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经颅直流电刺激对帕金森病伴快速眼动相睡眠行为障碍患者认知功能及神经功能的影响 *

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摘要 目的：探讨经颅直流电刺激对帕金森病伴快速眼动相睡眠行为障碍患者认知功能及神经功能的影响。**方法：**选择 2018 年 9 月 -2019 年 9 月在我院接受治疗的 69 例帕金森病伴快速眼动相睡眠行为障碍患者，采用随机数表法分为电刺激组（n=35）和对照组（n=34）。对照组给予常规抗帕金森病治疗，观察组在对照组的基础上给予经颅直流电刺激治疗。比较两组临床疗效、蒙特利尔认知评估量表（MoCA）、自主神经症状量表（SCOPA-AUT）、睡眠情况、汉密尔顿抑郁量表(HAMD)、Epworth 嗜睡量表（ESS）评分、匹兹堡睡眠指数（PSQI）、帕金森氏病综合评分量表（UPDRS）变化情况。**结果：**治疗后，电刺激组有效率 91.43%（32/35）较对照组 70.59%（24/34）显著升高，差异显著（P<0.05）；治疗前，电刺激组与对照组之间认知功能及神经功能结果无差异；治疗后，电刺激组与对照组 MoCA 均随着时间的推移均呈上升趋势，且电刺激组上升程度较较组更低，SCOPA-AUT 均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05）；治疗前，电刺激组与对照组之间临床睡眠情况结果无差异；治疗后，电刺激组与对照组总睡眠时间、睡眠效率均随着时间的推移均呈上升趋势，且电刺激组上升程度较对照组更低，醒觉指数均随着时间的推移呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05）；治疗前，电刺激组与对照组之间抑郁、嗜睡情况无差异；治疗后，电刺激组与对照组抑郁、嗜睡均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05）；治疗前，电刺激组与对照组之间 PSQI、UPDRS 评分无差异；治疗后，电刺激组与对照组 PSQI、UPDRS 评分均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05）。**结论：**在帕金森病伴快速眼动相睡眠行为障碍患者中应用经颅直流电刺激效果显著，可有效改善认知功能及神经功能水平。

关键词：经颅直流电刺激；帕金森病；快速眼动相睡眠行为障碍；认知功能；神经功能

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Effects of Transcranial Direct Current Stimulation on Cognitive and Neurological Functions in Patients with Parkinson's Disease with REM Sleep Behavior Disorder*

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ABSTRACT Objective: To study Effects of transcranial direct current stimulation on cognitive and neurological functions in patients with Parkinson's disease with REM sleep behavior disorder. **Methods:** 69 patients with Parkinson's disease and REM sleep behavior disorder who were treated in our hospital from September 2018 to September 2019 were selected and divided into electrical stimulation group (n=35) and control group (n=34) by random number table method. The control group received routine anti-Parkinson disease treatment, and the observation group received transcranial direct current stimulation treatment on the basis of the control group. The clinical efficacy, Montreal Cognitive Assessment Scale (MoCA), Autonomic neurological Symptoms Scale (SCOPa-AUT), sleep status, Hamilton Depression Scale (HAMD), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Index (PSQI), and Parkinson's disease Comprehensive Scale (UPDRS) were compared between the two groups. **Results:** After treatment, the effective rate of the electric stimulation group was 91.43% (32/35), significantly higher than that of the control group (70.59% (24/34), with a significant difference (P<0.05). Before treatment, there was no difference in cognitive function and neurological function between the stimulation group and the control group. After treatment, MoCA of both the electrical stimulation group and the control group showed an increasing trend over time, and the increase degree of the electrical stimulation group was lower than that of the control group. Scopa-aut showed a decreasing

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trend over time, and the decrease degree of the electrical stimulation group was lower than that of the control group (*P*<0.05). Before treatment, there was no difference in clinical sleep between the electrical stimulation group and the control group. After treatment, the total sleep time and sleep efficiency of both the electric stimulation group and the control group showed an upward trend with the passage of time, and the degree of increase of the electric stimulation group was lower than that of the control group, and the wake index showed a downward trend with the passage of time, and the degree of decrease of the electric stimulation group was lower than that of the control group (*P*<0.05). Before treatment, there was no difference in depression and drowsiness between the electric stimulation group and the control group. After treatment, depression and drowsiness in both the electric stimulation group and the control group showed a downward trend over time, and the degree of decline in the electric stimulation group was lower than that in the control group (*P*<0.05). Before treatment, there was no difference in PSQI and UPDRS scores between the electrical stimulation group and the control group. After treatment, PSQI and UPDRS scores in both the electric stimulation group and the control group showed a downward trend over time, and the degree of decline in the electric stimulation group was lower than that in the control group (*P*<0.05). **Conclusion:** Transcranial direct current (TDC) stimulation is effective in Parkinson's disease patients with REM sleep behavior disorder, which can effectively improve cognitive and neurological functions.

Key words: Transcranial direct current stimulation; Parkinson's disease; Rem sleep behavior disorder; Cognitive function; Nerve function

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前言

帕金森病是一种常见的神经变性疾病，患者除表现为运动迟缓、姿势步态异常等运动症状外还伴随众多非运动症状，近年来，帕金森病非运动症状亚型的研究备受瞩目，其中多表现为快速眼动相睡眠行为障碍[1-3]。快速眼动相睡眠行为障碍是以快速眼动睡眠期肌肉失迟缓，同时伴有与梦境相关的言语为特征的疾病，与运动症状比较，睡眠障碍更容易被患者及医护人员忽视，严重影响患者的生活质量[4,5]。相关研究表现，快速眼动相睡眠行为障碍在帕金森病患者中较为常见，对病情的进展有一定影响[6]。既往有研究显示[7]，帕金森病伴快速眼动相睡眠行为障碍患者更容易出现认知功能障碍及自主神经功能障碍，随着病情的发展认知功能障碍可进一步加重甚至发展为帕金森病痴呆，因此及时采取有效措施对延缓患者认知功能障碍具有重要意义[8]。经颅直流电刺激作为一种非侵入性脑刺激方法，具有无创伤、安全性好等优点受到较多研究者青睐，并被运用于帕金森病的治疗中，但其在帕金森病伴快速眼动相睡眠行为障碍的治疗中还需进一步探讨[9]。本研究通过使用经颅直流电刺激对帕金森病伴快速眼动相睡眠行为障碍进行干预，并观察其对认知功能及神经功能的影响，现报道如下。

1 资料与方法

1.1 一般资料

选择 2018 年 9 月 -2019 年 9 月我院 69 例帕金森病伴快速眼动相睡眠行为障碍患者。将所有患者采用随机数表法分为观察组和对照组，观察者男 21 例，女 14 例，年龄区间 48~75 岁，平均(58.63±3.52)岁，病程为 1~6 年，平均(3.12±0.86)年；对照组男 19 例，女 15 例，年龄区间 50~76 岁，平均(58.64±3.49)岁，病程 1~5 年，平均(3.08±0.81)年。两组患者基线资料比较无差异(*P*>0.05)，可比较。

参照《帕金森病的诊断》[10]，(1)伴睡眠障碍；(2)合并静止时手抖、难以姿势平衡；(3)运动迟缓。

纳入标准：(1) 符合相关诊断标准；(2) 病例资料无脱落；(3)可以积极配合治疗；(4)无生命危险者；(5)签署知情同意书。排除标准：(1)合并重症需急救者；(2)神志不清者；(3)合并全身感染性疾病者；(4)合并凝血功能异常患者；(5)心脑血管病变者；(6)病情加重者者；(7)依从性较差者；(8)体内有植入设备者。

1.2 方法

对照组抗帕金森病治疗包括多芭类、多巴胺受体激动剂等；观察组在对照组的基础上加用经颅直流电刺激：选用智能电刺激器，直流电刺激模式，将阳极电极放置前额叶及前额叶背外侧皮质区，前额叶定位参照脑电图，阴极电极置于双侧肩部，电刺激强度为 1.2 mA 治疗时间 20 min，每周治疗 5 次，共治疗 30 d。

1.3 观察指标

采用 MoCA、SCOPA-AUT 评定认知功能及神经功能；PSQI 评分：满分 21 分，分值越高睡眠障碍越严重；UPDRS 评分：包括精神、行为、情绪方面进行评价，积分之和为 UPDRS 评分总积分；HAMD 评分＞20 分认为伴有抑郁状态；采用睡眠分析软件测定睡眠情况。

疗效评定标准：参照《帕金森病的诊断和治疗进展》评定：使用 UPDRS 评分进行评价。显效：临床疗效百分比下降 50% 以上。有效：临床疗效百分比下降 21%~49%。无效：临床疗效百分比下降不到 20%

1.4 统计学分析

以 spss22.0 软件包处理，计量资料用均数±标准差($\bar{x}\pm s$)表示，组间比较使用独立样本 t 检验，疗效资料以率表示，χ^2 检验，*P*＜0.05 表示差异具有统计学意义。

2 结果

2.1 电刺激组与对照组之间治疗效果对比

电刺激组有效率 91.43%(32/35)较对照组 70.59%(24/34)显著升高，差异显著(*P*<0.05)见表 1。

2.2 电刺激组与对照组之间临床睡眠情况对比

治疗前，电刺激组与对照组之间临床睡眠情况结果无差

异；治疗后，电刺激组与对照组总睡眠时间、睡眠效率均随着时间的推移均呈上升趋势，且电刺激组上升程度较对照组更低，醒觉指数均随着时间的推移呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05），见表 2。

表 1 电刺激组与对照组之间治疗效果对比[n(%)]

Table 1 Comparison of therapeutic effects between the electric stimulation group and the control group[n(%)]

Groups	n	Excellent	Valid	Invalid	Total effective rate
Electrical stimulation group	35	18(51.43)	14(40.00)	3(8.57)	32(91.43)
Control group	34	16(47.06)	8(23.53)	10(29.41)	24(70.59)
χ^2 value					4.8999
P value					0.027

表 2 电刺激组与对照组之间临床睡眠情况对比（$\bar{x}\pm s$）

Table 2 Comparison of clinical sleep conditions between the electrical stimulation group and the control group（$\bar{x}\pm s$）

Groups	n	Total sleep time(min)		Sleep efficiency(%)		Awake index(Times /h)	
		Prior treatment	After treatment	Prior treatment	After treatment	Prior treatment	After treatment
Electrical stimulation group	35	300.47±21.36	361.25±21.58	64.62±14.78	75.48±18.24	38.21±11.52	22.14±8.93
Control group	34	299.58±21.57	319.56±23.27	65.02±14.86	67.56±13.15	38.15±10.96	36.78±9.34
t value		0.172	7.719	0.112	2.064	0.022	6.656
P value		0.864	0.000	0.911	0.043	0.982	0.000

2.3 电刺激组与对照组之间抑郁、嗜睡情况对比

治疗前，电刺激组与对照组之间抑郁、嗜睡情况无差异；治疗后，电刺激组与对照组抑郁、嗜睡均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05），见表 3。

表 3 电刺激组与对照组之间抑郁、嗜睡情况对比（$\bar{x}\pm s$，分）

Table 3 Comparison of depression and drowsiness between the electrical stimulation group and the control group（$\bar{x}\pm s$，points）

Groups	n	HAMD		ESS	
		Prior treatment	After treatment	Prior treatment	After treatment
Electrical stimulation group	35	9.84±4.25	6.12±2.11	10.16±2.74	7.02±1.23
Control group	34	9.83±4.31	8.24±3.25	10.18±2.69	8.13±1.75
t value		0.009	3.223	0.031	3.055
P value		0.992	0.002	0.976	0.003

2.4 电刺激组与对照组之间 PSQI、UPDRS 评分对比

治疗前，电刺激组与对照组之间 PSQI、UPDRS 评分无差异；治疗后，电刺激组与对照组 PSQI、UPDRS 评分均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低（P<0.05），见表 4。

表 4 电刺激组与对照组之间 PSQI、UPDRS 评分对比（$\bar{x}\pm s$，分）

Table 4 Comparison of PSQI and UPDRS scores between electrical stimulation group and control group（$\bar{x}\pm s$，points）

Groups	n	PSQIscore		UPDRSscore	
		Prior treatment	After treatment	Prior treatment	After treatment
Electrical stimulation group	35	17.15±5.18	4.73±2.18	38.24±4.28	31.02±4.15
Control group	34	17.01±5.29	7.88±3.20	38.35±3.79	38.85±4.21
t value		0.111	4.791	0.113	7.779
P value		0.912	0.000	0.910	0.000

3 讨论

快速眼动睡眠行为障碍是预测运动前期帕金森病的一种临床标记物，指在快速眼动睡眠时机体骨骼肌正常张力消失，并伴有反复梦境演绎行为的异常睡眠[11,12]。其发病机制较为复杂，有研究认为帕金森的病理开水在脑干，破坏导致快速眼动睡眠松弛，从而导致快速眼动睡眠行为障碍发生[13]。还有研究表明，快速眼动睡眠行为障碍是 α- 突触核蛋白病的标志，帕金森患者早期α- 突触核蛋白沉积导致去甲肾上腺素、多巴胺等神经元发生病理病变，使传导通路神经细胞坏死及神经递质无法

正常传递，累及脑干睡眠调控中心，最终导致睡眠结构改变[14,15]。Ambra S[16]等研究发现，帕金森病伴快速眼动相睡眠行为障碍患者睡眠效率低，影响患者的生活质量，因此，对帕金森病伴快速眼动相睡眠行为障碍进行有效干预对患者具有重要意义。

经颅直流电刺激是近年来发展比较迅速的物理疗法，也是一种非侵入性大脑神经调控技术，可通过在头皮持续给予微弱电刺激调节大脑皮质兴奋性，激活神经元，使神经元处于兴奋状态，且刺激后皮质兴奋性改变可持续 1h 左右，今年来已被用于帕金森病的治疗中[17-19]。有研究显示，经颅直流电刺激可通过微弱直流电刺激目标区域，调节皮质功能，进而达到影响脑功能的目的[20,21]。本研究结果显示，给予经颅直流电刺激治疗的患者有效率为 91.43%，明显高于给予药物治疗的患者，说明，经颅直流电刺激在帕金森病伴快速眼动相睡眠行为障碍中有较好的治疗效果。国外研究也显示，多次经颅直流电刺激后可产生累及效应，有助于提高疗效[22]。帕金森病伴快速眼动相睡眠行为障碍患者睡眠结构紊乱及觉醒次数增多，导致睡眠效率降低，总睡眠时间减少，进而导致日间过度嗜睡。本研究结果显示，治疗后，患者醒觉指数、抑郁、嗜睡、PSQI、UPDRS 评分均随着时间的推移均呈下降趋势，且使用经颅直流电刺激的患者下降程度较对照组更低，进一步证实了经颅直流电刺激可通过改善患者睡眠、抑郁、嗜睡情况提高临床疗效。Jankovic J[23]等研究也显示，对帕金森病伴快速眼动相睡眠行为障碍患者给予经颅直流电刺激治疗可改善患者日间嗜睡症状及抑郁情绪，与本研究结果相似。分析其原因可能是因为经颅直流电刺激可通过调节神经元静息膜电位、改变 γ- 氨基丁酸活性等途径建立新的神经末梢突触，增强突触性能，影响脑局部血流量提高患者的睡眠质量。

认知功能受损到一定程度会出现明显的社会行为退化从而形成痴呆，而在帕金森病患者中，痴呆的发病率约为 30%，而在帕金森病伴快速眼动相睡眠行为障碍与认知功能的关系尚不明确[24-26]。相关研究表明，当发生帕金森病伴快速眼动相睡眠行为障碍时可导致脑干网状神经结构异常，导致投射到大脑皮质调节机制异常，还可通过细胞与细胞间的传递模式导致前脑控制正常的认知障碍[27,28]。国外研究认为[29]，帕金森病伴快速眼动相睡眠行为障碍患者认知功能障碍主要表现为视空间与执行功能、语言方面。MoCA 量表是认知功能障碍患者较理想的筛查工具，对执行功能、复述等方面认知障碍时具有明显优势[30]。本研究将 MoCA 用于评估患者的认知功能，结果显示，治疗后患者 MoCA 随着时间的推移均呈上升趋势，且使用经颅直流电刺激的患者上升程度较较组更低，说明，发生帕金森病伴快速眼动相睡眠行为障碍时患者会出现认知功能障碍，而使用经颅直流电刺激可减少对认知功能的影响。分析其原因可能是因为经颅直流电刺激可促使皮质神经元兴奋，增强脑局部血液循环，使两侧脑半球通过交互性半球间抑制达到并维持功能相互匹配及平衡状态，且在刺激兴奋大脑皮质同时增强脑干上行网状功能，提高意识水平，从而加速患者认知功能的恢复。有研究认为，帕金森病伴快速眼动相睡眠行为障碍多存在自主神经功能紊乱，表现为蓝斑下核与同侧楔前叶的功能连接减弱[31,33]。本研究采用 SCOPA-AUT 量表评价患者神经功能情况，结果发现，SCOPA-AUT 均随着时间的推移均呈下降趋势，且电刺激组下降程度较对照组更低，Tozzi A 等研究在帕金森患者的初级运动皮质区给予经颅电刺激，可促进患者体内源性多巴胺的释放。国外研究也显示，经颅直流电刺激可通过微弱电刺激诱导神经可塑性，从而影响脑功能。分析其原因可能是因为经颅直流电刺激可增高功能减退的大脑皮质兴奋性，改善其相应功能，同时还能调节皮质抑制环路及多巴胺的含量，通过改善患者大脑皮层兴奋性及患者脑部血液流动状况进一步改善患者脑功能。

综上所述，在帕金森病伴快速眼动相睡眠行为障碍患者中应用经颅直流电刺激效果显著，可有效改善认知功能及神经功能水平。

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