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重复经颅磁刺激对慢性精神分裂症患者认知功能影响的初步研究

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摘要 目的:探讨重复经颅磁刺激(rTMS)对慢性精神分裂症患者认知功能的影响。**方法:**100例慢性精神分裂症患者,按照随机数字表法分为rTMS真刺激组和伪刺激组,每组各50例。采用阳性与阴性症状量表(PANSS)及副反应量表(TESS)评估患者治疗前后精神症状及不良反应;采用威斯康星卡片分类测验(WCST)及可重复的成套神经心理状态测量(RBANS)评价患者治疗前后认知功能。**结果:**治疗后,rTMS真刺激组PANSS总分、阳性量表分、阴性量表分、一般精神病量表分均明显降低($P<0.05$),且均明显低于伪刺激组($P<0.05$),两组治疗前后及组间TESS评分无明显差异($P>0.05$);rTMS真刺激组WCST中的概念化水平百分数明显高于伪刺激组($P<0.05$),总时间及错误思考时间短于伪刺激组($P<0.05$);rTMS真刺激组RBANS中视觉广度与延迟记忆成绩明显提高($P<0.05$),且视觉广度明显高于伪刺激组($P<0.05$);rTMS真刺激组2例患者首次治疗后出现轻度不适症状,随访3个月所有患者均无不舒适主诉。**结论:**rTMS治疗对慢性精神分裂症患者的部分认知功能有一定的改善作用,且安全性较高,值得进一步研究。

关键词:重复经颅磁刺激;慢性精神分裂症;认知功能

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Preliminary Study of Effect of Repetitive Transcranial Magnetic Stimulation on Cognitive Function in Patients with Chronic Schizophrenia

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ABSTRACT Objective: To investigate the effect of repetitive transcranial magnetic stimulation (rTMS) on cognitive function in patients with chronic schizophrenia. **Methods:** 100 cases patients with chronic schizophrenia were selected. They were divided into rTMS stimulation group and pseudo stimulation group according to the random number table method, and each group include 50 cases. The positive and Negative Syndrome Scale (PANSS) and the Treatment Emergent Symptom scale (TESS) were used to assess the clinical symptoms and side effects before and after the treatment; The Wisconsin Card Sorting Test (WCST) and Repeatable Neuropsychological State Measurement (RBANS) were used to assess the patients' cognitive function before and after treatment. **Results:** After treatment, the PANSS total score, the positive subscale score, the negative subscale score, the general psychopathological subscale score in the rTMS stimulation group were significantly reducing ($P<0.05$), and significantly lower than those in the pseudo stimulation group ($P<0.05$), but the TESS scores between the two groups did not differ significantly before and after treatment. The percentage of WCST in rTMS stimulation group was significantly higher than that in the pseudo stimulation group ($P<0.05$), and the total time and wrong thinking time was shorter than that in the pseudo stimulation group ($P<0.05$); The visual span and delayed memory performance of RBANS was significantly increased in the rTMS stimulation group ($P<0.05$), and the visual span was significantly higher than that in the pseudo stimulus group ($P<0.05$); There were 2 cases of patients with mild symptoms after the first treatment in rTMS stimulation group, all patients were without complaint followed up for 3 months. **Conclusion:** rTMS treatment on the part of the cognitive function of patients with chronic schizophrenia has a certain improvement effect, and higher security, it is worth further study.

Key words: Repetitive transcranial magnetic stimulation; Chronic schizophrenia; Cognitive function

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前言

重复经颅磁刺激 (repetitive transcranial magnetic stimulation, rTMS) 是一种重复刺激特定皮质的颅外大脑刺激技术,具

有操作简便、无创、痛苦小的优点。近些年国内外很多学者就其对精神分裂症患者的阴性症状与幻听等部分症状的治疗效果展开了研究。在 70 年代初人们已开始认识到认知功能障碍是精神分裂症患者除阳性症状与阴性症状外存在的又一组核心

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症状,发生率在 55.9%^[1,2],但在过去的很长一段时间都未得到足够的重视。慢性精神分裂症患者的认知功能紧密关系着其社会功能与职业功能^[3],所以改善患者的认知功能损害的程度对其回归社会具有十分积极的意义。本研究旨在探讨 rTMS 对慢性精神分裂症患者认知功能的影响,现报告如下。

1 资料与方法

1.1 一般资料

选择 2012 年 3 月 -2015 年 12 月间武汉市武东医院收治的 100 例慢性精神分裂症患者。纳入标准:① 符合国际疾病分类(ICD)诊断标准^[4];② 病程 2~15 年;③ 患者正在接受药物治疗;④ 磁刺激治疗期间药物种类、剂量不变;⑤ 初中及以上文化水平;⑥ 患者依从性良好,均可完成所有治疗和量表测验。排除标准:① 伴有严重的躯体疾病及精神发育迟滞者;② 既往存在癫痫、颅脑外伤史,或者排除影响本文研究结局的相关治疗措施(如 MECT);③ 脑电图异常者;④ 妊娠期或哺乳期妇女;⑤ 有严重攻击行为者。按照随机数字表法将其分为 rTMS 真刺激组和伪刺激组,每组各 50 例,其中 rTMS 真刺激组男 31 例,女 19 例;年龄 40~73 岁,平均(57.9±14.8)岁;病程 3~10 年,平均(5.5±2.8)年;伪刺激组男 27 例,女 23 例;年龄 39~79 岁,平均(55.8±15.1)岁;病程 3~13 年,平均(5.8±1.7)年。两组一般资料无明显差异($P>0.05$),具有可比性。所有受试者均知情同意,本研究通过伦理委员会批准。

1.2 治疗方法

两组均予利培酮片(厂家:齐鲁制药有限公司,国药准字:H20041808),4-6 mg/d,每日 2 次口服,用药剂量按患者的实际情况进行调整,出现 EPS 的患者给予抗胆碱药物,部分焦虑及睡眠障碍患者给予安定类药物。经颅磁刺激治疗仪器为 MagproX100 经颅磁刺激仪(英国 MAGSTIM 公司),“8”字形线圈,频率为 10Hz,强度为 100%运动阈值,刺激位置为左侧前额叶背外侧区,30 串刺激,每串刺激 5 s,间歇 30 s,每次 20 min,每日 1 次,每周连续 5 次,共治疗 4 周。rTMS 真刺激组方法:线圈和头部相切,将线圈轴朝向鼻梁;伪刺激组方法:线圈与头皮表面呈 180°,以产生无效刺激。

1.3 观察指标

采用阳性与阴性症状量表(PANSS)^[5]、副反应量表(TESS)^[6]评估患者治疗前后精神症状的变化以及是否出现相对的不良

反应。其中 PANSS 包括:阳性量表分(P1-P7);阴性量表分(N1-N7);一般精神病量表分(G1-16),并且 1- 无、2- 很轻、3- 轻度、4- 中度、5- 偏重、6- 重度、7- 极重度;TESS: ① 严重程度:无(0 分)、可疑或极轻(1 分)、轻度(2 分)、中度(3 分)、中度(4 分)。② 处理:0 无(0 分)、加强观察(1 分)、予拮抗药(2 分)、减少剂量(3 分)、减少剂量并予拮抗药(4 分)、暂停治疗(5 分)、中止治疗(6 分)。治疗前后分别采用威斯康星卡片分类测验(WCST)^[7]及可重复的成套神经心理状态测量(RBANS)^[8]对患者进行测试,由同一位专业医生进行评定,以保证评估结果的一致性。WCST 卡片共 128 张,由计算机网络系统自动生成每次测试结果的分析报告,主要的统计指标有:完成分类数、完成调查总应答数、正确应答数、错误应答数、选择错误率、完成第一个分类所需应答数、持续性应答数、持续性错误数、持续性错误率、非持续性错误、非持续性错误率、不能维持完整分类数、概念化水平百分数、总时间、错误思考时间。RBANS 共包括 5 个因子,包括即刻记忆、言语功能、视觉广度、注意力、延迟记忆,将各个因子的原始分按年龄分层的常模表转换为标准分。并在治疗前后进行躯体检查、血常规、生化检查、心电图、脑电图以及神经系统检查,记录患者不适主诉。

1.4 统计学方法

应用 SPSS17.0 统计软件进行数据分析,计量资料均以($\bar{x} \pm s$)表示,采用 t 检验;计数资料以率(%)表示,采用 χ^2 检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组治疗前后 PANSS、TESS 评分比较

治疗前两组 PANSS、TESS 评分均无明显差异($P>0.05$),治疗后 rTMS 真刺激组阳性量表分、阴性量表分、一般精神病量表分及 PANSS 总分均明显降低($P<0.05$),伪刺激组一般精神病量表分及 PANSS 总分明显降低($P<0.05$),且 rTMS 真刺激组均明显低于伪刺激组($P<0.05$);两组治疗前后 TESS 评分无明显差异($P>0.05$),组间比较无明显差异($P>0.05$)。见表 1。

2.2 两组治疗前后 WSCT 结果比较

治疗前两组 WSCT 各项目测试结果无明显差异($P>0.05$)。治疗后 rTMS 真刺激组选择错误率明显降低($P<0.05$),概念化水平百分数明显升高($P<0.05$),总时间及错误思考时

表 1 两组治疗前后 PANSS、TESS 评分比较

Table 1 Comparison of PANSS and TESS scores between two groups before and after treatment

Projects	rTMS true stimulus group(n=50)		Pseudo stimulation group(n=50)	
	Before treatment	After treatment	Before treatment	After treatment
PANSS total score	74.6±11.3	60.5±10.3**	71.4±11.6	65.7±11.4*
Positive quantity table	21.6±11.6	15.8±4.3**	20.7±7.5	18.9±4.6
Negative scale	19.5±2.6	16.7±2.4**	20.7±4.2	19.5±4.4
General psychiatric pathology	38.9±5.5	30.7±3.5**	37.6±3.6	35.3±2.5*
TESS score	1.8±0.4	1.6±0.6	1.7±0.6	1.6±0.8

Note: Compared with before treatment, * $P<0.05$; compared with pseudo stimulation group, ** $P<0.05$.

间明显缩短 ($P < 0.05$), 伪刺激组完成第一个分类所需应答数 ($P < 0.05$), 总时间及错误思考时间明显短于伪刺激组 ($P < 0.05$); 且 rTMS 真刺激组概念化水平百分数明显高于伪刺激组

表 2 两组治疗前后 WSCT 结果比较
Table 2 Comparison of WSCT results in two groups before and after treatment

Projects	rTMS true stimulus group(n=50)		Pseudo stimulation group(n=50)	
	Before treatment	After treatment	Before treatment	After treatment
Complete the classification number	4.6± 1.3	5.5± 0.3	4.4± 1.6	4.7± 1.4
Complete the test of total responses	121.6± 11.6	115.8± 19.3	117.7± 15.5	118.9± 14.6
Correct responses	51.5± 5.6	53.7± 7.4	52.7± 4.2	49.9± 8.4
Error responses	68.9± 10.5	63.7± 11.5	70.6± 13.6	72.3± 12.5
Selection error rate(%)	58.8± 5.4	50.7± 5.6*	59.8± 7.9	56.6± 10.8
Complete the first category of required responses	26.7± 6.4	26.2± 3.1	23.3± 6.9	30.5± 4.9*
Sustained response	39.9± 8.5	41.4± 6.7	37.0± 8.4	39.9± 8.5
Persistent error number	50.0± 12.4	47.4± 9.9	48.8± 12.4	49.6± 11.4
Persistent error rate(%)	71.8± 14.5	65.7± 11.1	68.5± 8.4	67.5± 8.1
Non persistent error	18.6± 3.2	17.3± 4.4	20.3± 6.4	20.1± 3.1
Non persistent error rate(%)	28.9± 4.5	30.5± 3.2	33.4± 8.3	33.4± 6.5
Can not maintain a complete classification number	14.9± 6.6	13.4± 5.3	11.5± 5.4	11.8± 6.3
Percentage of conceptual level	53.8± 4.0	65.5± 4.7*#	50.8± 6.4	46.8± 7.3
Total time(s)	538.5± 101.6	402.5± 78.5*#	494.8± 112.5	445.5± 77.4*
Correct thinking time(s)	202.8± 99.6	172.7± 59.6	213.5± 105.3	198.7± 57.6
Wrong thinking time(s)	335.8± 119.6	231.5± 61.5*#	307.8± 107.3	275.8± 79.7*

Note: Compared with the group before treatment, * $P < 0.05$; compared with the pseudo stimulation group, # $P < 0.05$.

2.3 两组治疗前后 RBANS 结果比较 ($P < 0.05$), 即刻记忆、言语功能、注意力及总分无明显变化
治疗前两组 RBANS 各项目测试结果无明显差异 ($P > 0.05$), 伪刺激组各项目无明显改变 ($P > 0.05$); 且 rTMS 真刺激组视觉广度与延迟记忆明显提高 刺激组视觉广度明显高于伪刺激组 ($P < 0.05$)。见表 3。

表 3 两组治疗前后 RBANS 结果比较
Table 3 Comparison of RBANS results in two groups before and after treatment

Projects	rTMS true stimulus group(n=50)		Pseudo stimulation group(n=50)	
	Before treatment	After treatment	Before treatment	After treatment
Immediate memory	57.1± 13.3	66± 17.3	56.6± 15.7	60.5± 14.4
Visual span	79.5± 15.3	91.5± 17.9*#	77.6± 16.2	77.9± 13.4
Speech function	90.7± 19.4	96.5± 15.6	88.5± 11.4	89.6± 17.8
Attention	89.5± 13.5	93.5± 15.6	86.4± 14.3	88.6± 18.3
Delayed memory	61.7± 16.4	69.5± 12.1*	60.8± 17.9	66.6± 10.8
Total score	67.7± 16.4	76.2± 13.1	63.9± 11.7	69.5± 14.3

Note: Compared with the group before treatment, * $P < 0.05$; compared with the pseudo stimulation group, # $P < 0.05$.

两组治疗前后经躯体检查、血常规、生化检查、心电图、脑电图以及神经系统检查均基本正常。rTMS 真刺激组 2 例患者首次治疗后出现轻度头痛, 其中 1 例伴麻木感, 持续时间约 5 min, 之后的治疗在不调整 rTMS 刺激参数的情况下未再出现不适症状。随访 3 个月, 所有患者均无不适主诉。

3 讨论

认知功能是指为个体通过自己的思维感知与认识客观物体所具备的水平及能力,当认知加工过程出现障碍时可能导致认知功能异常^[9]。精神分裂症为临床常见的重性精神障碍,这类患者多伴有认知功能损害,在治疗上以抗精神病药物治疗为主^[10],但通常药物只能改善患者的部分精神症状,对其认知功能的作用有限,导致患者的生活质量低下。本研究选择 rTMS 的刺激位置为左侧前额叶背外侧区,是因为前额叶背外侧皮层是实施认知控制的最重要脑区之一,与执行功能有关,是精神活动的最主要场所之一。

近些年,随着新兴技术的飞速发展,经颅磁刺激(TMS)开始应用于精神分裂症的治疗,是一种无创性的治疗手段。TMS 的治疗方法为在大脑的某个位置放一个绝缘的金属线圈,金属线圈可在局部产生 1.5~2.5T 强度的磁场,由于磁场处于不断变化中,所以又可产生一定强度的电流,电流进入皮质下组织后可引起皮质神经元进行超级化与去极化,使大脑神经元细胞的结构与功能发生变化,最终起到治疗的目的^[11]。目前已有不少国外研究^[12,13]提示 rTMS 对精神分裂症阴性症状的治疗价值,但由于精神分裂症患者的认知功能障碍是独立于阳性、阴性症状之外的一个症状,所以需单独进行研究,但也不排除 rTMS 同时对阴性症状与认知功能障碍有效的可能性。

本研究采用 rTMS 治疗慢性精神分裂症,结果显示 rTMS 真刺激组治疗后 PANSS 总分及各因子评分均降低,且明显低于伪刺激组,TESS 评分治疗前后及组间差异均无统计学意义,说明 rTMS 真刺激能更进一步改善慢性精神分裂症患者的精神症状,且副反应小。治疗后 rTMS 真刺激组 WSCT 中的选择错误率明显降低,概念化水平百分数明显升高,总时间及错误思考时间明显缩短,RBANS 中的视觉广度与延迟记忆明显提高,而且与伪刺激组比较有统计学差异,提示 rTMS 对改善慢性精神分裂症患者的概念形成能力、执行功能及视空间工作记忆有一定的帮助。其它也有多个研究可支持 rTMS 对精神分裂症认知功能的改善作用,如 Thimm A 等^[14]采用高频 rTMS 治疗 30 例精神分裂症伴认知功能障碍患者,真刺激组的工作记忆改善程度明显优于伪刺激组;研究显示,rTMS20Hz 能够明显改善精神分裂症患者(20 例)的视空间工作记忆与词汇流畅性;真刺激组(22 例)治疗 1 个月后 RBANS 中的除言语功能评分外,其余项目评分及总分均明显提高,而伪刺激组(22 例)仅延时记忆评分有明显提高。但也有个别研究显示 rTMS 对精神分裂症的脑功能无明显影响^[15]。

rTMS 治疗精神分裂症认知功能障碍的作用机制尚不十分清楚。研究认为,额—颞叶系统间的功能连接异常可能是该病的病理学基础^[16,17],故推测 rTMS 可能是通过纠正前额叶、颞叶间的功能连接紊乱以及改善其神经细胞的兴奋性来治疗精神分裂症认知功能障碍的。Anderson RJ 等^[18]研究发现 rTMS 可引起脑内的神经递质、多种受体以及调节神经元兴奋性的基因表达发生明显的改变,提示 rTMS 改善认知功能障碍的机制可能与其对脑功能的调节有关。有研究发现,抑郁症患者在经 rTMS 治疗后,其认知功能有所改善,相应地,其额区脑血流与脑代谢也得到改善,提示二者有一定的联系^[19]。

rTMS 治疗精神分裂症的安全性高,Dlabac-de Lange JJ 等^[20]研究比较了真刺激组与伪刺激组抗精神病药物的剂量,显然,前者的药物剂量更少。长期使用抗精神病药物可能导致多种副反应,而联合 rTMS 不仅可能有助于疗效的增强,而且还可减少服用药物的剂量,减少副反应,提高患者的治疗依从性。

综上所述,rTMS 真刺激治疗对慢性精神分裂症患者的部分认知功能有一定的改善作用,且安全性较高。然而目前 rTMS 治疗精神分裂症患者的认知功能损害尚处于初始阶段,研究的样本量普遍偏少,虽然已有不少研究表明 rTMS 对精神分裂症患者的认知功能障碍,尤其是操作记忆与执行功能方面,具有一定的改善作用,但是鲜见多中心、大样本的纵向研究。因此,要明确 rTMS 在精神分裂症认知功能方面的治疗价值,还需进一步研究。

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衡、灵活性和协调性。神经影像学、神经递质、神经营养因子、病理标记物等检测方法可能有助于进一步阐明有氧运动对AD的影响。

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