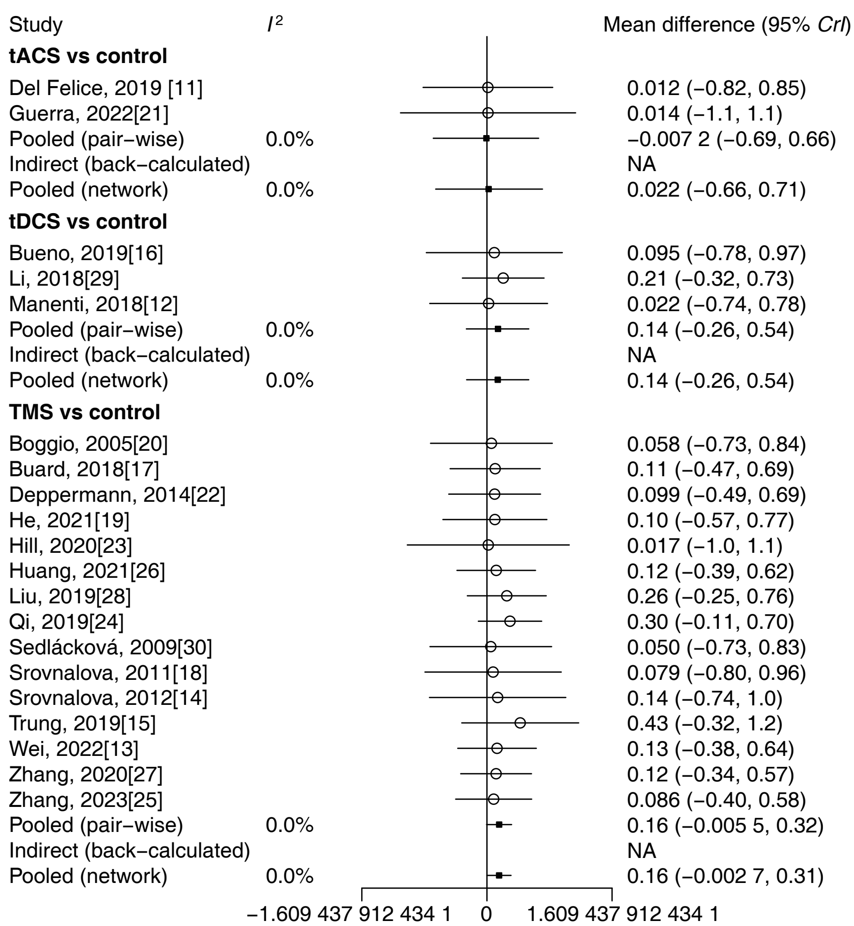

图 4　纳入研究中干预措施的直接和间接比较异质性森林图

Fig 4　Forest plots of heterogeneity of interventions compared directly and indirectly in included studies

tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; *CrI*: Bayesian credibility interval; NA: Not available.

表 2　不同干预措施对帕金森病执行功能影响的网状 meta 分析结果

Tab 2　Network meta-analysis of effects of different interventions on executive functions in patients with Parkinson's disease

SMD (95% *CrI*)

Intervention	tACS	tDCS	TMS
tDCS	−0.12 (−0.91, 0.65)		
TMS	−0.14 (−0.85, 0.54)	−0.03 (−0.47, 0.41)	
Control	0.01 (−0.68, 0.66)	0.13 (−0.53, 0.28)	0.16 (0.01, 0.32)

tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; *SMD*: Standardized mean difference; *CrI*: Bayesian credibility interval.

表 3　不同干预措施对帕金森病执行功能影响的概率排序结果

Tab 3　Probability ranking results of effectiveness of different interventions on executive functions in patients with Parkinson's disease

Intervention	Probability ranking				SUCRA
	1st	2nd	3rd	4th	
tACS	0.26	0.14	0.14	0.31	0.41
tDCS	0.35	0.26	0.21	0.17	0.61
TMS	0.37	0.30	0.17	0.01	0.72
Control	0.00	0.15	0.48	0.37	0.25

tACS: Transcranial alternating current stimulation; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; SUCRA: Surface under the cumulative ranking curve.

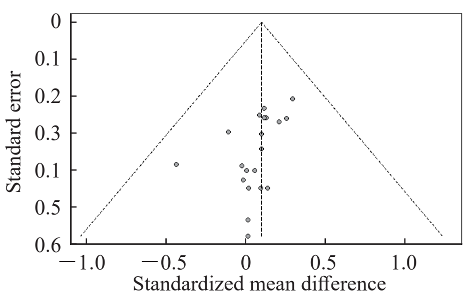

图 5　纳入研究的发表偏倚漏斗图

Fig 5　Funnel plot of publication bias of included studies

表 4　纳入研究的敏感性分析

Tab 4　Sensitivity analysis of included studies

Study	*SMD* (95% *CI*)	*P* value
Omitting Del Felice, 2019[11]	0.11 (−0.03, 0.25)	0.14
Omitting Manenti, 2018[12]	0.10 (−0.03, 0.24)	0.14
Omitting Wei, 2022[13]	0.10 (−0.04, 0.24)	0.17
Omitting Srovnalova, 2012[14]	0.10 (−0.02, 0.26)	0.16
Omitting Trung, 2019[15]	0.12 (−0.03, 0.24)	0.09
Omitting Bueno, 2019[16]	0.10 (−0.04, 0.24)	0.15
Omitting Buard, 2018[17]	0.11 (−0.03, 0.24)	0.11
Omitting Srovnalova, 2011[18]	0.10 (−0.03, 0.24)	0.14
Omitting He, 2021[19]	0.10 (−0.04, 0.24)	016
Omitting Boggio, 2005[20]	0.10 (−0.03, 0.24)	0.15
Omitting Guerra, 2020[21]	0.10 (−0.03, 0.24)	0.15
Omitting Deppermann, 2014[22]	0.10 (−0.04, 0.24)	0.16
Omitting Hill, 2020[23]	0.10 (−0.03, 0.24)	0.14
Omitting Qi, 2019[24]	0.07 (−0.07, 0.22)	0.31
Omitting Zhang, 2023[25]	0.10 (−0.04, 0.25)	0.16
Omitting Huang, 2021[26]	0.10 (−0.04, 0.24)	0.17
Omitting Zhang, 2020[27]	0.10 (−0.04, 0.25)	0.17
Omitting Liu, 2019[28]	0.09 (−0.05, 0.25)	0.22
Omitting Li, 2018[29]	0.09 (−0.05, 0.23)	0.20
Omitting Sedlácková, 2009[30]	0.10 (−0.05, 0.23)	0.14
Pooled estimate	0.10 (−0.04, 0.25)	0.15

SMD: Standardized mean difference; *CI*: Confidence interval.

本研究结果发现，TMS 与对照组相比明显改善了帕金森病患者的执行功能，而 tDCS、tACS 对执行功能的改善无统计学意义。在最佳概率排序结果中，TMS 可能疗效最优。但 TMS 对帕金森病患者执行功能的影响仍存在争议，如本研究纳入的 2 项研究中 TMS 对帕金森病患者的执行功能似乎没有改善[13-14]，未来需要对这一治疗技术的相关参数和机制进行更详细的探索。本研究纳入的 RCT 中有 2 项关于 tACS 的研究检测了帕金森病患者的执行功能[11,21]，有 3 项关于 tDCS 的研究检测了帕金森病患者的执行功能[12,16,29]，结果均显示帕金森病患者的执行功能有所改善，但受到纳入研究的数量限制，在 NMA 结果中 tACS 和 tDCS 对帕金森病执行功能的改善并无统计学意义。因此，未来还需要开展更多的对照试验，进一步探索 tACS 和 tDCS 是否有助于缓解帕金森病患者的执行功能障碍。

本研究的局限性在于可纳入分析的文献相对较少，并且部分纳入的研究显示出不明确的偏倚风险，各研究的刺激方案和参数也存在较大差异，难以对干预措施进行更具体或更详细的分析。我们考虑过将每个研究、每种干预策略进行分析，但这将大大降低 NMA 的统计能力。此外，本研究没有使用特定的量表来评估执行功能的有效性。

综上所述，根据当前有限的证据，TMS 对帕金森病患者执行功能的干预效果可能优于 tACS 和

tDCS。但受到纳入研究的局限性限制，该结论尚需进一步验证。

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