

对侧控制神经肌肉电刺激对脑卒中偏瘫患者脑功能连接的影响

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摘要 **目的:**应用功能性近红外光谱成像技术(fNIRS)分析对侧控制神经肌肉电刺激(CCNMES)对脑卒中偏瘫患者脑功能连接变化的影响。**方法:**选择2021年7月—2022年1月在常州市德安医院康复医学中心就诊的脑卒中上肢偏瘫患者48例,采用计算机生成的随机化列表按1:1分为对照组和观察组,每组24例。对照组接受神经肌肉电刺激(NMES)治疗,患侧前臂伸肌侧放置2个刺激电极以产生腕部伸展,刺激强度以可以产生最大程度的腕部伸展,但不引起患者不适为度,矩形脉冲60 Hz,脉冲宽度200 μ s,刺激周期为开15 s、关10 s。观察组接受CCNMES治疗,在健侧前臂伸肌侧放置2个表面电极和1个参考电极,在患侧前臂伸肌侧放置2个刺激电极以产生腕部伸展,患侧刺激强度以患侧手腕能够引起相同程度(健侧手腕上抬最大范围)的手腕伸展,但不引起疼痛为度,其他刺激参数设置与对照组相同,2组刺激总时间均为10 min。在每项任务中,应用35通道fNIRS测量脑卒中患者双侧前额叶皮层(PFC)、初级运动皮层(M1)和初级感觉皮层(S1)的含氧血红蛋白(HbO₂),分析2组总体功能连接(FC)强度和基于感兴趣区域(ROI)水平的功能连接强度平均值的差异。**结果:**与对照组比较,观察组总体功能连接强度明显更高,健侧初级运动皮层(cM1)与患侧前额叶皮层(iPFC)、cM1与患侧初级运动皮层(iM1)、健侧初级感觉皮层(cS1)与iPFC的FC明显更高,差异具有统计学意义($P < 0.05$)。**结论:**CCNMES可通过健侧上肢主动运动触发患侧上肢的感觉运动刺激,并诱导脑卒中偏瘫患者大脑皮质功能重组。

关键词 脑卒中; 偏瘫; 对侧控制神经肌肉电刺激; 功能性近红外光谱成像技术; 大脑皮质功能

脑卒中是我国成人致残的首位病因^[1],随着医疗技术的提高,脑卒中患者病死率明显降低,但仍约有55%~75%脑卒中患者伴有显著的上肢功能障碍^[2],表现为肩、肘、腕和手指关节的活动范围、力量和协调能力受损,导致日常生活活动能力严重下降,给家庭和社会带来沉重负担。目前,国内外脑卒中康复治疗指南推荐等级较高的上肢功能康复方法,如强制性运动疗法和任务导向性训练等^[3-4]。

这些方法虽有一定疗效,但对患者上肢远端的功能要求较高,仍存在一定的局限性。此外,许多日常活动任务需要熟练和协调地同时使用双手,由于上肢脑网络支配的复杂性,脑卒中后双手协作能力的恢复仍未得到深入研究^[5]。

对侧控制神经肌肉电刺激(contralaterally controlled neuromuscular electrical stimulation, CCNMES)作为一种新型的神经肌肉电刺激(neuromuscular

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electrical stimulation, NMES)技术,在 NMES 基础上结合了运动想象、动作观察和模仿,强调患者自主运动意识的参与。它通过健侧肢体的主动运动触发 NMES 装置,诱发患侧肢体相同部位做出相似运动。此外,通过健侧肢体的主动控制调节患侧肢体的电刺激强度,使患者的运动意向(中枢神经活动)和刺激的运动反应(周围神经活动)最大程度同步化^[6]。研究表明,CCNMES 能改善脑卒中后亚急性期和慢性期患者的上肢和手功能^[7-8]。CCNMES 作用的中枢机制尚不明确,可能与 CCNMES 通过双侧运动减轻了健侧半球对患侧半球的抑制有关^[9],但其皮质重组机制尚未见报道,尤其是与运动想象有关的双侧前额叶皮层(prefrontal cortex, PFC)和双侧感觉运动区之间的重塑作用尚不清楚。为此,本研究通过功能性近红外光谱成像技术(functional near-infrared spectroscopy, fNIRS)探索 CCNMES 对脑卒中患者脑功能网络的影响。

1 临床资料

1.1 病例选择标准

1.1.1 诊断标准 符合《中国各类主要脑血管病诊断要点 2019》^[10]中关于脑卒中的诊断标准,并经头颅 CT 或 MRI 证实。

1.1.2 纳入标准 ① 年龄 30~80 岁;② 皮质下及

单侧大脑半球病变;③ 病程 < 1 年;④ 偏瘫侧腕关节背伸主动活动度(active range of motion, AROM) < 70°;⑤ 偏瘫侧腕关节背伸被动活动度(sufficient passive range of motion, PROM) < 70°;⑥ 双侧上肢皮肤完好,无感觉障碍^[11]。

1.1.3 排除标准 ① 伴有严重心、肺、肝、肾系统疾病;② 佩戴心脏起搏器;③ 皮肤存在严重损害、感染、痛觉过敏或刺激部位不耐受;④ 严重认知及沟通障碍而无法遵从治疗指示。

1.1.4 中止和脱落标准 ① 患者在方案实施期间自行退出;② 患者依从性差,无法配合本方案实施。

1.2 一般资料

选择 2021 年 7 月—2022 年 1 月在常州市德安医院康复医学中心就诊的脑卒中上肢偏瘫患者 48 例。采用计算机生成的随机化列表按 1:1 分为对照组和观察组,分配情况用连续编号的密封不透明信封隐藏。2 组性别、年龄、病程、疾病类型、偏瘫侧、简易智力状态检查量表(mini-mental state examination, MMSE)评分、Fugl-Meyer 运动功能分级表(Fugl-Meyer assessment scale, FMA)评分差异均无统计学意义($P > 0.05$),具有可比性。见表 1。本研究方案已通过常州市德安医院医学伦理委员会批准(审批号: CZDALL-2021-003),且已在中国临床试验注册中心注册(注册号: ChiCTR2100048807)。

表 1 2 组一般资料比较

Table 1 Comparison of general data between two groups

组别	例数	性别		年龄/([$M(P_{25}, P_{75})$], 岁)	病程/([$M(P_{25}, P_{75})$], d)	疾病类型	
		男	女			脑梗死	脑出血
对照组	24	19	5	69.50(63.25, 73.25)	44.00(24.25, 86.50)	18	6
观察组	24	13	11	63.00(53.00, 68.75)	66.00(32.00, 146.75)	18	6
		偏瘫侧		MMSE 评分/([$M(P_{25}, P_{75})$], 分)	FMA 评分/([$M(P_{25}, P_{75})$], 分)		
		左侧	右侧				
		9	15	26.00(9.00, 27.50)	8.00(4.00, 26.00)		
		8	16	23.00(10.00, 28.00)	18.00(4.00, 30.00)		

2 方法

2.1 治疗方法

2.1.1 对照组 对照组接受 NMES 治疗。具体操作如下:患侧前臂伸肌侧放置 2 个 4 cm × 4 cm 的刺激电极以产生腕部伸展。刺激强度以可以产生最大程度的腕部伸展,但不引起患者不适为度,刺激参数设置:矩形脉冲 60 Hz, 脉冲宽度 200 μ s, 刺激周期为开 15 s、关 10 s, 刺激总时间 10 min。

2.1.2 观察组 观察组接受 CCNMES 治疗。具体操作如下:在健侧前臂伸肌侧放置 2 个 4 cm × 4 cm 的表面电极和 1 个参考电极,在患侧前臂伸肌侧放置 2 个 4 cm × 4 cm 的刺激电极以产生腕部伸展。在正式干预之前,嘱受试者将健侧手腕抬到最大范围,并保持在这个姿势,同时记录最大肌电值。治疗师随后调整患侧刺激强度,使患侧手腕能够引起相同程度的手腕伸展,但不引起疼痛。其他刺激参数设置与对照组相同,刺激总时间 10 min。

2.2 观察指标

采用fNIRS系统分析2组总体功能连接强度和基于感兴趣区域(region of interest, ROI)水平的功能连接强度平均值的差异。

2.2.1 fNIRS系统选择 采用连续波fNIRS系统(丹阳慧创医疗设备有限公司,型号:Nirsmart)进行数据采集。fNIRS系统由15个源和13个探测器构成35个通道,探测器与源之间的距离设置为30 mm,以确保穿过光极下的灰质。根据标准Brodmann脑定位,所有通道被分为7个ROI,分别是左侧前额叶皮层(left prefrontal cortical, LPFC)、中前额叶皮层(middle prefrontal cortical, MPFC)、右前额叶皮层(right prefrontal cortical, RPFPC)、左初级运动皮层(left primary motor cortex, LM1)、右初级运动皮层(right primary motor cortex, RM1)、左初级感觉皮层(left primary sensory cortex, LS1)和右初级感觉皮层(right primary sensory cortex, RS1)。见图1。fNIRS系统参数设置波长730、808、850 nm,采样率为11 Hz。

2.2.2 fNIRS数据采集 为尽可能减少头围等个体因素带来的误差,本研究采用标准脑定位方案,采用标准、统一的方式为患者戴上fNIRS采集帽并坐在椅子上,进行数据采集。整个采集过程,房间保持灯光昏暗,无噪声,患者尽量保持头部没有大幅

度动作。对照组刺激器在患侧手臂上诱发手腕伸展,刺激15 s,休息10 s,每个采集任务前均有10 s的基线数据采集。观察组在刺激器声音提示时,反复用力伸展双臂,在手腕完全伸展后保持静止15 s,放松10 s。2组均完成10 min任务态数据采集。采集方法见图2。

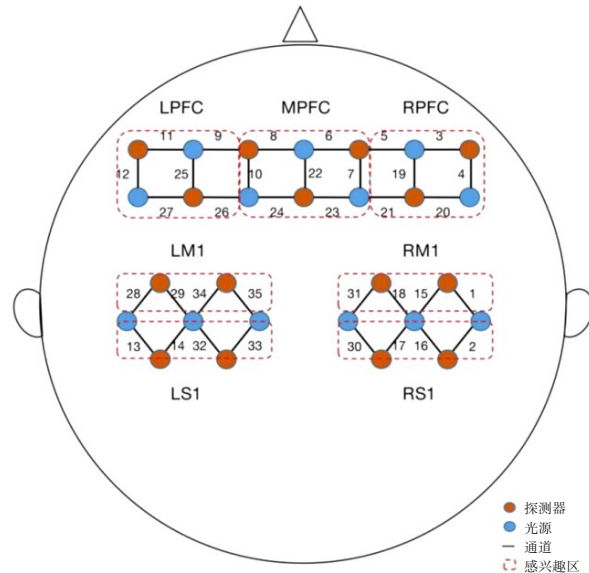


图1 fNIRS通道及ROI划分

Figure 1 fNIRS channel and ROI division

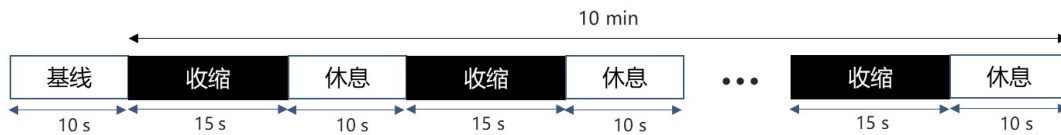


图2 功能近红外数据采集

Figure 2 Data acquisition of fNIRS

2.2.3 fNIRS数据处理

2.2.3.1 数据预处理 采用含氧血红蛋白(oxygenated hemoglobin, HbO₂)信号作为血流动力学反应指标,使用Matlab 2013b软件的Homer2工具箱进行数据预处理。预处理步骤为:①将原始NIRS光强转换为光密度信号;②采用运动伪影减少算法检测和纠正数据采集过程中头部运动引起的运动伪影(参数设置为tMotion=1,tMask=2.0,STDEVthresh=15.0,AMPthresh=5.0);③使用样条插值算法对运动伪影进行校正;④滤波:采用频率0.01~0.1 Hz的低通带通滤波器,以消除生理噪声和漂移的影响;⑤利用修正的Beer-Lambert定律将滤波后的光密度数据转换为HbO₂浓度。

2.2.3.2 功能连接分析 使用任务开始前10 s平均HbO₂浓度作为基线HbO₂值,将每个通道各时间点的HbO₂浓度减去基线HbO₂值得到各时间点HbO₂的变化值(ΔHbO_2),然后对每个ROI中所有通道的各时间点 ΔHbO_2 取平均值。统一定义左侧半球为患侧半球,反之为健侧半球,对右侧损伤的患者半球进行翻转。取任务开始后0~10 min数据进行功能连接分析,计算时间序列上各ROI的HbO₂相关系数 r 值。为便于比较和统计分析,通过Fisher $r-z$ 变换将其转换为 z 值,转换后的 z 值作为各ROI间功能连接(functional connection, FC)强度指标。

2.3 统计学方法

采用SPSS 26.0统计软件进行数据分析。计量资料符合正态分布以($\bar{x} \pm s$)表示,组间比较采用两独

立样本 t 检验; 计量资料不符合正态分布采用 $M(P_{25}, P_{75})$ 表示, 组间比较采用 Mann-Whitney U 检验; 计数资料采用 Pearson χ^2 检验或 Fisher 确切概率检验。 $P < 0.05$ 为差异具有统计学意义。

3 结果

3.1 2组总体功能连接强度比较

与对照组比较, 观察组总体功能连接强度明显更高, 差异具有统计学意义 ($P < 0.05$)。见表 2。

表 2 2组总体功能连接强度比较 ($\bar{x} \pm s$)

Table 2 Comparison of overall functional connection strength between two groups ($\bar{x} \pm s$)

组别	例数	总体功能连接强度
对照组	24	0.56 ± 0.21
观察组	24	0.80 ± 0.32 ¹⁾

注: 与对照组比较, 1) $P < 0.05$ 。

Note: Compared with the control group, 1) $P < 0.05$ 。

3.2 2组基于 ROI 水平的功能连接强度平均值比较

基于 ROI 水平的功能连接强度平均值比较图中, 不同颜色代表不同强度功能连接, 倾向于红色表示相关性更强, 即功能连接程度更强; 倾向于蓝色则表示相关性更弱, 即功能连接程度更弱。 ROI 间功能连接可视化图中, 红色连线表示 2 组间比较该条功能连接差异具有统计学意义 ($P < 0.05$)。与对照组比较, 观察组健侧初级运动皮层 (contralateral primary motor cortex, cM1) 与患侧前额叶皮层 (ipsilateral prefrontal cortical, iPFC)、cM1 与患侧初级运动皮层 (ipsilateral primary motor cortex, iM1)、健侧初级感觉皮层 (contralateral primary sensory cortex, cS1) 与 iPFC 的 FC 明显更高, 差异具有统计学意义 ($P < 0.05$)。患侧初级感觉皮层 (ipsilateral primary sensory cortex, iS1)、健侧前额叶皮层 (contralateral prefrontal cortical, cPFC)、MPFC 间的 FC 差异无统计学意义 ($P > 0.05$)。见图 3。

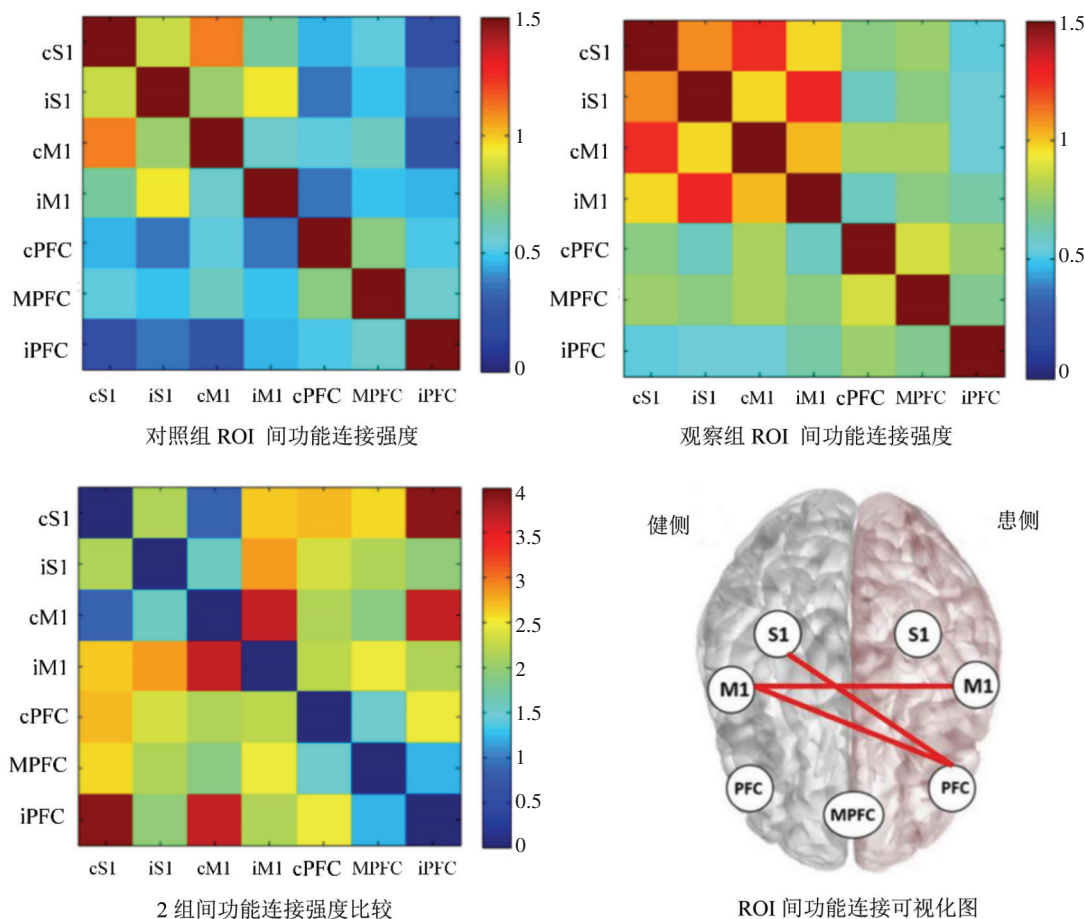


图 3 2组基于 ROI 水平的功能连接强度平均值比较

Figure 3 Comparison of average functional connection strength based on ROI levels between two groups

4 讨论

脑卒中后运动功能的恢复与大脑双侧半球运动相关脑区的功能重组紧密相关^[12]。fNIRS作为一种较新的功能神经成像技术,可实现多功能体位(如坐位、立位等)下运动相关的脑皮质活动状态检测,由此反映康复治疗过程中患者的神经重塑过程,为探索脑卒中后皮质网络损害、预后分析和治疗有效性提供帮助^[13]。

本研究结果发现,与对照组比较,观察组脑区总体功能连接强度较高,提示CCNMES可以促进脑卒中上肢偏瘫患者患侧M1和健侧M1的FC增强,促进患侧PFC与健侧M1、S1的FC增强。

大脑对侧半球同源脑区的激活和大脑半球之间的FC增强是脑卒中后肢体功能恢复的机制之一^[14]。本研究通过fNIRS检测发现在CCNMES治疗状态下,脑卒中偏瘫患者患侧M1和健侧M1之间的FC显著增强,提示CCNMES能增强双侧M1之间的皮质连接。M1在运动执行中起重要作用,尤其是支配对侧上肢远端肌群的运动,脑卒中后M1受损通常会导致对侧肢体运动功能障碍。这与研究显示脑卒中患者大脑半球间M1-M1的FC与患侧上肢的手灵活度显著相关的结果相似^[15]。此外,本研究发现CCNMES可以诱导脑卒中患者患侧M1和健侧M1之间的FC增强,与LI等^[16]和DU等^[17]研究发现rTMS治疗脑卒中患者患侧M1和健侧M1的FC增强,促进运动功能恢复的结果一致。基于“大脑半球间竞争”模型,脑卒中后运动功能障碍持续存在的部分原因是由于两个半球之间的不平衡^[18]。CUNNINGHAM等^[19]使用TMS评估CCNMES和NMES对大脑半球间抑制(interhemispheric inhibition, IHI)的影响,该研究发现与NMES比较,CCNMES可导致双侧M1之间IHI明显降低,增强患侧运动皮层对瘫痪肢体的运动输出。因此,本研究认为合并双侧同步运动的CCNMES可通过减少M1内皮质抑制而增强半球间患侧M1和健侧M1的FC,从而改善脑卒中后偏瘫患者上肢功能。

本研究结果显示,观察组患侧PFC分别和健侧M1、S1具有较强的连接。可能是由于CCNMES是一种积极主动的治疗模式,而NMES是被动的。NMES通过直接刺激偏瘫侧手腕肌群促进手腕和手指伸展,不需要患者进行任何努力。而CCNMES治疗可以更好地将患者运动意图与运动输出进行整合。在CCNMES治疗下,患者需要进行健侧手腕主动伸

展以触发患侧的电刺激,电刺激的强度直接受健侧手腕肌群收缩强度的调节。这一治疗过程结合了运动想象、模仿和观察,可以最大程度地调动患者的运动意图,促进运动再学习^[20]。运动再学习伴随着神经可塑性变化,可诱导局部脑区的激活并调节PFC和运动皮层^[21]。

本研究结果还显示,观察组双侧大脑半球之间的FC明显增强,可能与CCNMES是双侧的治疗模式有关。有研究显示,双侧上肢训练是脑卒中上肢偏瘫患者运动功能恢复的有效方法^[22]。双侧运动可以调动患侧半球的适应作用,特别是对于有明显运动皮质损害的患者。WHITALL等^[23]研究发现,除可改善患侧半球的功能外,双侧上肢训练还可更大范围激活健侧半球,从而改善上肢功能。通过fMRI进一步证实,双侧运动可引起双侧初级感觉运动皮层、前运动皮层和辅助运动区更显著的激活。但值得注意的是,与不同步双侧运动比较,大脑半球之间的整合作用在同步双侧运动时更明显^[19]。在本团队前期研究发现2种不同电刺激任务可对大脑皮质功能重组情况产生积极影响的基础上^[11],进一步扩大了样本量,通过fNIRS检测发现了静息态下无法观察到的皮质功能重塑的相关变化,进一步明确了CCNMES诱导的脑卒中偏瘫患者脑功能连接变化,有助于为CCNMES治疗脑卒中偏瘫患者提供理论依据。

5 小结

CCNMES可通过健侧上肢主动运动触发患侧上肢的感觉运动刺激,并诱导脑卒中患者皮质功能重组。但本研究仍存在一定的不足之处,如纳入患者病程较短;未深入探讨出血性脑卒中和缺血性脑卒中是否存在不同的皮质重组模式等。下一步研究将开展大样本临床随机对照研究,延长病程和细分脑卒中类型,为CCNMES治疗脑卒中偏瘫患者提供更科学的证据。

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was 30% of the child's body mass, and it was gradually adjusted to fully support the child's own body mass. The combined intervention group received gait induced FES in addition to the training of the BWSTT group. A low-frequency electronic pulse stimulator was used to stimulate the common peroneal nerve and anterior tibialis muscle of the children, and the stimulation intensity was set at the desirable movements of ankle dorsiflexion and valgus, and could be tolerated by the children, once a day, 20 minutes a time, five days a week, lasting for eight weeks. Before and after treatment, D (standing) and E (walking, running and jumping) zones of the 88-item gross motor function measurement 88 (GMFM-88) was used to assess the children's gross motor function; six-minute walking test (6MWT) was used to assess walking function; physiological expenditure index (PCI) was used to evaluate walking efficiency; and gait parameters of the children (such as stride length, stride width and stride speed) were analyzed. **Results:** Compared with that before treatment, GMFM-D and GMFM-E scores, 6MWT, stride length and stride speed were significantly higher and PCI and stride width were significantly lower in the three groups after treatment, and the differences were statistically significant ($P<0.05$). Compared with the control group, GMFM-D and GMFM-E scores, 6MWT, stride length and stride speed were significantly higher, and PCI and stride width were significantly lower in the BWSTT group and the combined intervention group after treatment, and the differences were statistically significant ($P<0.05$). Compared with the BWSTT group, the GMFM-D, GMFM-E scores, 6MWT, stride length and stride speed were significantly higher, and PCI and stride width were significantly lower in the combined intervention group after treatment, and the differences were statistically significant ($P<0.05$). **Conclusion:** Gait-induced FES combined with BWSTT can improve motor function, correct abnormal gait, and improve walking efficiency in children with SCP, which is recommended for clinical application.

KEY WORDS spastic cerebral palsy; gait-induced functional electrical stimulation; body-weight supported treadmill training; walking function; gait analysis

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Effect of Contralaterally Controlled Neuromuscular Electrical Stimulation on Brain Function Connectivity of Patients with Hemiplegia after Stroke

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ABSTRACT Objective: To explore the effect of contralaterally controlled neuromuscular electrical stimulation (CCNMES) on brain functional connectivity of hemiplegic patients after stroke by functional near-infrared spectroscopy (fNIRS). **Methods:** A total of 48 stroke patients with upper limb hemiplegia in the Rehabilitation Medical Center of Changzhou De'an Hospital from July 2021 to January 2022 were recruited and randomly divided into control group and observation group according to the computer-generated randomization list, with 24 cases in each group. The control group received neuromuscular electrical stimulation (NMES). Two stimulating electrodes were placed on the extensor side of the affected forearm to produce wrist extension, and the stimulation intensity was set at a level that could produce maximum wrist extension without causing discomfort to the patient, with a rectangular pulse of 60 Hz, a pulse width of 200 μ s, and a stimulation period of 15 s on and 10 s off. The observation group received CCNMES with two surface electrodes and one reference electrode placed on the extensor side of the healthy forearm, and two stimulating electrodes placed on the extensor side of the affected forearm to generate wrist extension. The intensity of stimulation on the affected wrist was set that the affected wrist could be extended to the same extent with the maximum extension of the healthy wrist without causing pain. The other stimulation parameters were the same as those of the control group, and the stimulation duration was 10 minutes in both groups. In each task, the oxygenated hemoglobin (HbO₂) in bilateral prefrontal cortex (PFC), primary motor cortex (M1) and primary sensory cortex (S1) of stroke patients were measured by the 35-channel FNIRS, and the differences in overall functional connectivity (FC) strength and mean FC strength based on region of interest (ROI) level between the two groups were analyzed. **Results:** Compared with the control group, the overall connectivity strength of brain regions in the observation group was higher, the FC in the contralateral primary motor cortex (cM1) and ipsilateral prefrontal cortex (iPFC), the cM1 and ipsilateral primary motor cortex, and the intact primary sensory cortex (cS1) and iPFC were significantly higher, and the differences were statistically significant ($P<0.05$). **Conclusion:** CCNMES can trigger the sensorimotor stimulation of the affected upper limb through the active movement of the healthy upper limb, and induce the functional reorganization of the cerebral cortex in stroke patients with hemiplegia.

KEY WORDS stroke; hemiplegia; contralaterally controlled neuromuscular electrical stimulation; functional near-infrared spectroscopy; cerebral cortex

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