Case Report

Brain plasticity after implanted peroneal nerve electrical stimulation to improve gait in chronic stroke patients: Two case reports

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Abstract

BACKGROUND: Recent studies have shown that stimulation of the peroneal nerve using an implantable 4-channel peroneal nerve stimulator could improve gait in stroke patients.

OBJECTIVES: To assess structural cortical and regional cerebral metabolism changes associated with an implanted peroneal nerve electrical stimulator to correct foot drop related to a central nervous system lesion.

METHODS: Two stroke patients presenting a foot drop related to a central nervous system lesion were implanted with an implanted peroneal nerve electrical stimulator. Both patients underwent clinical evaluations before implantation and one year after the activation of the stimulator. Structural magnetic resonance imaging (MRI) and [18F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) were acquired before and one year after the activation of the stimulator.

RESULTS: Foot drop was corrected for both patients after the implantation of the stimulator. After one year of treatment, patient 1 improved in three major clinical tests, while patient 2 only improved in one test. Prior to treatment, FDG-PET showed a significant hypometabolism in premotor, primary and supplementary motor areas in both patients as compared to controls, with patient 2 presenting more widespread hypometabolism. One year after the activation of the stimulator, both patients showed significantly less hypometabolism in the damaged motor cortex. No difference was observed on the structural MRI.

CONCLUSION: Clinical improvement of gait under peroneal nerve electrical stimulation in chronic stroke patients presenting foot drop was paralleled to metabolic changes in the damaged motor cortex.

Keywords: Functional electrical stimulation, brain plasticity, stroke, positron emission tomography, ActiGait, motor deficit, gait
1. Introduction

Twenty to thirty percent of patients who have had a stroke suffer from a foot drop (Lyons, Sinkjaer, Burridge, & Wilcox, 2002), which is the difficulty to lift the front part of the foot. Foot drop is a sign of an underlying neurological, muscular or anatomical problem, which affects the gait, increases the risk of falling and requires more effort to walk (Jørgensen, Nakayama, Raaschou, & Olsen, 1995). To help patients with stroke or multiple sclerosis to regain a functional gait and improving their autonomy, an implanted functional electrical stimulation (FES) device was recently developed (ActiGait, Ottobock, Germany). The ActiGait stimulates the dorsiflexor muscles at the right time to lift the foot and improves walking (Burridge et al., 2007). Beside gait improvement, it has been shown that patients receiving FES need less concentration and less effort to walk, and they can thus walk longer distance (Thrasher, Flett, & Popovic, 2006).

This 4-channel stimulator, surgically placed over the motor branch of the common peroneal nerve of the paralyzed leg, triggers a stimulation at every step to induce a dorsiflexion. To do so, a heel switch is placed in the shoe to detect when the foot is lifted and then triggers the control unit to activate the implanted stimulator that sends impulses at a selected frequency through the nerve and activates dorsiflexor muscles (i.e., tibialis anterior, extensor hallucis longus, extensor digitorum longus and peroneus tertius). In this sense, the electrical stimulation is delivered in between the ipsilateral foot lift and strike (i.e., the entire swing phase). This technique has been shown to improve patients’ gait (Burridge et al., 2007; Chantraine, Schreiber, Kolanowski, & Moissenet, n.d.; K Daniel Martin, Polanski, Schackert, & Sobottka, 2015; Klaus Daniel Martin et al., 2015) in terms of walking speed as well as ankle kinematic pattern, and is well-tolerated in patients with stroke (Schiemanck et al., 2015) and multiple sclerosis (Hausmann et al., 2015).

We here report two cases of chronic stroke patients suffering from a foot drop who have been implanted with ActiGait stimulator and who underwent a scanning exam with structural magnetic resonance imaging (MRI) and fluorodesoxyglucose positron emission tomography (FDG-PET) before and one year after the activation of the stimulator. The aim of this study is to assess the potential effects of the stimulator on brain metabolism and cortical plasticity.

Previous studies have shown that the clinical improvements of stroke patients can be related to an increase in brain metabolism within the ipsilateral damaged motor areas in case of good recovery, but it has also been related to an increased metabolism in the contralateral motor areas if the functional recovery was poor (Nelles, Jentzen, Bockisch, & Diener, 2011; Nelles, Jentzen, Jueptner, Muller, & Diener, 2001). Based on these studies, we hypothesized that this peripheral nerve stimulator, by improving patients’ gait, will influence cortical plasticity and modify brain metabolism in the motor cortex affected by the stroke and this, even in chronic patients who are no longer benefiting from a rehabilitation program.

2. Methods

2.1. Protocol

Two patients with chronic (i.e., more than 2 years in these cases) stroke and foot drop were included in this study. Patients underwent a surgery at the Department of Neurosurgery, Centre Hospitalier de Luxembourg, to place the ActiGait stimulator (Fig. 1) over the motor branch of the common peroneal nerve of the affected leg. The cuff was placed proximal to the knee joint but distal to the separation of the sensory and motor nerve branches. Three weeks after the surgery, but before the activation of the stimulator, patients underwent a MRI and a FDG-PET (i.e., baseline) at the University Hospital of Liege, CHU Sart-Tilman, Belgium. Then, the FES was activated and the patients came back for a second exam one year later (i.e., MRI and PET-1year – see Fig. 2). To avoid pain and muscular fatigue, a progressive use of the stimulator was applied by using it only half days the first two weeks after activation.

In order to follow patient’s functional evolution during gait, clinical assessments were performed approximately one month before surgery and one year after surgery. These assessments were always performed by the same experience operator (AR) and included a 6-minute walking test, a 10-meters walking test and a Four Square Step Test (FSST – (Blennerhassett & Jayalath, 2008)). FSST assesses the dynamic balance of patients by measuring their ability to step over objects forward, sideways, and backwards.

The protocol was approved by the National Ethics Committee of Luxembourg and patients gave their informed consents before participation.
2.2 Patients

The two patients included in this study matched the following criteria: foot drop following a stroke, complete growth of the lower limbs, hemiparesis, more than 12 months post-stroke (i.e., chronic phase), stable physical condition (i.e., no motor or functional improvement for the last 12 months) and positive results with an external FES stimulator (i.e., clear gait improvement). Patients did not present peripheral nerve lesions of the affected leg, lesions of the skin or sensitive skin, uncontrolled epilepsy, diabetes, previous neurological diseases or other unstable medical conditions.

2.3 FES settings

The FES settings were defined for each patient during the activation of the implant by a medical doctor (EK) and a research engineer (FM). They were optimized to fit the gait pattern of the patients during the first month of the implant use. The final settings are given in the results section for each patient.

2.4 Brain MRI

Using a 1.5T magnet (Siemens Trio Tim, Munich, Germany), structural images (T1-3D: 120 slices, TR = 16, TE = 4.8, voxel size = 1 × 1 × 1 mm³, FOV = 256 × 256) were acquired one week before and one year after the activation of the stimulator. The 1.5T magnet was favored over a higher field magnet due to FES-related safety concerns. All MRI scans were visually inspected by a certified neuroradiologist (CDP).

2.5 FDG-PET scan

FDG-PET cerebral metabolism data were acquired before the activation of the stimulator and one year later using a Gemini TF Big Bore (Philips Medical...
System) according to a standard clinical protocol (Martin et al., 2015). An intravenous injection of 300 MBq FDG was administered 30 minutes before the scan. PET data was preprocessed using spatial normalization, smoothing (using a Gaussian kernel of 12 mm full width at a half maximum) and proportional scaling, implemented in Statistical Parametric Mapping toolbox (SPM8) (Laureys et al., 2000; Phillips et al., 2011). The design matrix separately modeled patients’ (PET-baseline and PET-1year) and 34 healthy controls’ PET scans as published elsewhere (Thibaut et al., 2015). Results were considered significant at family-wise whole-brain volume-corrected for multiple comparisons (FWE, $p < 0.05$).

3. Results

3.1. Clinical data

Patient 1 is a 15 years old boy who suffered from a hemorrhagic stroke (congenital malformation) over the left hemisphere 25 months before his inclusion in the present study. The ActiGait stimulator was set to a pulse width of 75 μs, an amplitude of 1.2 mA and a frequency of 20 Hz. Clinically, the stimulator was able to correct foot drop and thus secured the patient’s gait. Moreover, the daily use of the stimulator conduced to a substantially recovering of the gait capacities after one year, with a gain of 230 meters at the 6-minute walking test, a decrease of 300 ms at the 10-meter walking test, and a better dynamic balance as observed at the FSST (improvement of 1.17 s).

Patient 2 is a 54 years old man who suffered from an ischemic stroke over the right hemisphere 28 months before the implantation of the ActiGait stimulator. The stimulator was set to a pulse width of 125 μs, an amplitude of 1.2 mA and a frequency of 30 Hz. While the stimulator was again able to correct foot drop in this patient, the use of FES for a year failed in conducing to a recovery of the gait capacities with a slight improvement of 10 meters only at the 6-minute walking test and no gain at the 10-meter walking test. The dynamic balance of this patient was, however, enhanced with an improvement of 3.5 s at the FSST.

3.2. MRI

MRI images of patient 1 (Fig. 2A) showed a focal porencephalic cavity in the precentral area of the left hemisphere, extending to the centrum semiovale and the inferior frontal lobe, with enlargement of the cella media of the left lateral ventricle.

MRI images of patient 2 (Fig. 3) showed encephalomalacia with tiny poroencephalic cavities in the precentral area, centrum semiovale and corona radiata of the right hemisphere. Enlargement was also observed in the fronto-parietal cortical sulci, mainly on the right side, and in the frontal horn and cella media of the right lateral ventricle.

No differences between the two structural MRI scans (baseline and 1 year) were identified at visual inspection.

3.3. FDG-PET

Statistical analyses identified: A) brain areas showing hypometabolism during PET-baseline compared to healthy controls, B) brain areas showing hypometabolism at PET-1year compared to healthy controls, and C) brain areas showing a relatively preserved metabolism in PET-1year as compared to PET-baseline.

Patient 1: PET-baseline showed regional hypometabolism in the left primary, supplementary and pre-motor areas, as well as in the left cingulate cortex and the thalamus. PET-1year showed hypometabolism in the same brain regions as PET-baseline. Difference between PET-baseline and PET-1year showed les hypometabolism in the right supplementary and pre-motor areas, as well as in the left cingulate cortex and the left thalamus (Table 1 and Fig. 4).

Patient 2: PET-baseline showed regional hypometabolism in the right premotor and supplementary motor areas, the right medial frontal gyrus (frontal eyes field) and the right cingulate cortex. PET-1year showed hypometabolism in the same brain regions. The comparison between the two PET-scans showed less hypometabolism in the right supplementary and pre-motor areas, as well as in the cingulate cortex and frontal eye field (Table 1 and Fig. 4).

4. Discussion

In this study, we report the case of two chronic stroke patients who benefited from an implanted drop foot stimulator – ActiGait. These patients had different clinical outcomes, one demonstrating both gait capacities and dynamic balance enhancements (patient 1) while the other presented only dynamic...
Fig. 3. Structural MRI results. From left to right: T1-3D sagittal, axial and coronal images before the activation of the stimulator and one year later. For patient 1, note the focal poroencephalic cavity involving the left precentral area and centrum semiovale. For patient 2, note the encephalomalacic lesion involving the right precentral area, centrum semiovale and corona radiata.

### Table 1

Coordinates of peak voxels (in standardized stereotaxic MNI space) of less impaired metabolism in PET-1 year as compared to PET-baseline, for patient 1 and 2

<table>
<thead>
<tr>
<th>Region (Brodmann area)</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative increase in metabolism – Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left medial frontal gyrus – B6</td>
<td>-8</td>
<td>-20</td>
<td>72</td>
<td>5.68</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Left precentral gyrus – B4</td>
<td>-20</td>
<td>-22</td>
<td>70</td>
<td>5.48</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>-8</td>
<td>-20</td>
<td>6</td>
<td>5.28</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Left cingulate gyrus – B24</td>
<td>-14</td>
<td>-14</td>
<td>44</td>
<td>5.07</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Relative increase in metabolism – Patient 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right medial frontal gyrus – B8</td>
<td>12</td>
<td>32</td>
<td>42</td>
<td>7.03</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Right cingulate gyrus – B32</td>
<td>12</td>
<td>22</td>
<td>46</td>
<td>6.98</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Right middle frontal gyrus – B6</td>
<td>46</td>
<td>6</td>
<td>50</td>
<td>6.29</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Whole-brain family-wise errors corrected for multiple comparisons.

Balance enhancement (patient 2). However, both patients demonstrated brain plasticity changes after one year of stimulation in the damaged motor areas, as well as in the anterior cingulate cortex.

Previous studies showed the clinical effectiveness of an implanted FES to improve patients’ gait (Burridge et al., 2007, 2008; Chantraine et al., 2016; Ernst et al., 2013; Hausmann et al., 2015; Klaus Daniel Martin et al., 2015; Schiemanck et al., 2015), but no studies have so far assessed its effect on brain plasticity. Only one animal study explored the changes occurring in the brain (as measured by
Fig. 4. FDG-PET results. First line represents the hypometabolic areas (in blue) before the activation of the stimulator as compared to healthy controls. Second line represents the hypometabolic areas one year after as compared to healthy controls. Third line represents the difference between the two exams (hypometabolic areas at 1 year < hypometabolic areas at baseline), with a relative increase in brain metabolism in red. Note that the increase in metabolism one year after the activation of the stimulator is mostly in the areas that were originally affected by the stroke.

brain immunochemistry labeling with microtubule-associated protein-2 and neurofilament-200 markers) after the implantation of FES in rats model of focal stroke (Cecatto, Maximino, & Chadi, 2014). The authors reported motor recovery after active FES (daily stimulation during 20 to 40 minutes for 14 days) as compared to sham FES; but they did not identify any change at the cortical level. It might be possible that the technique used was not sensitive enough (e.g., the MRI in our case) or that a longer period of stimulations (e.g., 12 months as in our protocol) was needed to induce objective changes at the cortical level.

In our study, we hypothesized that implanted FES used for one year should induce brain plasticity either over the damaged motor cortex. Our results showed that residual cortical plasticity mainly occurred in the damaged motor regions and in the anterior cingulate cortex (known to be part of the motor control network (Hoffstaedter et al., 2014)) in two patients with chronic stroke. After a stroke, recovery of the damaged brain area has already been shown to correlate with better functional outcome whereas poor recovery has been linked to an increased activity in the contralateral side of the lesion (Nelles et al., 2011). Therefore, we suggest that the peripheral nerve stimulation promotes a direct recovery of the brain injury, rather than finding an adaptive way to circumvent the impaired area (i.e., increased brain metabolism in the contralateral healthy hemisphere).

In this cases report, ActiGait stimulator was clinically able to correct foot drop in both patients. Patient 1 significantly improved at the 6-minute and the 10-meter walking tests, as suggested by Tang et al. (Tang, Eng, & Rand, 2012) (i.e., more than 34.4 m difference) and Perera et al. (Perera, Mody, Woodman, & Studenski, 2006) (i.e., substantial change of 0.14 m/s). Because no minimum clinically important difference has been established for the FSST, we could not evaluate the clinical significance of the observed improvements for that test. Patient 2, despite the correction of his foot drop, did not show any significant gait capacities improvement one year after the activation of the stimulator (i.e., no gain at 10-meter walking test and gain inferior than the minimum clinically important difference at the 6-minute walking test) (Perera et al., 2006). Nevertheless, he showed increased brain activity in the lesioned hemisphere. This supports the idea that, even if the foot drop is corrected with only a slight functional improvement, cortical plasticity can occur over the damaged area after using a peripheral nerve stimulator. It should be noted that patient 2 had more widespread brain lesions and was older than patient 1 who did show considerable gait progress. These differences might explain why clinical improvements of that patient were smaller.

No structural changes were observed on the MRI suggesting that structural MRI may not be sensitive enough to detect cortical improvements that followed
clinical enhancement in patients with brain lesions. Therefore, FDG-PET, that assesses the functional brain activity, seems to be more adequate to evaluate such changes. Indeed, the uptake of FDG by brain tissues is a marker of glucose uptake and therefore, a marker of brain metabolism, which reflects functional neural activity.

This report has some limitations that need to be taken into account. First, there are no control patient (i.e., PET-scan after one year, without implanted FES), and therefore, the results may be due to spontaneous recovery. Indeed, some patients spontaneously recovered and showed an increase in brain metabolism within motor areas ipsi- or contralateral to the stroke (Nelles et al., 2011). Nevertheless, these improvements happened most of the time within one year post-insult. In our case, the two patients were included 2 years post-insult and they did not show any functional improvement for at least one year before the implantation of the stimulator. Some could argue that the observed metabolic changes might be due to patient’s brain metabolism inter-variability between the two scans (e.g., unequal incubation durations or different time of the day) and not the consequence of an improvement in brain metabolism. PET-scan acquisitions were, however, strictly the same for the two scans (before and after), as well as for the two patients. In addition, studies investigating FDG-PET test-retest reliability demonstrated a low intra-individual variability of cerebral glucose consumption and regional metabolic distribution between two scans, separated by 3 months (Maquet, Dive, Salmon, von Frenckel, & Franck, 1990) and 6 months (Schaefer et al., 2000). Therefore, both clinical and brain metabolic improvements are thought to be related to the implanted FES and not to natural recovery. In addition, this report included only two patients with different clinical outcomes. The inclusion of a large sample of patients should help us understanding the mechanisms underlying the functional and cortical enhancements as well as better characterizing patients who could benefit or not of this implanted FES.

5. Conclusion

Cortical metabolism improvement over the damaged motor areas were observed one year after the implantation of a peroneal nerve electrical stimulator to correct foot drop in two patients who suffered from a chronic stroke. This recovery of near-to-normal brain metabolism occurred in both patients even if only one showed significant gait enhancement. Further studies on a larger sample of patients should confirm these results and provide more information on the neuronal correlates of gait improvement.

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Conflict of interest

The authors have no conflict of interest to report.

Author contributions

AT acquired the imagining data, analyzed PET data and wrote the MS. FM designed the clinical tests protocol, analyzed the associated data and reviewed the MS. CDP interpreted and compared the MRI scans. CS designed the clinical tests protocol. AR acquired the clinical tests data. EK and FC performed patients’ follow-up. RH and CB supervised PET acquisitions. JFT supervised MRI acquisitions. PF designed the clinical tests protocol and ensured its validation by the National Ethics Committee of Luxembourg. SL designed the protocol and reviewed the MS. OG designed the protocol, acquired the data, supervised and reviewed the MS.

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