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Neuroplastic changes mediate motor recovery with implanted peroneal nerve stimulator in individuals with chronic stroke: an open-label multimodal pilot study

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Dear Editor. Almost one quarter of stroke survivors experience foot drop leading to walking disturbance, fatigue and risk of falling.[1] This limitation affects functional mobility, autonomy and quality of life.[2] Several therapeutic approaches that reinforce dorsiflexors include physical therapy, electromyostimulation, functional electrical stimulation (FES), or maintenance of the

ankle in an appropriate position during gait (e.g., orthosis). In addition, anti-spastic medication can be used to facilitate dorsiflexion and improve gait.

An implanted FES device has been developed to facilitate the use of FES. This technique has been shown to improve gait and is well tolerated by users.[3,4] An open-label longitudinal study evaluated the effect of an implanted FES stimulator (ActiGait®, Ottobock, Germany) on gait after 1 year of use in individuals with chronic stroke.[5] The authors found a significant improvement in dorsiflexion, similar to what was observed with surface FES. Two other studies by Berenpas and collaborators compared the effects of implanted FES to conventional ankle-foot orthosis in individuals with chronic stroke, showing superior improvement in knee stability, ankle plantarflexion power, and propulsion with FES versus ankle-foot orthosis [6] as well as better adaptation of the gait pattern to environmental disturbances.[7] The same team also demonstrated that long-term use of implanted FES could increase muscle thickness and normalize motor-evoked potential on the paretic side.[8]

In the present study, we assessed the potential effects of implanted FES on both behavior and cortical plasticity in individuals after stroke by using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and structural and functional MRI (fMRI).

We included individuals who presented foot drop due to stroke > 9 months after stroke, hemiparesis, no functional improvement (i.e., no significant changes on the 6-min walk test [6MWT] and 10-m walk test [10MWT] performed during daily clinical follow-up) within the last 6 months, stable medical condition, positive results (i.e., improvement in gait) with an external FES, positive MRI results of the knee after FES implantation (i.e., distance between the stimulator and skin < 40 mm) and written informed consent. Exclusion criteria included peripheral nerve lesions of the affected leg, lesion of the skin or a sensitive skin, diabetes, previous neurological diseases and MRI/FDG-PET contraindication. The protocol was the same

as described in a previous case report.[9] Patients underwent surgery to place the FES stimulator (ActiGait®) over the motor branch of the common peroneal nerve. Three weeks after the surgery but before activation of the stimulator, patients underwent MRI and FDG-PET (i.e., baseline). Then, the FES was activated and patients came back for a second examination the following year (i.e., 1-year MRI and FDG-PET). The FES was programmed to send a current of 1.1 mA for each patient. Pulse rate and duration were defined for each patient during activation of the implant. The FES was optimized during the first month of implant use to fit the patients' gait pattern. Behavioral evaluations performed before and after activation of the FES tested walking and endurance, speed, and dynamic balance with the 6MWT, 10MWT and Four Square Step Test (FSST), respectively. Clinical assessments were performed at 1 year while the stimulator was ON. The study was approved by the National Research Ethics Committee of Luxembourg. All individuals with stroke and healthy controls gave their written consent and the study followed the STROBE statement.

Neuroimaging data of patients with a lesion over the right hemisphere were flipped to have all brain lesions on the same side (i.e., left). FDG-PET data were preprocessed with spatial normalization, smoothing (Gaussian kernel 12 mm full width at a half maximum) and proportional scaling, implemented in Statistical Parametric Mapping toolbox (SPM8). The design matrix separately modeled PET scans for individuals with stroke (PET 1 and PET 2) and 34 age-matched healthy controls, as published elsewhere.[11] We used a T1-based voxel-based morphometry analysis of brain structure (VBM8) along with SPM8 to search for potential morphological differences in grey matter (GM) density, as described.[12] We used DARTEL-based spatial normalization and smoothed the data with Gaussian isotropic kernel (8 mm of full-width-at-half-maximum). In total, 300 T2*-weighted resting-state fMRI volumes were acquired by using a 1.5T Siemens TIM Trio MRI scanner. Pre- and post-processing were as described [13]. For measuring fMRI resting-state functional connectivity, a seed-based approach

was used with the connectivity toolbox CONN. The seed-correlation analysis extracts fMRI BOLD time series from a region of interest and determines the temporal correlation between this signal and the time series from all other brain voxels. We compared the functional connectivity between 2 regions showing peak results in the FDG-PET analysis (i.e., ispsilateral and contralateral premotor cortex – BA6) and the time series from all other brain voxels in the brain before and 1 year after the stimulator activation in all stroke individuals. For VBM and fMRI analyses, data for stroke individuals were compared to an age-matched group of 8 healthy volunteers. All results were considered statistically significant at $p<0.05$ (false discovery rate [FDR]).

Thirteen patients successfully completed the study (5 females, mean [SD] age 46 [12] years, 4 right- and 9 left-sided, 6 hemorrhagic and 7 ischemic stroke; mean time since stroke 29 [16] months; see Table). All patients presented functional improvement for at least one assessed function (i.e., 6MWT, 10MWT, and FSST).

For FDG-PET, statistical analyses demonstrated hypometabolism in the lesioned hemisphere at baseline, mostly in motor and frontal regions (Fig. A, red and purple). At 1-year follow-up, brain metabolism was increased in the primary and secondary sensorimotor cortex, premotor area, cerebellum and associative areas such as frontal, parietal and occipital regions (Fig. A, red). At baseline, VBM analysis showed extensive regional GM atrophy in the damaged hemisphere, involving the lateral fronto-parietal and temporal hemisphere, caudatum, thalamus and cerebellum (Fig. B, red and purple). At 1-year follow-up, GM was increased in the ipsilateral (to the brain lesion) sensorimotor regions and inferior frontal cortex (Fig. 1B, red) and decreased in the ipsilateral (to the brain lesion) orbitofrontal cortex, cingulate cortex and occipital cortex (Fig. 1B, blue). For fMRI analysis, one participant was excluded because of excessive movement artifacts. In comparing baseline to 1-year follow-up, functional connectivity significantly increased between the seed in the motor cortex of the lesioned

hemisphere (x = 24, y = 4, z = 72) and the insula and operculum in the same damaged hemisphere (x = -42, y = 8, z = 2; cluster p-FDR=0.04) (Fig. C). We found no significant difference with the contralateral motor seed.

Our group results support that after using ActiGait® for 12 months, metabolic, structural, and functional connectivity change in the lesioned hemisphere in individuals with chronic stroke and foot drop. These findings suggest that structural and functional brain reorganization continue to occur with prolonged use of implanted FES in individuals with chronic stroke. However, we also found reduced GM at 1 year in the damaged hemisphere (orbitofrontal, cingulate and occipital cortices), which could reflect global brain atrophy and/or be related to symptom worsening that was not collected in the present study.

We show that peripheral stimulation can modulate and improve connectivity even years after the stroke (the longest time since injury was 5.9 years). This improvement within the damaged hemisphere may be clinically more promising as compared with increased activity in the controlesional brain area given that individuals with stroke who recover some brain activity in the damaged hemisphere have better functional outcomes than those with an increase in brain activity in the undamaged hemisphere only.[14] We observed increased metabolism at 1-year follow-up in a large network involved in movement planning and execution, namely the primary and secondary sensorimotor cortex (postcentral gyrus), premotor area (precentral gyrus), cerebellum and associated areas such as frontal (frontopolar prefrontal cortex), parietal (supramarginal gyrus) and occipital (superior occipital gyrus) regions. Furthermore, the motor cortex showed increased functional connectivity with the insula, a brain region thought to be involved, among others, in motor control.[15] The improvement in function within this network and not just in the primary motor cortex could reflect the recovery of the ability to perform more complex movement and not just simple or automatic motor tasks. In this context, our

findings suggest an improvement in foot drop but also a more widespread functional recovery of gait function.

One main limitation of this study is the lack of a control group of stroke individuals and foot drop without implanted FES. So far, no controlled randomized clinical trial of individuals with chronic stroke has evaluated the effect of implanted FES on foot drop, so discriminating natural recovery from an intervention effect in both the present study or previous ones focusing on clinical outcomes is difficult.[16] Another potential limitation is our limited sample size. Because of the small sample and its heterogeneity, any generalizability of our results is cautioned.

In conclusion, the present study shows that motor recovery following implanted FES in individuals with chronic stroke parallel functional and structural brain changes in the affected brain hemisphere. Large randomized controlled clinical trials, including a placebo group and combining functional assessments with neuroimaging techniques, are warranted to disentangle natural from treatment-related improvement and confirm the positive effects of this peroneal nerve stimulator in stroke rehabilitation. Neuroimaging and neurophysiological recordings could also help identify biomarkers of functional improvement and better target a sub-group of individuals who could benefit from this therapeutic approach. Peroneal nerve stimulation provides a unique, painless and promising way to help individuals with stroke enhance their gait function, although the related intervention is invasive and implies some risks.

Conflict of interest. None declared.

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Figure legend

Figure. A) 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) results. Hypometabolic brain areas at baseline (in red) and at 1-year follow-up (in blue, covered by the hypometabolism at baseline), compared to controls. In purple, the overlap between the 2 comparisons. Hence, red color shows the areas of hypometabolism present at baseline but not at 1-year follow-up. No areas were more hypometabolic at 1-year follow-up. **B)** Voxel based morphometry (VBM) result. Brain areas of gray-matter (GM) atrophy at baseline (in red) and at 1-year follow-up (in blue), compared to controls. In purple, the overlap between the 2 comparisons. Hence, red color shows the areas of GM atrophy present at baseline but not at 1-year follow-up; blue color shows the areas of GM atrophy present at 1-year follow-up and not at baseline. **C)** Functional MRI (fMRI) connectivity result. The motor cortex of the affected hemisphere is more connected to a region overlapping the insula and operculum after 1 year of functional electrical stimulation (FES; in red). Statistical maps are thresholded at $p<0.05$ false discovery rate corrected at the whole brain level (A, B, C) and are rendered on the axial, midline and coronal surfaces (A, B) or the axial surface only (C) on an MRI template.

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