International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 5, Issue 1, pp: (332-338), Month: April - September 2017, Available at: www.researchpublish.com

Possible Influence of Perturbation Implication, a Neurorehabilitation Model, On Brain Plasticity Using NIRS System

[1]ÖZSEZiKLi Bülent Abut, [2]ÇETİN Güven, [3]MENGİ Murat, [4]ALTAN Mehmet, [5]METİN Gökhan, [6]HANOĞLU Lütfü,

[1]PT, PhD, İstanbul Medipol University Health Sciences Department of Physiotherapy and Rehabilitation and Ozsezikli Physiotherapy and Rehabilitation Group
[2]PT, MSc. Ozsezikli Physiotherapy and Rehabilitation Group
[3]PhD İstanbul University Cerrahpaşa School of Medicine Department of Physiology
[4] MD İstanbul University Cerrahpaşa School of Medicine Department of Physiology
[5]MD, Prof. İstanbul University Cerrahpaşa School of Medicine Department of Physiology
[6]MD, Prof. İstanbul Medipol University School of Medicine Department of Neurology

Abstract: **Improvements in the treatment of stroke lead to an increase in the number of patients living with the consequences of stroke. Although stroke induces cognitive impairment, a lack in mobility or difficulties in walking are common problems for stroke survivors and restoring the walking pattern is one of the main targets in the rehabilitation procedures. Perturbation application is helpful in creating a suitable environment in gait training and it drives problem solving.**

In our study we aimed to investigate the instantaneous and direct effectiveness of perturbation in stroke patients on the brain during walking by using Near Infrared Spectroscopy (NIRS) and also evaluated the cognitive functions of these patients by Mini Mental Test and Montreal Cognitive Assessment.

Study groups were composed of 6 healthy and 6 stroke survivors. Perturbation was applied to subjects by using Re-Step Rehabilitation System and NIRS was used to analyse the instant effect of perturbation on oxygen consumption dynamics of the brain. Although HHb did not change in both groups, HbO_2 value showed significant changes in healthy group during walking protocol of the study. Healthy Group Mini Mental Test score was found to be increased significantly when compared to Patient Group.

We may suggest that the perturbation implantation increases the prefrontal circulation which is activated during motor planning and central input processing, especially in healthy group compared to stroke patients. This determination may consequently be thought as increase in activity in neural centers related to the task and parallel effect of plasticity.

Keywords: **NIRS, HbO_2, perturbation, stroke, neuro-rehabilitation.**

1. INTRODUCTION

Improvements in the treatment of stroke lead to an increase in the number of patients living with the consequences of stroke [1]. Although stroke induces cognitive impairment, a lack in mobility or difficulties in walking are common problems for stroke survivors and restoring the walking pattern is one of the main targets in the rehabilitation procedures [2]. Perturbation application is helpful in creating a suitable environment in gait training and it drives problem solving [3, 4]. Perturbation during walking forces the motor centers to adapt to unexpected situations by the changes generated and stimulates the person to tackle the gait disturbance in different ways. Perturbation application in the rehabilitation may improve the patients walking performance through increasing the reactive balance control, stability, gait speed and decreasing double support time, step times [3, 5, 6]

In the traditional rehabilitation approaches, the effectiveness of the rehabilitation programs are mainly shown by the difference between the pre and post therapy evaluations of the patients, however showing the instantaneous and direct effects of the therapy program is difficult. Current evaluation methods depends on both the patients' and the health professional's comments and observations so these evaluation methods may be lacking in objectivity and instant effect of therapy. Therefore Near Infra Red Spectroscopy (NIRS) may be used in the evaluation of the patients who are in a therapy program and the evaluations can be performed both instantaneously and after the therapy program.

NIRS is a neuro-imaging technique based on hemodynamic principles and allows for the non-interventional evaluation of the brain during motion [7]. NIRS enables the real-time monitoring of the cerebral blood flow and oxygenation from various areas of the brain even during exercise and therapy and can measure indirectly the activity alterations in the different cortical zones [8]. Its nature as a non-interventional, portable system, it may be used during exercise due to the easy exclusion of the motion-dependent disturbances and provision of objective measurements.

In our study we aimed to investigate the instantaneous and direct effectiveness of perturbation in stroke patients on the brain during walking by using NIRS measurements and also evaluated the cognitive functions of these patients by using Montreal Cognitive Assessment (MOCA) and Standardized Mini Mental Test (MMT).

2. MATERIALS AND METHODS

Patients involved in this study were recruited from 127 patients who were diagnosed as stroke between 01.06.2015 and 15.10.2015 at Stroke Unit of the Hizmet Hospital, Istanbul. Of all those patients, 6 patients (4 male, 2 female) aged between 35-60 years and who are right hand dominant, diagnosed as left hemiparesis, having no neurological events at least for last 3 months, having 3 or less Modified Rankin Scale score, having no orthopedically handicap for walking were included in the study randomly. In accordance with the patient group the control group was also formed with 6 healthy subjects (4 male, 2 female) between the ages of 30-41. All the subjects included in the study read and signed a consent form that was approved by the University's Policy and Review Committee on Human Research.

Perturbation protocol:

Perturbation was applied to subjects by using Re-Step Rehabilitation System (Re-Step™, Step of Mind Ltd.,Israel) which enables to implement personal perturbation pattern during walking [3]. At the beginning of the study protocol, subjects walked with daily shoes (DS) for 3 minutes and this set was followed by a 3 minutes of walking with Re-step shoes (RS) without any perturbation. Following this 6 minutes of walk participants rested for 5 minutes and then 5 nonperturbated-perturbated cycles of walking applied and sets were ended with non-perturbated walking. Whereas the perturbation sets (45 sec.) were set stable, the non-perturbated sets were set variable (40-120 second) assuming that the perturbation effect will be more apparent. Duration and sequences of the protocol are given in Table 1.

During perturbation protocol to ensure the same walking pattern from all subjects, participants were focused on the sign that was placed in the middle of therapist's hat. Also subjects were instructed for not to talk and move their eyebrows. As well as walking protocol, every detail which could affect the measurements such as ankle sprain, talking or coughing etc. was recorded with a camera and excluded from the statistical analyses.

Table 1: Walking protocol of the study. *This set has no perturbation during walking.

SET	TIME (second)
Daily shoes (DS)	180
Re-step shoes* (RS)	180
Rest (R)	300
Non-perturbation-1 (NP1)	120
Perturbation-1 (P1)	45
Non-perturbation-2 (NP2)	40
Perturbation-2 (P2)	45
Non-perturbation-3 (NP3)	50
Perturbation-3 (P3)	45

Non-perturbation-4 (NP4)	40
Perturbation-4 (P4)	45
Non-perturbation-5 (NP5)	55
Perturbation-5 (P5)	45
Non-perturbation-6 (NP6)	70

Near Infra-Red Spectroscopy Recordings:

Near Infra-Red Spectroscopy PortaLite™ NIRS system (Artinis Medical Systems, Netherlands) was used to analyze the instant effect of perturbation on oxygen consumption dynamics of the brain frontal lobe. Sensors were placed according to EEG 10-20 system on corresponding points, Fp1 and Fp2, on right and left prefrontal lobe [7, 9] and HbO_2, HHb were measured. The sensors make measurements by receiver on 30, 35, 40 mm distant from receiver through light sources, which standard nominal 760 to 850 nm wavelength [10] and 1 to 50 Hz frequency sampling time. During NIRS analysis we excluded some recordings which may cause artefacts in the record such as twisting of a leg, coughing, etc. Mean values of the data obtained from the last 10 seconds of each independent set of walking protocol was evaluated.

Cognitive Tests:

All the subjects were evaluated by using Montreal Cognitive Assessment (MOCA) and Standardized Mini Mental Test (MMT) to examine the cognitive status of the subjects. The cognitive tests were applied by an independent clinical psychologist prior to walking protocol.

Statistical Analyses:

Statistical analyses were performed by SPSS version 13.0. Mann Whitney-U test was used to make comparisons between the groups. Wilcoxon Rank Test and General Lineer Model, Repeated Measure ANOVA analysis and then Least Significant Differences tests were used to make comparisons within the groups. For correlation analyses Pearson Correlation Test was used. In all comparisons values <0.05 were considered statistically significant.

3. RESULTS

All the results are given in Table 2. When the effect of RS compared to DS analyzed, there was no significant difference between the groups and within the patient group in means of HbO_2 and HHb. However RS lead a significant increase in HbO_2 value within the healthy group (p=0,046, Table 2).

When the HHb and HbO_2 values were compared within groups during perturbation sets (P1-P6), there was no significant difference in patient group. On the other hand, in healthy group, HbO_2 value of P2 set was significantly higher than P1 set (p=0,042). Also value of P4 set was significantly higher than P1 and P2 sets (p=0,003; p=0,049, respectively, Table 2). When the HHb and HbO_2 values were compared within groups during non-perturbation sets (NP1-NP6), there was no significant difference in both groups of study (Table 2).

When the HHb and HbO_2 values obtained during perturbation and non-perturbation sets were compared within groups, there was no significant difference between sets in patient group. In HbO_2 parameter of healthy groups; NP1 set compared to P1, P2 and NP6 sets (p=0.000; p=0.009; p=0.048 respectively), NP2 set compared to P2 set (p=0.049), NP6 set compared to NP3 set (p=0,043) were found to be decreased significantly (Table 2). On the other hand, P1 set compared to NP2, P2, NP3, NP4, P4 and NP5 sets (p=0,023; p=0,042; p=0,004; p=0,042; p=0,003; p=0,007, respectively), P2 set compared to NP3 and P4 sets (p=0,021; p=0,049, respectively), NP4 set compared to NP6 set (p=0,047), P4 set compared to NP6 set (p=0,047), NP5 set compared to NP6 set (p=0,049) were found to be increased significantly in the same group (Table 2). There was no significant difference in HHb parameter between sets of healthy group.

Table 2: HbO_2 and HHb values of the groups

	Healthy Group		**Patient Group**	
SET	**HbO_2**	**HHb**	**HbO_2**	**HHb**
DS	1,20 ± 0,48	-0,26 ± 0,10	-0,10 ± 0,70	-0,42 ± 0,31
RS	2,25 ± 0,74[a]	-0,36 ± 0,25	0,63 ± 0,98	-1,54 ± 1,37
R				
NP1	0,87 ± 0,40[b, c, d]	-0,35 ± 0,28	1,88 ± 0,97	0,85 ± 1,30

P1	-0,28 ± 0,37[e, f, g, h, i, j]	0,06 ± 0,10	1,31 ± 1,34	0,99 ± 1,26
NP2	0,66 ± 0,40[k]	-0,33 ± 0,29	1,85 ± 1,04	0,63 ± 1,32
P2	0,30 ± 0,44[l, m, n]	-0,33 ± 0,27	1,98 ± 1,10	0,66 ± 1,31
NP3	0,70 ± 0,33	-0,40 ± 0,30	2,91 ± 1,35	0,78 ± 1,30
P3	0,64 ± 0,47	-0,42 ± 0,28	1,60 ± 1,01	0,56 ± 1,32
NP4	0,74 ± 0,27[o]	-0,39 ± 0,32	2,00 ± 1,21	0,58 ± 1,33
P4	0,67 ± 0,35[p,q ,r]	-0,42 ± 0,30	2,37 ± 1,30	0,60 ± 1,33
NP5	0,70 ± 0,35[s]	-0,49 ± 0,27	2,40 ± 1,24	0,64 ± 1,33
P5	0,45 ± 0,38	-0,39 ± 0,24	2,53 ± 1,14	0,65 ± 1,34
NP6	0,83 ± 0,44[t]	-0,55 ± 0,29	2,76 ± 1,20	0,78 ± 1,30

[a]: DS healthy compared to RS, [b]: healthy NP1 compared to P1, [c]: healthy NP1 compared to P2, [d]: healthy NP1 compared to NP6, [e]: healthy P1 compared to NP2, [f]: healthy P1 compared to P2, [g]: healthy P1 compared to NP3, [h]: healthy P1 compared to NP4, [i]: healthy P1 compared to P4, [j]: healthy P1 compared to NP5, [k]: healthy NP2 compared to P2, [l]: healthy P2 compared to P1, [m]: healthy P2 compared to NP3, [n]: healthy P2 compared to P4, [o]: healthy NP4 compared to NP6, [p]: healthy P4 compared to P1, [q]: healthy P4 compared to P2, [r]: healthy P4 compared to NP6, [s]: healthy NP5 compared to NP6, [t]: healthy NP6 compared to NP3

In the cognitive tests; Healthy Group MMT scores were found to be increased significantly (p=0,026, Table 3) when compared to Patient Group. There was no significant difference in MOCA scores between two groups. Also, MOCA and MMT scores were found to be positively correlated in both groups. (p=0,002, r=0,961; p=0,009, r=0,920 respectively)

Table 3: Cognitive test results

GROUP	MMT score (MEAN±SE)	MOCA score (MEAN±SE)
HEALTHY	27,67 ± 1,23	23,67 ± 1,65
PATİENT	22,67 ± 1,26[*]	16,83 ± 2,18

[*]: Compared to healthy group MMT.

4. DISCUSSION

Walking is not comprised of merely a motor component. Routine walking is a complex task involving high-level cognitive inputs [11]. A cognitive motor interference that will disturb the automaticity of walking through perturbation application obligates the subjects to experience and use many processes like paying attention in a target-oriented manner, planning, initiating, executing, and monitoring the motion. In this context, we assumed that there would be much more cognitive inputs to brain through perturbation. Also there would be an increase in the metabolic activation and cerebral circulation.

Compared to walking on a straight road, walking on an inclined road involves different motor control operations and possibly various cognitive processes. This was shown to be associated with affected physical and executive function[12]. In stroke patients cognitive motor interferences cause significant improvements in walking pace, stride length, rhythm, Berg balance test performance, pressure center oscillation, 2 and 6-minute walks, 10 and 400-meter walks, and functional independence measurement[13]. Perturbation application to patients with hemiparesis and cerebral palsy (CP) lead to a mechanical improvement in gate function, balance and stability [3-6].

The attempt to measure the cortical activity during walking was first performed by La Fougere using PET scan, but the results achieved was not sufficient to show the activity in this zone [14]. fMRI and EEG were also used and EEG records were taken with patients walking or running on a treadmill in a study. However, movements of neck muscles and eyeballs can affect the quality of records during EEG measurements[15].

In the present study we measured the HbO_2 and HHb instantaneously during walking from the corresponding locations of the brain by using NIRS. Transition from walking with DS to walking with RS, the HbO_2 values of both patients and the healthy group showed an increase (Table 2). Within these increases, only those for the healthy group was significant. Reviewing the perturbation walking sets for our walking protocol; the HbO_2 values for the patient group - except P3 set - showed increases with progressing sets, yet the differences between the values in the sets were not significant. However, the HbO_2 values of the healthy group showed increases with progressing sets and these increases were significant until the P4 set.

The general character of the change in HHb value was the same for both groups. The decrease seen at the transition from P1 set to P2 set at the beginning continued on the same level for the subsequent sets without statistical significance.

In the entire walking protocol; the HbO_2 parameter for the healthy group decreased in absolute value in every P set following an NP set, then showing increase again in the subsequent NP set (Table 2). The value for the HHb parameter showed increase in the P1 set after which it decreased to the baseline level in the subsequent NP2 set, and then remained relatively constant in the following sets. The HHb value of the patient group formed a response similar to that of the healthy group. The differences between the HbO_2 values measured in the repeating P and NP sets were not significant and did not show a specific order like the one in the healthy group.

As the ReStep shoes are designed with a different purpose than daily shoes, in the RS sets of the study, the circulation in the cortical areas we measured with NIRS system was increased. It is possible that this situation arises as a result of the metabolic activation of the neuronal structures associated with the related task. This effect of the perturbation application is seen in a more pronounced fashion in the healthy group compared to the patient group.

In a study, Kurz et al. identified an increase in HbO_2 and a decrease in HHb by using fNIRS, during walking backwards compared to walking onwards in healthy adults. They showed that the variability during walking took place due to increased cortical activity in the primary sensorimotor cortices, supplementary motor area (SMA) and prefrontal cortices (PFC) in response to the challenge of backward walking. The importance of SMA in the coordination during the rhythmic arm and leg movements was also emphasized [16]. It was also shown that the activity of walking when done together with the task of speaking increased the PFC activity in young and old subjects. The researchers emphasized that PFC was active during activities usually requiring attention [17].

In a study, the increased PFC activation that appear in the first half of the attentive striding task compared to normal walk lead to an increase in HbO_2 and decrease in HbR in healthy individuals. This hemodynamic activation also took place before starting both normal walk and attentive striding. Thus, it was shown that PFC was activated especially during tasks that required attention[18].

Maidan et al. studied the freeze of gait (FOG) that occurs during turns in Parkinson patients. While the patients were walking, a significant increase in HbO_2 amount was noted in predetermined turns before and during FOG, whereas no significant increase was identified in unexpected turns. In light of these results, the relationship between FOG episodes and frontal lobe HbO_2 changes were highlighted due to the relationship between motor planning, information processing, and FOG and this zone played a significant role in executive functions in PFC[9]. In our study, although stroke patients showed increases in HbO_2, these changes were significant only in healthy subjects. However, there are also researches arguing that not only the frontal lobes and the closely-connected networks are activated for executive functions, but some other anterior and posterior regions also help these cognitive areas [19, 20]. Further and more detailed researches are needed to shed light on these subjects.

All of these studies point out the functional gains of perturbation. As it is seen, the cumulative data pertaining to the uses of a cognitive motor interference, such as perturbation, in improving the functionalities of individuals of different age and health statuses and correcting the mechanical measures of motion dynamics is increasing every day. However, it remains to be explained why we couldn't find a significant activation in the frontal region of our stroke group during the perturbation interferences in our study. At this point, we can note that the individuals in the patient group have such a lesioned cerebral structure that it cannot increase their metabolism instantaneously and the presence of the cortical areas with executive functions affected in association within possibility. Keeping in mind that in our study the MMT scores among the cognitive tests made were lower in our patient group compared to the healthy group, we think that this kind of an opinion is worth being taken into consideration.

In a study by Friedman et al. the post-stroke recovery process in the gait function of patients (n=197) was followed and the MMT score of the mobile individuals were found to be 22.0 ± 7.6. This result is very close to the MMT score (22.67±1.26) of the subjects in the stroke group in our study. This situation provides an important support in terms of the reliability of the cognitive test results in our study, although number of subjects is low [21].

Also, it is important to emphasize the need for studies showing acute effects towards higher motor control centers, other than the long-range results of perturbation application. Because, the results of a study showed that the effect of the relationship between the parameters such as changes in the walking pace, age, and cognitive motor interference (CMI) on the gait function, as well as the relationship between the level of cognitive status and CMI, are important in understanding the control mechanisms of walking. In particular, it was suggested that cognitive tasks involving internal factors disturbed the gait performance more than the tasks involving external factors do [22].

On the other hand, the individuals with stroke, participating in our study were able to continue the walking protocol until the end and finish the test even though their cognitive levels were affected compared to the healthy group (table 3). In this context, we can say that their physical performance was not very bad, and the reason for this may be the fact that the subjects included in this group were involved according to level 2 or 3 in the Modified Rankin Scale [23].

In a study conducted by Mawase et al on patients with CP, the patients could nor adapt as well as the healthy subjects in the first application performed on a treadmill with perturbation application. In this study the adaptation parameter was identified as the center of pressure symmetry during walking. After 30 therapy sessions applied throughout the process, the adaptation was found to increase significantly as a response to perturbation in the CP group [24]. This information explains why the individuals subjected the first time and to maximum perturbation in our study was unable to adapt.

The first limitation in our study is the low number of sensors in the system used for the measurement of Hb parameters. For this reason, the activation analysis could be performed only on the prefrontal area, not all cortical zones that could be effective during walking.

The second limitation is the number of subjects. The subjects that would participate in the study were selected according to various criteria that would enable us to establish the effectiveness of the perturbation application -the technique we study- to conduct our study in standard conditions and to obtain reliable results. In this context, the study was conducted with minimum number of subjects that may show the statistical significance. On the other hand, taking into consideration the similar studies in the literature, we can say that the number of our subjects and the measurements we performed is sufficient.

5. CONCLUSION

We may suggest that the perturbation implementation increases the prefrontal circulation which is activated during motor planning and central input processing, especially in healthy group compared to stroke patients. Therefore we may suggest that this mechano-proprioceptive approach on plasticity may be a useful tool in neurorehabilitation. But considering the lack of sources in literature, we believe that this treatment paradigm should be questioned and analysed with further studies. In addition, we believe that NIRS may measure and evaluate the direct and instant effects during rehabilitation and may help health professionals in the field to gain new perspectives and lead to objectivity.

ACKNOWLEDGEMENTS

We thank Prof. Candan Algun, Associated Prof Simona Bar Haim and Ben Gurion University Laboratory for Rehabilitation and Motor Control of Walking, Associated Prof Dr.Yakup Krespi and Stroke Unit of the Hizmet Hospital, Memorial Group.

REFERENCES

[1] Feigin, V. L.; Forouzanfar, M. H.; Krishnamurthi, R.; Mensah, G. A.; Connor, M.; Bennett, D. A.; Moran, A. E.; Sacco, R. L.; Anderson, L.; Truelsen, T.; O'Donnell, M.; Venketasubramanian, N.; Barker-Collo, S.; Lawes, C. M.; Wang, W.; Shinohara, Y.; Witt, E.; Ezzati, M.; Naghavi, M.; Murray, C.; Global Burden of Diseases, I.; Risk Factors, S.; the, G. B. D. S. E. G. "Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010", Lancet 2014, 383, 245-54.

[2] Mok, V. C.; Wong, A.; Lam, W. W.; Fan, Y. H.; Tang, W. K.; Kwok, T.; Hui, A. C.; Wong, K. S. "Cognitive impairment and functional outcome after stroke associated with small vessel disease", J Neurol Neurosurg Psychiatry 2004, 75, 560-6.

[3] Bar-Haim, S.; Harries, N.; Hutzler, Y.; Belokopytov, M.; Dobrov, I. "Training to walk amid uncertainty with Re-Step: measurements and changes with perturbation training for hemiparesis and cerebral palsy", Disabil Rehabil Assist Technol 2013, 8, 417-25.

[4] Bar-Haim, S.; Harries, N.; Belokopytov, M.; Lahat, E.; Kaplanski, J. "Random perturbation: a potential aid in treatment of children with cerebral palsy", Disabil Rehabil 2008, 30, 1420-8.

[5] Woollacott, M.; Shumway-Cook, A.; Hutchinson, S.; Ciol, M.; Price, R.; Kartin, D. "Effect of balance training on muscle activity used in recovery of stability in children with cerebral palsy: a pilot study", Dev Med Child Neurol 2005, 47, 455-61.

[6] Shumway-Cook, A.; Hutchinson, S.; Kartin, D.; Price, R.; Woollacott, M. "Effect of balance training on recovery of stability in children with cerebral palsy", Dev Med Child Neurol 2003, 45, 591-602.

[7] Perrey, S. "Non-invasive NIR spectroscopy of human brain function during exercise", Methods 2008, 45, 289-99.

[8] Bediz, C. S.; Güdücü, Ç. "Egzersiz ve Beyin : Karakutu Artık Işık Alıyor", Genel Tıp Dergisi 2015, 2015;25, 1.

[9] Maidan, I.; Bernad-Elazari, H.; Gazit, E.; Giladi, N.; Hausdorff, J. M.; Mirelman, A. "Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures", J Neurol 2015, 262, 899-908.

[10] Piper, S. K.; Krueger, A.; Koch, S. P.; Mehnert, J.; Habermehl, C.; Steinbrink, J.; Obrig, H.; Schmitz, C. H. "A wearable multi-channel fNIRS system for brain imaging in freely moving subjects", Neuroimage 2014, 85 Pt 1, 64-71.

[11] Hausdorff, J. M.; Yogev, G.; Springer, S.; Simon, E. S.; Giladi, N. "Walking is more like catching than tapping: gait in the elderly as a complex cognitive task", Exp Brain Res 2005, 164, 541-8.

[12] Lowry, K. A.; Brach, J. S.; Nebes, R. D.; Studenski, S. A.; VanSwearingen, J. M. "Contributions of cognitive function to straight- and curved-path walking in older adults", Arch Phys Med Rehabil 2012, 93, 802-7.

[13] Wang, X. Q.; Pi, Y. L.; Chen, B. L.; Chen, P. J.; Liu, Y.; Wang, R.; Li, X.; Waddington, G. "Cognitive motor interference for gait and balance in stroke: a systematic review and meta-analysis", Eur J Neurol 2015, 22, 555-e37.

[14] la Fougere, C.; Zwergal, A.; Rominger, A.; Forster, S.; Fesl, G.; Dieterich, M.; Brandt, T.; Strupp, M.; Bartenstein, P.; Jahn, K. "Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison", Neuroimage 2010, 50, 1589-98.

[15] Gwin, J. T.; Gramann, K.; Makeig, S.; Ferris, D. P. "Removal of movement artifact from high-density EEG recorded during walking and running", J Neurophysiol 2010, 103, 3526-34.

[16] Kurz, M. J.; Wilson, T. W.; Arpin, D. J. "Stride-time variability and sensorimotor cortical activation during walking", Neuroimage 2012, 59, 1602-7.

[17] Holtzer, R.; Mahoney, J. R.; Izzetoglu, M.; Izzetoglu, K.; Onaral, B.; Verghese, J. "fNIRS study of walking and walking while talking in young and old individuals", J Gerontol A Biol Sci Med Sci 2011, 66, 879-87.

[18] Koenraadt, K. L.; Roelofsen, E. G.; Duysens, J.; Keijsers, N. L. "Cortical control of normal gait and precision stepping: an fNIRS study", Neuroimage 2014, 85 Pt 1, 415-22.

[19] Collette, F.; Hogge, M.; Salmon, E.; Van der Linden, M. "Exploration of the neural substrates of executive functioning by functional neuroimaging", Neuroscience 2006, 139, 209-21.

[20] Stuss, D. T.; Alexander, M. P. "Executive functions and the frontal lobes: a conceptual view", Psychol Res 2000, 63, 289-98.

[21] Friedman, P. J. "Gait recovery after hemiplegic stroke", Int Disabil Stud 1990, 12, 119-22.

[22] Al-Yahya, E.; Dawes, H.; Smith, L.; Dennis, A.; Howells, K.; Cockburn, J. "Cognitive motor interference while walking: a systematic review and meta-analysis", Neurosci Biobehav Rev 2011, 35, 715-28.

[23] Banks, J. L.; Marotta, C. A. "Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis", Stroke 2007, 38, 1091-6.

[24] Mawase, F.; Bar-Haim, S.; Karniel, A.; Shmuelof, L. "Locomotor adaptation in Cerebral Palsy patients is constrained by their increased performance variability".