2011 IEEE International Conference on Rehabilitation Robotics
Rehab Week Zurich, ETH Zurich Science City, Switzerland, June 29 - July 1, 2011

An fMRI pilot study to evaluate brain activation associated with locomotion adaptation

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***Abstract*—The goal of robotic therapy is to provoke motor plasticity via the application of robotic training strategies. Although robotic haptic guidance is the commonly used motor-training strategy to reduce performance errors while training, research on motor learning has emphasized that errors are a fundamental neural signal that drives motor adaptation. Thus, researchers have proposed robotic therapy algorithms that amplify movement errors rather than decrease them. Studying the particular brain regions involved in learning under different training strategies might help tailoring motor training conditions to the anatomical location of a focal brain insult. In this paper, we evaluate the brain regions involved in locomotion adaptation when training with three different conditions: without robotic guidance, with a random-varying force disturbance, and with repulsive forces proportional to errors. We performed an fMRI pilot study with four healthy subjects who stepped in an fMRI compatible walking robotic device. Subjects were instructed to actively synchronize their left leg with respect to their right leg (passively guided by the robot) while their left leg was affected by any of the three conditions. We observed activation in areas known to be involved in error processing. Although we found that all conditions required the similar cortical network to fulfill the task, we observed a tendency towards more activity in the motor/sensory network as more "challenged" the subjects were.**

January 20, 2011

I. Introduction

There is increasing interest in using robotic devices to provide haptic guidance in a desired pattern of kinematics during movement practice (e.g. [1], [2], [3], [4]). Haptic guidance is a motor-training strategy in which a human or machine trainer physically interacts with the participant's limbs during movement training. The idea behind haptic guidance is a haptic device that demonstrates the correct movement trajectory in order for the Central Neural System (CNS) to replicate it. It is believed that haptic guidance could provide the CNS with additional proprioceptive and somatosensory cues to help enhance movement planning, as well as enable to attempt more advanced strategies of movement.

This work was supported with funds provided by the Swiss National Science Foundation 3200030 129937. Laura Marchal-Crespo holds a scholarship from the Fundacion Caja Madrid.

Although haptic guidance is often used in motor training and rehabilitation, there is currently little evidence that robotic guidance is more beneficial for human motor learning than unassisted practice. In fact, a long-standing hypothesis in motor learning research is the Guidance Hypothesis, which states that physically guiding a movement impairs motor learning [5], [6]. A number of studies have confirmed this hypothesis, finding that physically guiding movements does not aid motor learning and may in fact hamper it [2], [4], [7], [3].

Assisting-type robotic therapy algorithms have the effect of reducing movement errors. However, research on motor learning has emphasized that errors are a fundamental signal that drives motor adaptation [8], [9], [10], [11]. Thus, researchers have proposed robotic therapy algorithms that amplify movement errors rather than decrease them. In [12] amplifying errors during reaching by persons with chronic stroke with a robotic force field resulted in straighter movements when the force field was removed. Similarly, in [11], increasing limb phasing error in post-stroke participants' gait through a split-belt treadmill induced a long term increase in walking symmetry. In [13], training a reaching task with amplified errors was more beneficial for least impaired stroke patients, whereas more impaired stroke patients benefited more from haptic guidance. This result is consistent with [14], where training with amplified errors produced greater learning to play a pinball-like game than training with haptic guidance in higher-skilled participants, while for the less-skilled participants, training with haptic guidance was more beneficial. An extended approach to error amplification ("haptic disturbance") was proposed in a recent motor learning study [15]. The "haptic disturbance" was applied as randomly-varying feedforward forces to disturb the participants' movements while training a tracking task. Training with noise force disturbance resulted in better tracking skills than unassisted training, and than training with a more conventional error-amplification strategy (repulsive forces proportional to tracking errors).

The goal of robotic therapy is the development of robotic devices to perform rehabilitation exercises which provoke motor plasticity. However, currently there is not a solid scientific understanding of how this goal can be best achieved. Nevertheless, it is still an open question how different rehabilitation strategies contribute to restorative processes of the CNS [16]. Evaluation of brain regions involved in learning can provide valuable information on observed behavioral outcomes related to learning processes. The results from studying the particular brain regions involved in learning might have important therapeutic implications in terms of tailoring motor training conditions to the anatomical location of a focal brain insult. To achieve this goal, we target to evaluate the brain regions involved in learning when training with different forms of robotic guidance and error amplification, while performing functional Magnetic Resonance Imaging (fMRI).

In this paper we focus on locomotion adaptation, using a novel fMRI compatible walking robotic device. There is no comparable published literature with respect to cortical underpinnings of a complete gait-like movement. Therefore, our hypothesis derive from studies that investigated isolated joint movements like ankle or knee movements [17] or imagination of walking [18], [19], [20]. We hypothesized to find activity in somatosensory/motor related areas (S1/M1) and supplementary and pre-supplementary motor areas (SMA/pSMA). Hypothetically, the mirror neuron system might be implicated during training when the task is too easy. Patterns of activity of mirror neurons have been noted principally in pars opercularis of the inferior frontal gyrus [21], [22], in premotor cortex [21], [23], and inferior parietal lobule [24]. On the other hand, when the guidance makes the task more challenging, more activity is expected to be observed within all somatosensory/motor related areas, as well as in brain areas involved in error processing, such as the anterior cingulate cortex [25], posterior medial frontal cortex [26], and cerebellum [27], [28]. Because some of the paradigms presented here requested a high degree of motor related inhibition effort (subject were requested to remain their right leg passive), activation within dorsolateral prefrontal, medial prefrontal and possibly anterior insular subdivisions were additionally hypothesized. Furthermore, according to animal studies, activation is the brainstem is also expected. However, the interpretation of those remained difficult because of biasing influences due to movement.

II. METHODS

In order to perform the fMRI investigations during robotic training, we developed a robotic system able to perform defined gait movements, measure relevant parameters, and do not disturb the imaging process (Fig. 1).

A. MARCOS

MARCOS is a one degree of freedom robot, developed in our lab, that can provide active (machine-driven) and passive (subject-driven), gait-like movements during fMRI, without affecting image quality. MARCOS is actuated by two pneumatic cylinders per leg (Fig. 1). Pneumatic actuation allows for fine position and accurate force control [29], while requiring neither ferromagnetic materials nor fluids with high susceptibility which may interfere with the fMRI environment. Furthermore, pneumatic actuation allows for a more compliant robotic device, compared to motor driven robots. The cylinders connected to the knees are controlled by proportional flow-valves. The cylinders connected to the feet are controlled by pressure-control valves and a proportional valve. The reaction forces between the subject and robot are measured through force sensors located in the knee orthosis attachments, and the foot plates (Fig.1). A total of four resistant strain gauges on aluminum substrate serve as force sensors. The position of each cylinder piston is measured redundantly by optical encoders (MS20, RSF Elektronik AG) with a ceramic scale and a foil potentiometer.

Movements performed with MARCOS are comparable to periodic, on the spot stepping. For each leg, the knee and foot are attached to a modified pneumatic cylinder (DNC 40-320-P-K10-S11 (Knee), DNC 32-350-P-K10-S11 (Foot), Festo). All ferromagnetic parts in the pistons were replaced by aluminum and brass house-made parts. The gait pattern is controlled mainly by the knee cylinder, while the foot cylinder is able to generate a foot load that simulates ground reaction forces of up to 400 N on the foot sole (Fig. 1). The gait-like movement was adapted from natural walking characterized by a well-defined [30] series of flexion and extension movements at both hip (range $0°$ to $40°$) and knee ($0°$ to $50°$). Each foot moves along a linear guide (Fig. 1). The position and the slope of this linear guide can be separately adjusted to enable different angular displacements at the hip and knee [31]. The foot orientation is fixed. The angular displacements of the ankle range from $45°$ to $90°$.

B. Control modes

MARCOS can work in four different modes: (1) passive, (2) active, (3) force disturbance, and (4) error amplification. In passive mode, MARCOS guides the gait pattern, while the subject remains passive. In active mode, the subject is in charge of the movement generation, and the robot follows the subject movements. In force disturbance mode, a random force generated by the knee cylinder is superimposed to the active mode, in order to disturb the movement generated by the subject. In error amplification mode, MARCOS works mainly in active mode, however it amplifies the tracking error created by the subject, adding a force on the knee proportional to the tracking error.

1) Passive mode: The control strategy in the passive mode combines a feedback position controller in parallel with an iterative learning feedforward controller (ILC). The position controller enforces the desired knee trajectory through the length of the cylinder attached to the knee, with the proportional flow valves. The actuation variable from the position controller is proportional to the difference between the desired knee position and the measured actual position. One of the after effects of using proportional valves is their well known non-linear behavior. Such effect was compensated using a linearized model of the proportional valves response.

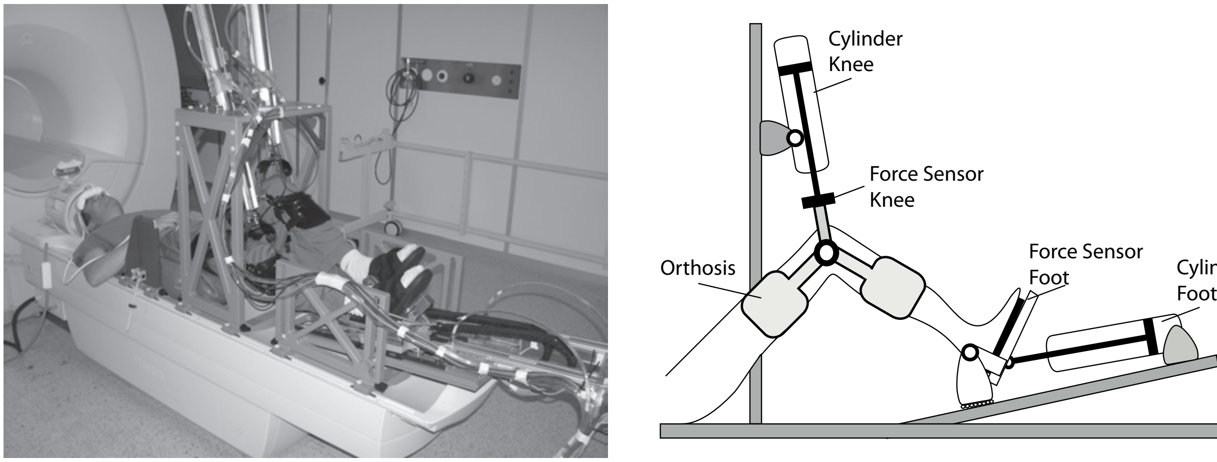

Fig. 1. Left: The fMRI compatible robotic stepping actuator MARCOS in the 1.5T MR scanner. MARCOS can provide active (machine-driven) or passive (subject-driven), gait-like movements. Right: The MARCOS system sketch (only 1 leg depicted for clarity). MARCOS is actuated with two pneumatic cylinders per leg. The reaction forces between the subject and the robot are measured through force sensors located in the knee orthosis attachment and the foot plate. The position of each cylinder piston is measured redundantly by optical encoders.

The ILC benefits from the gait cyclic movement to learn how to periodically improve the overall control performance. It calculates a feedforward control signal for the current cycle out of the error trajectory of the previous cycle, in a similar fashion as in [32]:

$$u_k(t) = g \cdot e_{k-1}(t + \Delta t) + f \cdot u_{k-1}(t) \tag{1}$$

Thus, the control signal from the ILC at cycle k at each discrete time t, is proportional to the tracking error created in the previous cycle e_{k-1}, and the control signal in the previous cycle $u_{k-1}(t)$, at the same discrete time. The proportional gain g is the learning gain, and f is the robot forgetting factor. We introduced a time shift Δt in the tracking error e_{k-1} to compensate for the delay in the system, due mainly to the long air tubing.

2) Active mode: In active mode, the subject is in charge of the movement generation, while the robot follows the subject movements. One of the positive features of pneumatic actuation is their high compliance: cylinders can be switched to a force-free state by connecting each chamber to the atmosphere. However, the effect of friction on the cylinders is large and the subject is required to apply relatively large forces to overcome the friction force. Compensation of undesired robot-dynamics is critical in order to allow the participants to intend the task by themselves, minimizing the interaction forces between subject and robot.

The control strategy for the active mode is a zero force controller (i.e. the force at the knee was controlled to zero) with control gain $P1$. The user should not feel the weight of the orthoses W and the friction force of the cylinder. The non-linealities from the different chamber sizes in the cylinder are taken into account adding the extra term in the equation $P_2 \cdot x$, where x is the position of the knee piston (similar to [33]). The weight W of the orthosis plus the force sensor in the knee cylinder (total of 8N) are taken into account as an offset in the measured force, and thus subtracted from the measured force F_{meas}.

$$u_{knee} = -(P_1 + P_2 \cdot x)(F_{meas} - W) \tag{2}$$

3) Noise force disturbance mode: In order to test the effect of a more demanding walking task on the brain activation, we designed a new controller able to apply random perturbation forces on the knee. The knee cylinder applied the disturbance as random force pulses every 0.5 seconds during 0.1 seconds. The force magnitude was randomly generated by a Band-Limited White Noise block in Simulink, and ranged between $\pm$ 100 N. The noise disturbance worked on top of a zero-force controlled as described in the active mode subsection, thus adding the force disturbance control variable to the control variable from the zero-force controller.

4) Error amplification mode: In order to test the effect of error amplification on brain activation, we designed a new controller able to amplify the errors generated when trying to follow a requested knee movement. The actuation variable from the error amplification controller is proportional to the difference between the desired knee position and the measured actual position, similarly to the position controller in the passive mode. However, the proportional gain in this mode is negative (K_{amp}=-2 N/m), thus the force generated by the knee cylinder is smaller as smaller is the error, and increases with the tracking error. We saturated the amount of force in order to guarantee the subject's safety, and limit the task difficulty. The error amplification controller works on top of a zero-force controlled, thus adding the error amplification control variable to the control variable from the zero-force controller.

C. Protocol

A pilot study with four healthy subjects was performed in the MR-Center of University of Zurich and ETH Zurich, on a Philips Achieva 1.5T MR system equipped with an 8 channel SENSETM head coil. Subjects physical information, and the color code assigned during data

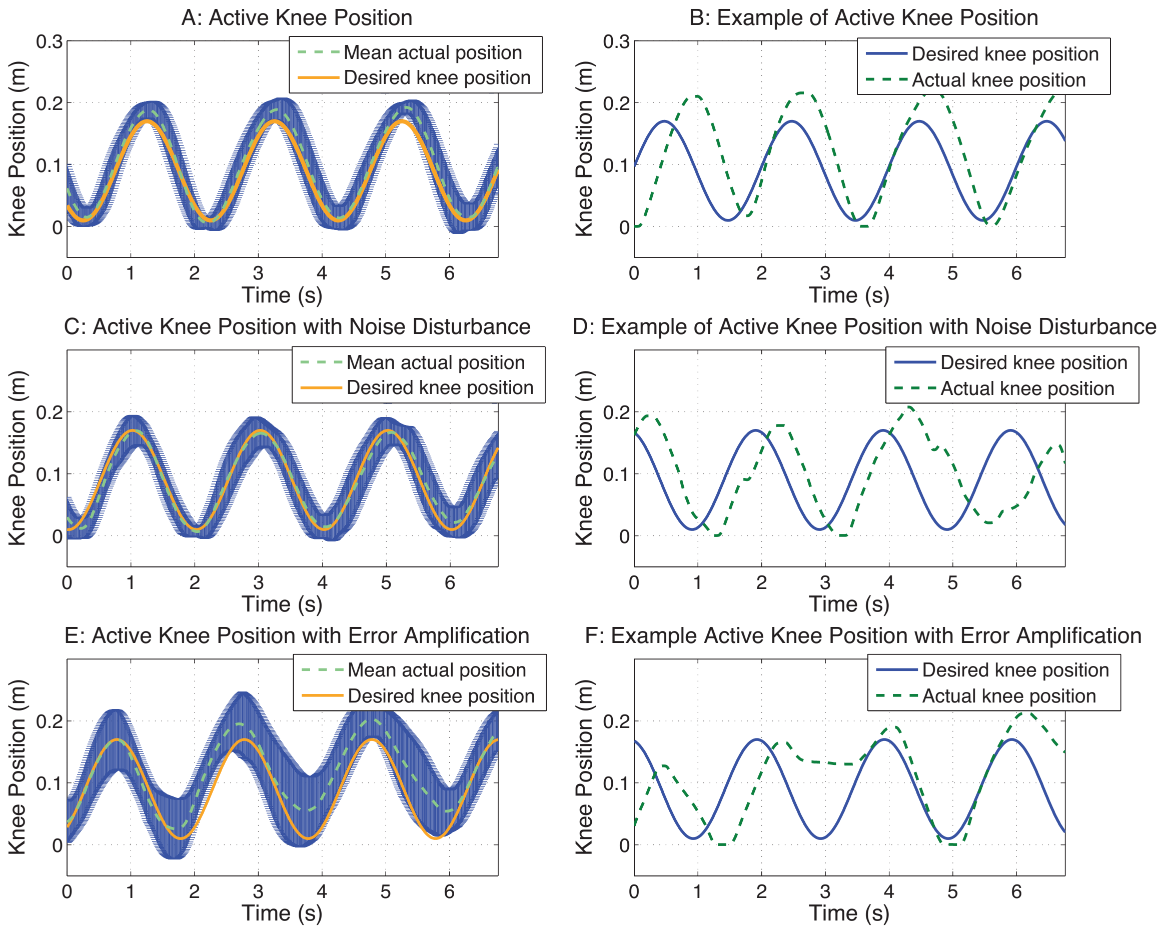

Fig. 2. Desired and actual knee movements under 3 different non-assisting strategies. A: Mean knee position and 1^{st} STD in active mode (dashed line), and desired knee position (solid line). B: Example of knee position in active mode (dashed line), and desired knee position (solid line). C: Mean knee position and 1^{st} STD in noise force disturbance mode (dashed line), and desired knee position (solid line). D: Example of knee position in noise force disturbance mode (dashed line), and desired knee position (solid line). E: Mean knee position and 1^{st} STD in error amplification mode (dashed line), and desired knee position (solid line). F: Example of knee position in error amplification mode mode (dashed line), and desired knee position (solid line).

analysis, is as follows (Color/Height/Weight/Gender/Age): Red/176cm/66kg/female/30, Blue/177cm/72kg/male/38, Green/188cm/82kg/male/26, Gray/176cm/70kg/male/29. The 3rd subject (”green”) was totally naive to the robot, while the other 3 subjects had already some experience with the robotic device. Informed consent was obtained from each subject before the evaluation session. Subjects were positioned with their legs fixed to the orthosis of MARCOS, and were instructed to try to remain their right leg passive, while it was physically moved by the robot, following a sinusoidal movement of amplitude 0.09m and frequency 0.5Hz (Fig. 2). They were instructed to move actively their left leg to achieve an alternating movement (gait like), trying to synchronize the legs with similar amplitude and frequency.

Three different paradigms were tested: 1) the right leg was passively moved, while the subject tried to synchronize the left leg in active mode, 2) same as 1), but the left leg was in force disturbance mode, 3) same as 1), but the left leg was in error amplification mode. Each condition consisted of 20 trials. Each trial consisted of 9 seconds moving the legs as instructed, followed by a rest-phase (5s). Subjects were instructed to have their eyes closed and relax. Respective commands were given via an MR compatible head-set.

The functional acquisitions used a T2* weighted, single-shot, field echo, echo-planar-imaging (EPI) sequence of the whole brain (TR = 3 s, TE = 50 ms, flip angle = 82°, FOV =220 mm x 220 mm, acquisition matrix = 128 x 128, in-plane resolution = 1.7mm x 1.7 mm, slice thickness = 3.8 mm, SENSE factor 1.6, resulting in 35 slices).

Image processing and analysis were performed using SPM8 (Welcome Department of Cognitive Neurology, London, http://fil.ion.ucl.ac.uk/spm). Functional images were normalized into standard stereotactic space using the Montreal Neurological Institute template (MNI). Spatial smoothing was performed by applying a Gaussian filter of 8mm FWHM. A high-pass filter was applied to remove slow temporal drifts with a period longer than 128 s. A first level statistical analysis (t-test) was conducted for all four subjects, by modeling each single condition in a general linear model (GLM) using the canonical hemodynamic response function. This data analysis

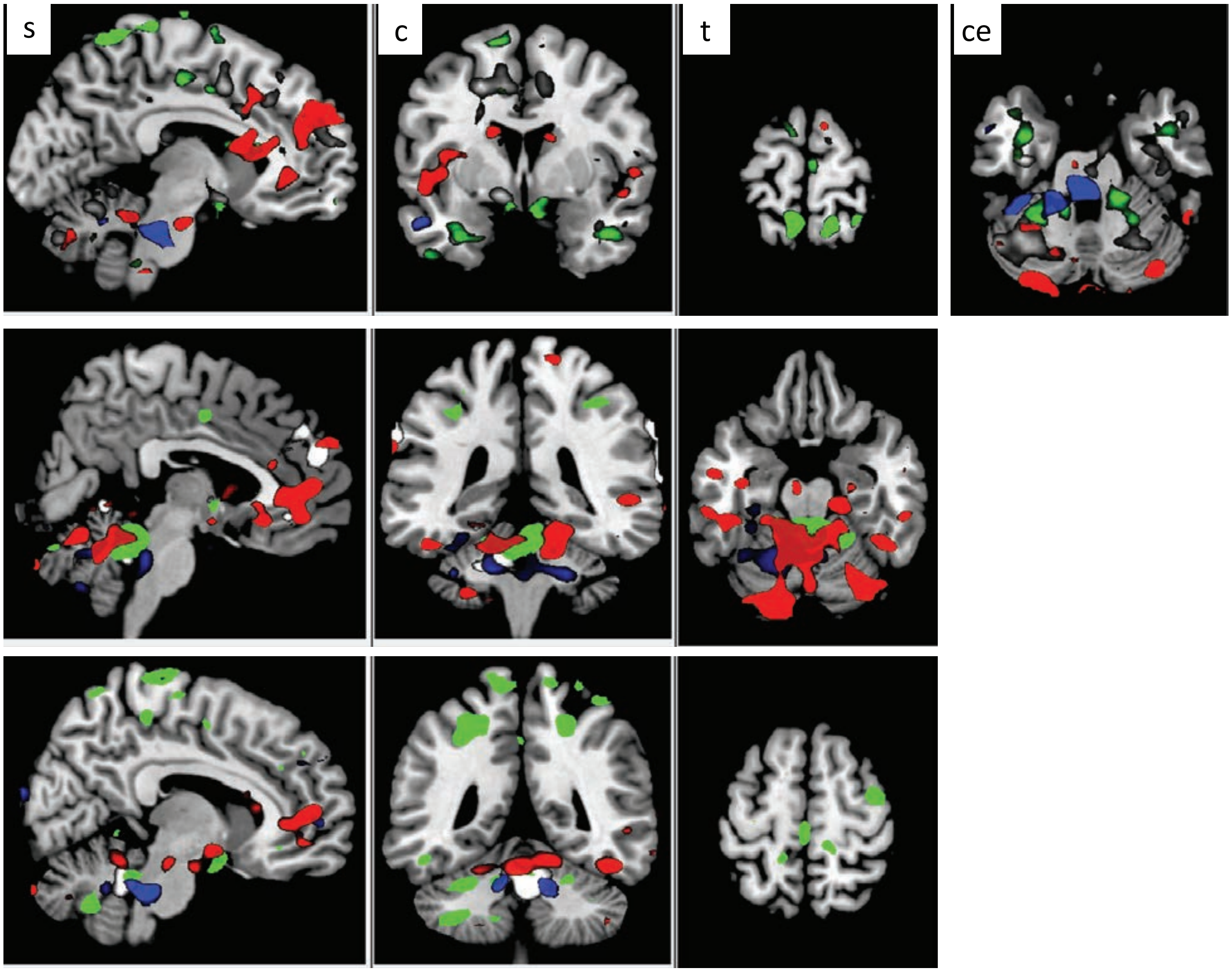

Fig. 3. Brain responses of four subjects (red, blue, green, gray) according to movement 1 (upper row), 2 (middle row) and 3 (under row) projected onto the ch2better template implement in MRICron. Depicted are meaningful sagital (s), coronar (c), transversal (t) and a cerebellar (ce) sections to give a basic overview of the activity pattern. A stringent statistical threshold with family-wise correction $p < 0.05$ and 10 voxel extent has been applied.

was performed on a subject-by-subject basis to identify the activated neuronal network involved in each movement task, compared to the rest periods. A stringent statistical threshold with family-wise correction $p < 0.05$ and 10 voxel extent has been applied.

III. First results

The effect of the disturbance force mode on the knee trajectory in one subject is showed (Fig. 2C & D) as an example. In solid line is showed the desired knee trajectory the participant was requested to follow with one knee (a sinusoidal of amplitude 0.09 m and frequency 0.5 Hz), and the performed movement in dashed line. The noise force disturbance had the effect of a short and fast change in the movement's smoothness. Note that such a short pulse increased the standard deviation of the tracking error (compare Fig. 2C with active movement in Fig. 2A), but was not expected to increase significantly the overall tracking error, due to the short time it was applied.

The effect of the error amplification mode on the knee is depicted (Fig. 2E & F). The solid line is the desired knee movement the participant was requested to follow (same as above), and the dashed line is the performed movement. The error amplification increased the tracking error, that lasted for relative long periods of time. Note that increasing the tracking errors made the task demanding when errors were large, but did not have any effect when the error was small. With this new mode, both, the overall absolute tracking error, and the error standard deviation, increased (compare Fig. 2E with active movement in Fig. 2A).

The pilot fMRI measurements showed promising results. One of the crucial aspects of the pilot study are the head movement artifacts. In all the demonstrated tasks, we encountered some of them, but basically, they remained within an acceptable range (< 2.5 mm).

All four subjects had significant cerebral responses in a widely distributed network; however, they differ in some respect (Fig. 3). The activity covers several aspects of sensorimotor areas like primary motor/sensory cortices, supplemental motor cortex, subdivisions of the cingulate cortex, frontal and latero-frontal areas, subcortical structures as thalamus, basal-ganglia as well as parts of the insular cortex. The highest coincidence in terms of activity can be observed in cerebellar subareas. Subject with brain activation showed in red (Fig. 3) had most activity, while subject with activation showed in gray (Fig. 3) had fewest activation across the conditions.

IV. Conclusion

We designed and implemented four different control strategies for a novel fMRI compatible robotic device that can robotically assist or resist during stepping in the fMRI: (1) passive mode, (2) active mode, (3) force disturbance mode, and (4) error amplification mode. In passive mode, MARCOS guided the gait pattern, while the subject remained passive. In active mode, the subject was in charge of the movement generation, while the robot was controlled to zero-force. In force disturbance mode, a random force disturbed the subject own generated movement. During error amplification, MARCOS increased the task difficulty amplifying the tracking error by generation of a force on the knee proportional to the tracking error.

MARCOS provided the possibility to measure the brain activation during gait-like movements of the lower limbs with fMRI. The most important joints (ankle, knee, and hip) were included in this movement. With the indispensable reluctance to conclude based on single subjects analysis, all three conditions required the similar cortical network to fulfill the task. Furthermore, it seems that the "special characteristics" of the applied movements are rather demanding for the brain, as a wide distributed network is involved to accomplish the different aspects of the conditions. Alongside the basically expected response patterns of the primary sensorimotor network, we observed strong frontal cortex, insula and cingulate cortex activation in some of the subjects, and strong activation in cerebellar subareas in all subjects. These specifics are pointing to a possibly high cognitive load induced by the demanding movements. According to the observed brain responses, our very basic hypotheses could be verified: we observed strong activation in brain areas known to be involved in error processing.

We did not find strong differences between the 3 strategies, due to the reduced number of subjects in the pilot study. However, we observed a tendency towards more activity in the motor/sensory network as more "active" and "challenged" the subjects were (i.e: red and green subjects in Fig. 3). Thus, error amplification strategies appear to have a great potential to improve robotic therapy outcomes. By increasing the task difficulty, the training could constantly solicit activity in the error-processing brain areas and could pressure the motor system to continuously update its motor commands and help promote the creation of new ones that benefit functional recovery [34].

The possible differences in brain activation between haptic guidance, active movement, and the two error amplification strategies presented in this paper will be further analyzed in a randomized intra-subject experimental study with a larger group of healthy subjects. We will run a learning paradigm experiment in the fMRI in order to examine if the brain activation pattern changes as learning progresses, if activation is dependent on the individual skill level and the strategy trained, and which brain areas are activated if aftereffects are observed. The different paradigms will be tested always starting with haptic guidance. Then, the following three conditions here presented, will be performed in randomly order. Each condition will consist of 30 trials. Each trial will consist of 9 seconds moving the legs as instructed, followed by a rest-phase (5s). Between conditions, the subjects will be requested to perform the task in active mode during 100 seconds to test for aftereffects. In the long run, we further aim at investigating patients with neural injuries with different levels of impairment in order to find the strategies that better optimize neuroplasticity based on the impairment level and location of the neural insult.

Acknowledgment

The authors gratefully acknowledge the contribution of Heike Vallery and Peter Wolf for their valuable support.

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