Resting-State Functional Connectivity in Stroke Patients After Upper Limb Robot-Assisted Therapy: A Pilot Study

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Abstract. Motor deficit is a prominent feature among stroke survivors. Robot-assisted therapies have been proposed as a strategy to boost rehabilitation, by allowing therapy to be provided in a more reproducible and intense manner, while quantitatively monitoring patient's improvement. However, those approaches have so far not shown superiority over conventional treatments. One potential solution to reach better outcomes would be to personalize the treatment. In this regard, a better understanding of the mechanisms underlying motor recovery is pivotal to tailor therapy to each patient. Here, we explored the cortical changes occurring during robotic training. We recorded resting-state fMRI before and after the treatment in three sub-acute post-stroke survivors, and we investigated the functional connectivity between motor regions. We observed a cortical reorganization following training, consistent with motor improvements.

1 Introduction

Fifteen million people worldwide experience a stroke every year, and most of the survivors are affected by motor deficits [1]. In the last decades, new neurorehabilitative strategies have emerged, such as robot-assisted therapies. By allowing therapy to be

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given over longer periods of time and in a more reproducible and intense manner, robotic devices aim to optimally engage the remaining neural pathways to promote better and faster recovery. Nevertheless, recovery from a neurological condition is still very challenging and most patients struggle to translate their improvements into daily life activities [2]. One of the limitations of the current approaches could stem from the lack of personalization. In this regard, a better understanding of the mechanisms underlying motor recovery is necessary to further improve the existing therapies. Functional magnetic resonance imaging (fMRI) offers a way to non-invasively probe neural activity, so as to investigate neural correlates of stroke recovery. In the context of neurorehabilitation, resting-state recordings (with no overt task) stand as a particularly attractive tool that can be used even with severely affected patients. Such recordings have been deployed to estimate the functional connectivity between distinct brain regions, hence highlighting network disturbances following stroke lesions, not only in the vicinity of the infarct, but also between homologous cortical areas of the contralesional hemisphere [3]. However, only a few studies have focused on cortical changes induced by robotic training [4, 5]. Here, we present pilot results regarding changes in resting-state functional connectivity (rsFC) in sub-acute stroke patients undergoing robot-assisted therapy.

2 Materials and Methods

2.1 Participants and Intervention

We recruited three sub-acute stroke patients (Table 1, Fig. 1) from the University Hospital of Geneva, suffering from right hemiplegia. All participants underwent a robot-assisted therapy for 4 weeks in addition to their conventional treatment. Before and after training, Fugl-Meyer clinical assessments for upper extremities and resting-state fMRI evaluations were performed.

Table 1. Clinical and demographic data

Patient ID	Gender	Age	FM (pre)	FM (post)
S1	Female	69	49	56
S2	Male	84	7	14
S3	Male	78	7	19

2.2 MRI Acquisition

Images were acquired on a 3T Siemens Prisma scanner. Resting state fMRI was performed with T2* weighted EPI imaging (TR = 1.5 s, TE = 35 ms) for a total of 320 volumes, with a spatial resolution of $3.75 \times 3.75 \times 5\ mm^3$. Subjects had their eyes closed throughout the imaging session. High-resolution T1-weighted structural images were also acquired.

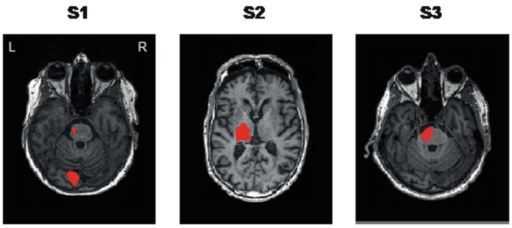

Fig. 1. T1 anatomical scans for the three subacute stroke subjects (S1-S3). The lesion (in red) is overlaid on each subject's anatomical scan.

2.3 MRI Analysis

All processing and analyses were done with FSL and Matlab. The following processing steps were applied: (i) slice-timing correction, rigid body realignment and grand mean intensity normalization; (ii) removal of outlier volumes (framewise displacement >0.5 mm) and linear interpolation of the missing data; (iii) high-pass frequency filtering (0.01 Hz). Outliers volumes were recensored following frequency filtering and preprocessed data were cleaned using a GLM analysis to regress out motion parameters, cerebrospinal fluid signal, white matter signal and global signal. Using the residuals from this analysis, we extracted the time courses from six regions (primary motor cortex M1, supplementary motor area SMA and premotor cortex PMC, in both hemispheres). Pearson's correlation coefficients were used to quantify the connectivity between those regions of interest.

3 Results

3.1 Interhemispheric M1 Connectivity

During the first evaluation ('pre'), the interhemispheric M1 rsFC was found to differ between subjects (Fig. 2). As expected from previous studies [3], the strength of the connectivity was correlated with the functional evaluations. S1, who had a FM score of 49/66 indicating a moderate impairment, had a high interhemispheric M1 rsFC ($r = 0.74$). In comparison, S2 and S3, who exhibited severe deficits (FM = 7), had a low interhemispheric M1 rsFC ($r = 0.39$ and 0.33, respectively). Interestingly, the relative improvement observed during the training was proportional to the change in interhemispheric M1 rsFC between 'pre' and 'post' evaluation. Notably, clinical scores for S1 between 'pre' and 'post' training were fairly comparable, with a relative improvement of 14%. Similarly, the observed rsFC remained stable ($\Delta r = 0.01$). On the other hand, there was a larger increase of the rsFC for S2 ($\Delta r = 0.1$) and S3 ($\Delta r = 0.32$), reflecting their larger functional improvement (100% and 174%, respectively).

3.2 Global Network Changes

In order to globally evaluate neural reorganization, we also included two additional motor regions in our analysis: SMA and PMC, for both hemispheres. The resulting networks are presented in Fig. 2 and emphasize an evolution of cortical organization throughout motor recovery and training. As for the 'pre' evaluation, patterns pertaining to the level of impairment can be observed. Consistently with literature [6], rsFC of ipsilesional M1 and contralesional PMC was perturbed for S2 and S3. In general, the connectivity was superior for S1. Notably, ipsilesional M1 and contralesional SMA appeared to be functionally connected for this patient (r = 0.60), which has been shown to correlate with good motor recovery at six months after stroke [7]. This is in line with the mild impairment of this patient at the end of the training (FM = 56). Moreover, this connection was preserved in the 'post' evaluation (r = 0.59). As for S2, whose deficits largely persisted after rehabilitation (FM = 14), interhemispheric rsFC remained limited. In comparison, S3 exhibited some patterns associated to motor improvement (FM = 19), such as an increased PMC interhemispheric connectivity [6].

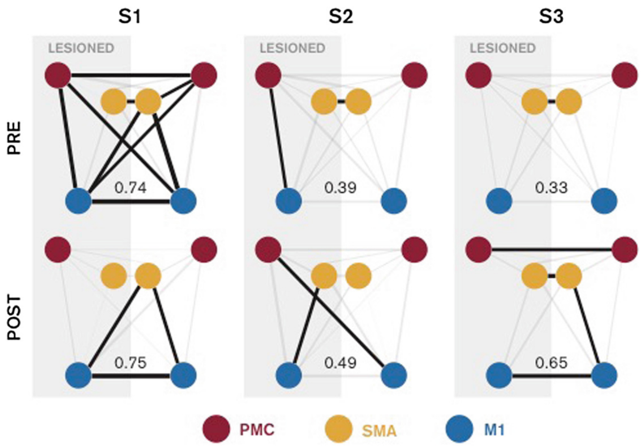

Fig. 2. Changes in motor functional connectivity. Nodes represent brain regions and edges depict correlations (black if >= 0.5, grey if < 0.5). Only positive correlations are shown. The width of the edges is proportional to the strength of the correlation and correlations coefficients are indicated for M1 interhemispheric connectivity.

4 Discussion and Conclusion

This initial exploration of the impact of robotic training on cerebral motor networks highlighted a cortical reorganization occurring during motor recovery and rehabilitation. These changes appeared to be clinically relevant, in accordance with existing literature [3]. Further investigation in a larger population undergoing different rehabilitative treatments is needed in order to evaluate how rehabilitation could capitalize on these neural markers of recovery to predict subject's response to robot-assisted therapy, as well as to personalize the treatment based on the neural state of the patients.

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