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## Closed-loop Brain-Machine-Body Interfaces for Noninvasive Rehabilitation of Movement Disorders

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### Abstract

Traditional approaches for neurological rehabilitation of patients affected with movement disorders, such as Parkinson's disease (PD), dystonia, and essential tremor (ET) consist mainly of oral medication, physical therapy, and botulinum toxin injections. Recently, the more invasive method of deep brain stimulation (DBS) showed significant improvement of the physical symptoms associated with these disorders. In the past several years, the adoption of feedback control theory helped DBS protocols to take into account the progressive and dynamic nature of these neurological movement disorders that had largely been ignored so far. As a result, a more efficient and effective management of PD cardinal symptoms has emerged.

In this paper, we review closed-loop systems for rehabilitation of movement disorders, focusing on PD, for which several invasive and noninvasive methods have been developed during the last decade, reducing the complications and side effects associated with traditional rehabilitation approaches and paving the way for tailored individual therapeutics. We then present a novel, transformative, noninvasive closed-loop framework based on force neurofeedback and discuss several future developments of closed-loop systems that might bring us closer to individualized solutions for neurological rehabilitation of movement disorders.

### Keywords

brain-machine-body interface; closed-loop systems; movement disorders; noninvasive; rehabilitation

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### 3. Introduction

Movement disorders such as Parkinson's disease (PD) and dystonia are broadly considered as basal ganglia (BG) disorders. However, this reductionist localization fails to capture the span of the pathophysiology of these disorders as well as the physical, mental, and societal impact of disease at the individual level. The complex interactions and the multitude of neuroanatomical pathways involved require a system-level characterization and understanding of the neuronal networks underlying the expression, spread, and dynamics of the mechanisms taking place in these neurological disorders. This is emphasized by the widespread plastic changes that occur in distributed neuronal networks at different spatiotemporal scales as the nervous system adapts to disease. Furthermore, there is inherent individual variability in the symptoms and responses to treatments exhibited by patients. This variability may depend on individual genetic and epigenetic differences, on differences in disease progression, and in the capacity of the adaptive processes to cope with it. Therefore, therapeutic approaches tailored to a given patient, addressing the patient's specific condition and the disease's degree of severity may prove superior to generic diagnosis and treatment.

Current treatments for movement disorders, including medications, botulinum toxin injections, physical rehabilitation, and deep brain stimulation (DBS), are targeted to specific symptoms, or a combination thereof<sup>1,2,3</sup>. Despite such advances, these treatments present significant limitations, including undesirable effects, limited efficiency, and lack of specificity, and fail to address the dynamic nature of movement disorders such as PD and dystonia. Dopamine replacement medications are used worldwide to alleviate the motor symptoms of PD. However, other motor (e.g. freezing of gait) and non-motor (e.g. depression, dementia, hallucinations) symptoms are dopamine-resistant, as is well documented<sup>4</sup>. Long-exposure to dopamine replacement therapy<sup>5</sup> may induce several serious debilitating side effects that often outweigh the therapeutic benefits, such as worsening of limb proprioception<sup>6</sup>, the development of a dopamine dysregulation syndrome and motor fluctuations, just to name a few. In some patients, motor fluctuations can be treated with DBS. However, its invasive nature, the additional risks and complications associated with the surgery, and in device implantation, as well as the overall cost of this therapeutic alternative and its restrictive eligibility criteria renders its adoption by a majority of patients highly unlikely.

In dystonia, the current treatments for abnormal and involuntary muscle movements consist of combinations of physical rehabilitation therapy, medications, botulinum toxin, and DBS. All of these methods have limited efficacy<sup>7</sup>. In essential tremor (ET), typical treatments consist of oral medications, including beta-blockers, benzodiazepines, and mysoline, or primidone. Such therapy can improve tremor in approximately 50% of the patients, although this fraction diminishes as the disease progresses to more severe stages<sup>8</sup>. Due to their undesired and potentially severely debilitating side effects, invasive surgical options for movement disorders, such as lesion therapy and DBS, are generally considered a last resort when traditional therapies fall short in improving the patient's quality of life.

Thus, new noninvasive therapeutic approaches are clearly needed for the neurological rehabilitation of patients suffering from movement disorders. An ideal therapeutic approach would be one tailored to the individual by being based on the pathophysiology of the specific patient's conditions underlying disease and associated patterns of brain and body activity. Such a therapy should be adaptive and selective so as to track the changing states of the patient and disease. Indeed, in many brain disorders, symptoms fluctuate dynamically, depending on factors such as cognitive and motor load, and concurrent drug therapy. It is thus crucial to have feedback loops provide real-time adjustment of the therapeutic parameters. A timely, precise regulation might potentially improve the therapeutic effects while limiting unwanted and adverse side effects.

In this paper, we review closed-loop systems for rehabilitative purposes with a focus on noninvasive brain-machine-body interfaces towards neurofeedback remediation of movement disorders, in particular for PD (Figure 1). We start with an overview of activity-dependent neuroplasticity in brain-machine interface (BMI) paradigms in Section 4. In Section 5, we review invasive and noninvasive closed-loop systems for rehabilitation of movement disorders. In Section 6, we present a new noninvasive framework for rehabilitation in PD, combining simultaneous imaging of the brain and body dynamics with model-free and model-based approaches for closed-loop paradigms. We then discuss the future developments of closed-loop systems for rehabilitation purposes in Section 7 and conclude in Section 8.

#### 4. Brain-machine interfaces and neuroplasticity

BMI technology can be used for neurological rehabilitation in two fundamentally different ways<sup>9</sup>. The earliest use of BMIs was to bypass neuromuscular signaling pathways, providing a means for paralyzed patients to interact with their environment in a way that does not depend on muscle control<sup>10</sup>. This strategy has been, and still is, the focus of a great body of research, allowing patients suffering from various neuromuscular conditions to interact and communicate with their environment via artificial actuators, including a computer cursor<sup>11</sup>, a neuroprosthetic limb<sup>12</sup>, and virtual<sup>13</sup> or real devices, such as a robotic arm<sup>14</sup>, or electric wheelchairs<sup>15</sup>. The use of BMIs for communication is often referred to as assistive. In the past several years, several researchers have proposed another strategy that consists of using BMIs for rehabilitation purposes by inducing activity-dependent plasticity of the central nervous system (CNS) to restore motor function, as has been reviewed elsewhere<sup>9,16,17</sup>. Activity-dependent CNS plasticity can occur at different spatiotemporal scales and represents the foundation for motor re-learning in rehabilitation. This is not limited to the healthy nervous systems<sup>18</sup>, but is also relevant in disorders such as PD<sup>19</sup>.

The use of BMIs to investigate learning and adaptation is beyond the scope of this review and has been reviewed recently<sup>20</sup>. We present here only a brief overview of studies demonstrating how learning to control a BMI induces plastic changes in various part of the CNS. Many studies have shown that single cortical neurons change their tuning properties following learning of neuroprosthetic control<sup>21,22,23</sup>. The magnitude of these changes mimicked the subjects' performance to control the BMI and became more stable as the performance plateaued<sup>23</sup>. By analyzing the activity of neurons in the motor cortex that were

not used for BMI control, other authors found large-scale changes in neuron firing properties and contribution to the task<sup>24</sup>. In particular, a difference was observed in these neurons' modulation depth. The neurons that were not used for BMI control showed a reduction of the modulation depth in comparison to the neurons used for BMI control. This effect was only apparent in the late learning stages. Several other studies using BMI paradigms in monkeys later demonstrated that neuroplasticity actually extends to larger cortical networks associated with motor control<sup>21,24,25,26</sup> and is not restricted to the motor cortex. For example, monkeys trained to reach and grasp virtual objects by controlling a robot arm through a closed-loop BMI showed functional reorganization in the dorsal premotor cortex, supplementary motor area, and primary somatosensory cortex, as well as in the primary motor cortex<sup>21</sup>. However, it is interesting to note that plasticity during BMI learning and control is not restricted to the cortex, and also occurs in subcortical structures involved in natural motor control that are directly relevant for PD, such as the basal ganglia. Indeed, it has been recently shown that corticostriatal circuits in rodents undergo plasticity during abstract task learning that do not directly involve physical movements<sup>27</sup>. In this study, rats were trained to control the pitch of an auditory cursor by modulating the activity of the primary cortex in the absence of body movements. By simultaneously recording the activity of neurons in the primary motor cortex and dorsal striatum – two regions involved in motor learning – with microelectrode arrays, the authors were able to show that striatal neurons modulated their activity during learning and that more striatal neurons were recruited as learning progressed. A comparison of the activity of motor and striatal neurons revealed that learning was accompanied by dynamical changes of the functional interaction between these two neural populations, consistent with the formation of a BMI-specific network<sup>28</sup>. Moreover, deletion of striatal N-methyl-D-aspartate (NMDA) receptors impaired both learning and corticostriatal plasticity, providing direct evidence that cortico-basal networks are required not only for learning physical skills, but also for learning abstract skills, like motor planning or neuroprosthetic control. Overall, these studies suggest that BMI paradigms can provide new therapeutic methods by encouraging and guiding CNS plasticity to restore motor function.

## 5. Closed-loop systems in rehabilitation

In closed-loop systems, feedback controls and regulates the output of a dynamical system, allowing it to adapt to perturbations of its inputs<sup>29</sup>. This adaptive power opens new research avenues for personalized therapies in neurological rehabilitation by tracking fluctuations in a patient's neurological and disease states.

### 5.1 Invasive rehabilitation systems

For PD, closed-loop systems have dramatically improved the efficiency of DBS protocols<sup>30,31,32</sup>. Classical open-loop DBS employs a surgically implanted electrode and battery-powered pulse generator that deliver a constant high-frequency (~130-185 Hz) pulse train to specific subcortical structures, including the subthalamic nucleus (STN), the internal segment of the globus pallidus (GPi) or the ventral intermediate (Vim) nucleus of the thalamus. DBS can successfully alleviate many symptoms of motor disorders and has been approved by the Food and Drug Administration (FDA) to treat ET, PD and dystonia.

Nonetheless, the mechanism of action of DBS is not fully understood, resulting in possibly suboptimal selection of DBS waveforms (frequency, pulse width, and intensity) based on clinical expertise and heuristics. Furthermore, it can take up to six months to find optimal stimulation settings giving best results.

Early closed-loop modeling studies<sup>30,33,34</sup> of DBS suggested the superiority of closed-loop systems relative to open-loop systems and indicated that stochastic DBS waveforms could be effective alternatives to the traditional constant high-frequency protocols<sup>30,33</sup>. Stochastic waveforms offer the advantages of limiting the side effects induced by constant, periodic, high-frequency DBS inputs<sup>35</sup>, such as gait and speech disturbances, dyskinesia and hemiballism, as well as improving the battery life of DBS stimulators and perhaps yielding improved therapeutic outcomes. Recently, closed-loop systems for DBS to treat PD have been successfully implemented in monkeys<sup>31</sup> and humans<sup>32</sup>. Using the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) primate model of PD, Rosin *et al.*,<sup>31</sup> delivered a single pulse or short pulse train (7 pulses at 130 Hz) through a pair of electrodes implanted in GPi at a predetermined and fixed delay of 80 ms, following the occurrence of a single action potential recorded either in GPi or in the primary motor cortex (M1). By sensing the ongoing activity in M1, their closed-loop DBS protocol delivering short pulse trains was superior in alleviating parkinsonian symptoms than a single-pulse closed-loop protocol, as well as a standard open-loop protocol (continuous 130 Hz). Moreover, their closed-loop DBS reduced oscillatory activity in GPi and M1 to a greater extent than the standard open-loop DBS.

To minimize the neurosurgical intervention in humans, Little *et al.*,<sup>32</sup> developed an adaptive DBS in which a quadripolar macroelectrode in the STN was used for recording and stimulation. Specifically, the beta activity in the local field potential (LFP) served as a feedback signal to control when the stimulation was delivered. LFPs were filtered, rectified and smoothed using a moving average filter to produce an online scalar value of the beta amplitude that triggered the stimulation via thresholding defined by the user. The stimulation delay was 30 to 40 milliseconds. Adaptive DBS was 30% more effective than the standard continuous DBS despite delivering less than half of the current, and improved all three cardinal symptoms of PD, i.e. tremor, bradykinesia and rigidity. Interestingly, preliminary results from the same authors suggest that it might be possible to differentially control tremor and bradykinesia by using the same control signal<sup>36</sup>. LFPs are used as a control signals for closed-loop DBS for several practical reasons (see review<sup>37</sup>): LFPs are easily and stably recorded from the implanted electrode, they correlate with the patient's clinical motor and non-motor states, and they are modulated by DBS.

However, control signals for DBS do not necessarily need to originate from the brain; other bodily signals can also be used. In particular, electromyographic (EMG) activity has been used for feedforward and feedback control of DBS for patients with ET<sup>38</sup>. In this study, EMG activity of the deltoid muscle was recorded with surface electrodes and the tremor-frequency power was used to switch on or off DBS following crosses of on-trigger and off-trigger thresholds, respectively. Using the essential tremor rating scale (ETRS), the authors reported a complete suppression of bilateral intentional tremor and an almost complete

recovering of hand function after bilateral stimulation of the bilateral thalamic Vim/Vop nuclei in closed-loop mode.

Taken together, the encouraging results of these studies demonstrate the power of adaptive closed-loop systems to control the time-varying fluctuations of pathological oscillatory network activity in movement disorders such as PD and ET.

It is worth mentioning an innovative approach for closed-loop DBS systems, despite the fact that it has not yet been used to treat movement disorders. Indeed, some authors have taken a step further and included the physician/clinician in their automated neuromodulation system by using an agent-environment model<sup>39</sup> borrowed from artificial intelligence. Afshar *et al.*,<sup>40</sup> developed an investigational platform for closed-loop DBS comprising an implanted sensing and stimulating device for recording and stimulation brain activity, a learning (classifier) and a control-policy algorithm, and telemetry to communicate with the physician/clinician. According to their methodology, the nervous system represents the environment while everything else is part of the agent. The agent consists of inertial (three-axis accelerometer) and bioelectrical sensors, the classification and control-policy algorithms, the stimulating part of their implanted device as well as the physician/clinician who plays the role of a critic. By including another human in the loop, they made their system twofold adaptive. On one hand, the classifier estimates the neural state of the patient from the sensed neural activity while the control-policy algorithm maps this state estimate to an optimal stimulation protocol and thus can adapt to dynamic fluctuations. On the other hand, the physician/clinician can evaluate the performance of the classification and control-policy algorithms from the data collected via telemetry and can independently adjust parameters of each algorithm. This allows the clinician to monitor and adjust the performance of the DBS more frequently than in standard medical care models. Although this promising extended closed-loop system has been implanted and tested on an animal (ovine) model of epilepsy<sup>40,41</sup> for more than 15 months as proof of concept, further work is necessary to evaluate the potential benefits for patients suffering from movement disorders.

## 5.2 Noninvasive rehabilitation systems

Closed-loop systems have also been used successfully in noninvasive rehabilitation methods using either augmented-reality devices or transcranial current stimulation of the motor cortex.

**5.2.1 Augmented-reality approach**—Some authors have extended the notion of BMI (brain-machine interface) to that of body-machine interface<sup>42,43</sup>, in which signals from the peripheral, rather than from the central nervous system, are used to control and communicate with external devices. By relying on movements and adding new channels for communication and control, body-machine interfaces provide several advantages relative to BMIs. First, noninvasive interfaces may not present risks of surgical complications. Second, the rate of information transmission of body motion systems are currently an order of magnitude higher (5 bits/s)<sup>44</sup> than that of EEG signal-based BMI systems (0.05-0.5 bits/s)<sup>45,46</sup>. Third, body-machine interfaces acknowledge the importance of the body in movement disorders and that the body can benefit from remaining active in many important

ways. A larger range of clinical applications are now emerging that extend the brain- and body-machine interfaces and neural prostheses paradigms to brain-machine-body interfaces<sup>47</sup>, interfacing across the central and peripheral nervous systems for remediation of neurological disorders.

However, it remains to be determined how people with movement disorders, such as PD, dystonia, and ET will benefit from these interfaces, as this is a relatively new field of research and they have mainly been tested so far for the rehabilitation of patients with spinal cord injury<sup>42,48</sup>. For PD, apart from the study by Yamamoto and colleagues<sup>38</sup> which used EMG signal to control DBS in ET (see Section 5.1), the only noninvasive approach successfully tested was for gait rehabilitation. Baram *et al.*, analyzed<sup>49</sup> and developed<sup>50</sup> an augmented-reality device for gait improvement for moderately affected PD patients (mean clinical severity according to Hoehn and Yahr staging was stage  $3.04 \pm 0.84$ ). Their device is composed of a head-mounted three-axis rotational accelerometer, a body-mounted three-axis translational accelerometer, and a see-through head-mounted visual display, all connected to a wearable computer. This device can operate in two modes. In the open-loop mode, the visual display superimposes virtual tiles on the real floor. These move perpetually towards the observer at constant speed, irrespective of the patient's body movements. In the closed-loop mode, the patient's movements, monitored with rotational and translational accelerometers, are used to adapt the visual display so that the virtual tiles appear fixed in space, as a real floor. An adaptive noise canceler filter was used to learn and eliminate the patient's tremor dynamics from the accelerometers' signals. Fourteen PD patients were tested on the device in both open- and closed-loop modes. In closed-loop mode, performance improved for all but one patient with an average increase of about 30% in speed and stride length — about twice that for open-loop mode.

Using an advanced version of their device mounted on top of normal glasses, the same group reported similar improvements in walking abilities for patients with multiple sclerosis<sup>51</sup>. In another study<sup>52</sup>, the same group complemented the visual feedback (optical flow) with auditory feedback by providing a click after each step. This helped to produce and sustain a balanced rhythmic gait. PD patients were tested during an initial visit and after a two-week at-home use of the device. The test took place at least 12 hours after the last dose of anti-parkinsonian medication (since patients were recruited on the basis of their off-medication-related gait impairment) and consisted of five conditions: without wearing the device, wearing the deactivated device, receiving visual feedback only, with visual-auditory feedback turned on, and again without wearing the device. The benefits of the at-home therapy were more clearly observed after the two week period: nearly 70% of the patients showed at least 20% improvement in gait velocity, stride length, or both. Two major limitations of this work were that it only addressed the freezing of gait of patients during “off-time” and that the long-term benefits of this therapeutical approach were uncertain. In a follow-up study addressing these limitations<sup>53</sup>, Espay *et al.*, evaluated the longer-term benefits of their closed-loop apparatus for PD patients showing freezing of gait mainly during “on-time” after four weeks of at-home training. However, due to the severity of the disease and advanced disability of this population of the patients, only two of the 16 originally recruited patients completed the study and the authors only reported brief results

from a single responder, a 62 year old woman with 15 years disease duration, who showed a significant gait improvement up to 16 weeks post-training. After that period, the training benefits started to decrease. Interestingly, the initial benefits were renewed for this patient with further training. Although this augmentedreality apparatus shows encouraging results for patients at an early stage of PD, this latter study highlights the difficulty of at-home rehabilitation for patients at an advanced stage of PD in which severe motor and cognitive disabilities may limit their opportunities to complete the training sessions required for rehabilitation. The main limitation of these augmented-reality studies is the lack of device use monitoring. The patients were verbally instructed to use the device for at least 30 minutes, twice a day, but no attempt was made to monitor the frequency and duration of individual device use. This stresses the need for recording systems for at-home use of rehabilitation devices so as to account for outcome variability and improve individualized therapeutic solutions. Telemetric solutions for collecting information about device usage and/or to include the physician/clinician in the loop, as proposed for some DBS systems<sup>40</sup>, appear to be solutions worth trying to integrate in future noninvasive rehabilitation methods.

Several other different physical therapies have been tested for improving balance and gait control in PD patients, such as bicycling<sup>54</sup>, dance<sup>55</sup> and tai chi<sup>56</sup>. To date, none of these therapies have used feedback control. Thus, research on body-machine interface might also shed light on new body-related biomarkers that could be used as feedback signals for closed-loop rehabilitation strategies based on physical therapy oriented towards improving balance and gait in PD patients.

**5.2.2 Noninvasive stimulation techniques**—Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are three noninvasive stimulation techniques that have the potential to either induce neuroplasticity or to suppress maladaptive changes in targeted cortical networks. These stimulation methods have been successfully applied to treat various neurological disorders, including movement disorders<sup>57,58</sup>, such as PD, dystonia, and ET. For example, meta-analyses of the use of rTMS in PD indicate a significant improvement of motor symptoms with high-frequency rTMS in M1<sup>59,60</sup>. However, to the best of our knowledge, only tACS has been used in a closed-loop system for rehabilitation of movement disorders. Recently, Brittain *et al.*, reported encouraging results for resting tremor suppression<sup>61</sup>. The authors first stimulated the motor cortex of PD patients at tremor frequency, but did not couple that rhythm with the ongoing tremor. Instead, the rhythms drifted in and out of phase alignment with each other. The periods of phase cancellation allowed them to identify the stimulation phase that caused the greatest reduction in tremor amplitude. In a second series of experiments, Brittain and colleagues tracked the phase of the peripheral tremor using accelerometers and fed that signal into a high-performance digital interface that operated as a real-time computer that delivered the stimulation current (constant stimulation for 30 seconds; peak-to-peak stimulation current, 2mA) over the motor cortex. This closed-loop setting reduced the tremor amplitude by 50% on average for all five PD patients tested. Notably, stimulation at tremor frequency was more efficient than at its first harmonic rhythm.

As for DBS, the neurophysiological mechanisms of action of rTMS, tDCS and tACS are not fully understood and could greatly benefit from modeling studies investigating feedback control in order to test alternative waveform protocols and guide further experimental research.

## 6. Extended neurofeedback paradigm for rehabilitation in Parkinson's disease

The previous sections have emphasized the widespread interest of closed-loop BMIs for rehabilitation purposes. However, several critical issues related to their acceptance and usability need to be addressed before the adoption of BMI technology in clinical and personal settings. In particular, the translation of automated closed-loop systems for neurological rehabilitation of movement disorders necessitates further development in the following areas of research<sup>40,62</sup>: a) improved understanding of the distributed brain dynamics underlying healthy and pathophysiological conditions; b) the development of more sophisticated noninvasive neural sensors in terms of spatiotemporal resolution and usability/comfort for patients<sup>16</sup>; c) development of adaptive algorithms that can cope with the dynamic nature of progressive neurological disorders<sup>30,40</sup>; d) implementation of model-based control<sup>40,63</sup> for assimilating observable data, reconstructing unobservable variables and performing short-term prediction of the system state; and e) design and construction of low power systems for preserving battery life and minimizing clinical interventions for battery replacement.

In this section, we present a transformative framework of a noninvasive closed-loop brain-machine-body interface (Figure 1) addressing these issues. It is based on the dual adaptation of neural circuits and learning algorithms<sup>64,65,66</sup>, and integrates advances in neuroscience and engineering approaches to assess, predict and respond to distributed brain dynamics in PD.

A main motivation of modern neuroscience, as exemplified by the BRAIN initiative (<http://www.nih.gov/science/brain/>), is to link the activity of neurons to specific behaviors. In order to bridge the large dynamic range of spatial and temporal scales spanned by the underlying sensory-motor and cognitive processes active during motor control and adaptation, these issues are approached from three complementary perspectives. First, a top-down perspective driven by cognitive neuroscience and psychophysiology. Second, a bottom-up perspective driven by computational neuroscience and models of network dynamics. Finally, both top-down and bottom-up perspective approaches are merged at an intermediate spatiotemporal level and are implemented in neuromorphic hardware. These different perspectives are then combined to develop a noninvasive brain-machine-body interface framework for rehabilitation of PD patients and, eventually, other movement disorders. We anticipate that the characterization of the distributed cortical brain dynamics with EEG during motor tasks (top-down) and the associated pattern of spiking activity in the basal ganglia-thalamocortical circuits (bottom-up) will bring us closer to an understanding of movement disorders such as PD.

## Future neurorehabilitative systems for motor disorders

Recent technological advances including dry wireless noncontact sensors and neuromorphic hardware will likely provide the necessary tools for improved at-home rehabilitative devices. The next generations of dry wireless non-contact sensors for recording and stimulation of the brain activity will provide wearable systems that will allow transposing existing noninvasive clinical systems for personal at-home use. Furthermore, neuromorphic hardware offers the promise of small, embedded, low power devices in which on-board algorithms can be easily implemented.

The general brain-machine-body interface framework is intended to be versatile and to accommodate diverse biosignals and control strategies for robotic therapy devices. It is composed of two adaptive interfaces, in which both the user (patient) and the interface/ algorithms can adapt to each other. This represents a dual learning system, in which both the patient and the interface learn, although at different time scales. The brain-machine-body interface can be model-free (Figure 1; upper loop) or model-based (Figure 1; lower loop) and allows assessment of the relative merits of these two approaches for a wide range of motor tasks and various types of augmented feedback.

In brief, the brain-machine-body interface framework takes inspiration from BMI-induced neuroplasticity (Section 4), adaptive control theory<sup>67</sup>, robotic therapy (Section 6.1), and closed-loop adaptive systems. It includes brain and body signals monitored continuously and in real-time by the mobile brain/body imaging (MoBI) modality, such as EEG, EMG, motion capture and eye tracking (Section 6.2). These signals serve as inputs to an adaptive model implemented in hardware and embedded into diverse actuators used for sensory and proprioceptive feedback, such as haptic robots, cyber gloves or exoskeletons. The adaptive model (Section 6.3) controls the actuator's force and the sensory feedback closes the sensory-motor loop (Section 6.4). It is expected, after sufficient training, that the sensory feedback will trigger synaptic changes in the corticostriato-thalamic circuits that will then modify positively the outcomes of the pathophysiological condition of PD patients, as proposed by other authors<sup>9,14,15</sup>. Ultimately, the neuroplastic changes induced by practice with the brain-machine-body interface are expected to provide long-term benefits post-training. We submit that occasional repetitions of the training cycle will help sustaining plastic changes as it has been observed for other noninvasive rehabilitation methods<sup>53</sup> (see Section 5.2).

In this framework, the multiple spatiotemporal-scale neuromorphic model can be used as an external module to further investigate and test these synaptic changes at different levels. It is also possible to use a model-based approach by training a multiple-input and multiple-output (MIMO) module in which co-adaption of the MIMO controller and the patient's brain is produced by reinforcement learning<sup>39</sup> based on a model of the interaction between the patient's brain and body signals and the external world as represented by the assisted motor task (e.g. reaching, grasping). This model-based approach (Section 7.1) takes inspiration from the coupling of the BMI user—the PD patient—with an intelligent controller via reinforcement learning<sup>64,65,66,68</sup> and goal selection<sup>69</sup> so as to take into account the richness of the dynamic interactions between the user and their external world.

In the following sections, we begin with an overview of control strategies for robotic therapy devices and then discuss the main components of the two adaptive closed-loop systems shown in Figure 1. We also present preliminary results using EMG for tremor suppression in PD patients using force feedback.

### 6.1 Control strategies for robotic therapy

The use of robotics for rehabilitation therapy<sup>70</sup> in real and virtual<sup>71</sup> environments has been increasing drastically over the last two decades<sup>72,73</sup>. In parallel, control strategies specifying how these robotic devices interact with patients have also evolved. These strategies are broadly divided into two categories making motor tasks either easier or more difficult (or challenging) for patients and are referred to as assistive or challenge-based, respectively. The assistive strategies are the most developed and are intended to automatize the traditional physical and occupational therapies used in clinical rehabilitation for both lower and upper extremity training. The rationale of these strategies is multiple: i) moving the limb that volitional control can not achieve provides novel somatosensory perception that helps promoting neural plasticity<sup>74</sup>; ii) effort is thought to be crucial for inducing motor plasticity<sup>75</sup>; iii) assistance during motor task allows patients to progress faster<sup>76</sup>; iv) repetition of a pattern of sensory inputs will strengthen it and improve motor performance when unassisted<sup>77</sup>; and v) active assistance may improve patients' motivation during rehabilitation<sup>78</sup>.

The underlying principle of assistive strategies is to create a restoring force via mechanical impedance when patients deviate from a defined trajectory for a given motor tasks such as reaching, grasping and walking. A *deadband* – an area near the desired trajectory in which no assistance is provided – is often introduced to take into account human movement variability<sup>79</sup>. EMG has also been used to drive assistance for motor rehabilitation of stroke patients. In this case, assistance is provided when the processed EMG signals crosses a threshold<sup>80</sup>, or as a force proportional to the EMG signal<sup>81</sup>.

Challenge-based strategies on the other hand, such as resistive training and error-amplification, offer complementary insights to assistive ones<sup>72</sup>. Resistive training provides resistance to the patient's limb and is used extensively by physiotherapists in traditional clinical rehabilitation. With robotic devices, resistance typically takes the form of a constant or proportional force applied to the patient's limb during motor execution. Error-amplification is often employed based on the observation that kinematic errors during movement execution are an essential signal-driving motor adaptation<sup>76</sup>.

The effectiveness of these different control strategies for robotic therapy is typically assessed against the patient's baseline motor performance for a given motor task. In general, robotic assistance significantly decreases motor impairments following neurological injuries, such as stroke and spinal cord injury (see reviews<sup>72,82,83</sup>). For PD, Bai *et al.*, verified the feasibility of a compensation method for hand movement of visual target tracking by adding assistance force in a simulation study<sup>84</sup>. Two preliminary studies reported encouraging results for improving gait for robot-assisted treadmill training using the commercially available Lokomat orthosis<sup>85,86</sup>. To date, it is unknown which control strategy is the most effective for which rehabilitation tasks, mainly because of the cost and time-consuming

clinical trials needed to test each rigorously. However, challenge-based strategies for PD seem to be a promising avenue for future research on gait rehabilitation in PD as suggested by the positive outcomes of traditional progressive resistance exercises on walking<sup>87</sup> and the reduction of body weight-support across training sessions in one pilot study of robotic locomotor training<sup>85</sup>.

## 6.2 Signaling for brain-machine-body interfaces

Use of human-machine interactions for motor rehabilitation or enhancement is impeded by the limited knowledge of sensory-motor learning and control dynamics that occur when humans are physically and mentally coupled to machines. A quantitative theory of human movement control is thus essential –its development would both advance our understanding of cognitive motor neuroscience and help in designing and developing new machines that interact with humans. Despite recent findings suggesting that many motor skills can be decomposed into sequenced combinations of goal-directed and habitual control<sup>88,89</sup>, and that the balance between these two modes of action control is disrupted in PD<sup>90</sup>, the precise role and switching mechanisms of these two modes remains largely unknown. System-level frameworks of dual modes of action control account for various psychophysical observations in healthy subjects and several PD symptoms (see review<sup>88</sup>). However, these approaches also emphasize the importance and necessity of establishing the intrinsic sensory-motor and cognitive mechanisms underlying motor control during real-world tasks in healthy and pathophysiological conditions<sup>88,91,92,93</sup>. This is indeed a prerequisite for the design of novel, non-intrusive, and efficient neuroprosthetic tools for rehabilitation purposes. Yet, classical paradigms to investigate human motor behavior rely on simple tasks and often neglect to appreciate the system-level interplay between perceptual and cognitive factors.

Whereas traditional imaging modalities typically allow for and record only minimal participant behavior performing single, stereotyped tasks, the high-time resolution and noninvasive nature of EEG make it the ideal candidate for recording brain activity on the time scale of natural motor behavior<sup>94</sup>. Moreover, EEG sensors are light enough to allow near complete freedom of movement in contrast to most other imaging modalities. The recently developed MoBI modalities<sup>95,96</sup> deals with the main limitations of current brain imaging techniques. The MoBI concept allows correlation of neural and musculoskeletal activities during motor tasks by simultaneously recording EEG while monitoring 3D movements kinematics of the limbs, body, head, and eyes, either in real environments<sup>97</sup> or in 3-D multimodal immersive virtual environments<sup>98,99</sup> (Figure 2). The modular structure of the MoBI software environment facilitates the development of new applications (Figure 3) and includes several tools allowing real-time inference on brain signals such as those measured by EEG<sup>100,101,102,103</sup>. Among other things, this enables identification and localization of the neural sources from brain EEG, muscles EMG and eye movements during real world tasks.

High-density scalp EEG recording of PD patients, while modulating STN activity with DBS, demonstrated that potentially relevant biomarkers for therapeutic effectiveness can be recorded non-invasively<sup>104</sup>. In this study, altering the output of the STN using DBS helped

normalize both the ability to inhibit an action and beta power around the time of the response inhibition recorded with EEG over right frontal cortex. Thus, cortical EEG in PD patients may serve as one effective marker of the degree of abnormal basal ganglia-cortical circuit function in PD.

Motion capture of body movements is equally important to better characterize sensory-motor control in healthy and pathophysiological conditions and provides complementary information to EEG signals. For example, the contribution of basal gangliathalamocortical circuits to sensory-motor control in PD can be investigated indirectly by comparing the motor control abilities of patients with or without dopamine medication, and healthy individuals. Using a reach-to-grasp task, Lukos *et al.*,<sup>105</sup> quantified eye-hand coordination and online visuomotor control in PD patients by monitoring hand kinematics and eye movements during the reaching and grasping of a virtual rectangular object with haptic feedback (Figure 4). PD patients off medication poorly coordinated arm and hand movements, and showed marked trajectory anomalies in their online responses to perturbations of the object to be grasped, with increased hesitations and movement segmentation. Moreover, PD patients tracked their hands with their gaze during the reach, and overly depended on visual guidance, indicating an impaired feedforward control. Dopamine medication increased the speed of movement but did not improve the ability to correct their movements online or improve arm-hand coordination. This suggested that basal ganglia-cortical loops play a critical role in eye-hand coordination and adaptive online responses for reach-to-grasp movements, and that restoration of tonic levels of dopamine in the basal ganglia may not be suited to correct this impairment in PD patients.

The development of new wireless, dry, and noncontact EEG biosensors<sup>106,107,108,109</sup> (see review<sup>110</sup>) allows one to use the MoBI methodology outside the laboratory and the analysis of complex motor tasks involved in real world environments. This would provide valuable data on the elements of sensory-motor processing possibly most impaired in parkinsonism<sup>111</sup>, and those elements that may most crucially depend upon BG function and cannot be compensated for by other brain systems. Wireless biosensors are also invaluable for future wearable devices and at-home rehabilitation. Progress has been made for analyzing and visualizing EEG data in real-time for BMI systems<sup>112</sup>. The feasibility of real-time estimation and 3D visualization of source dynamics and connectivity of human brain dynamics<sup>113</sup> has recently been demonstrated using wearable high-density (32-64 channels) dry, wireless EEG systems. Specifically, custom wearable hardware and signal processing allowed the real-time data extraction, preprocessing, artifact rejection, source reconstruction, multivariate dynamical system analysis (including spectral Granger causality) and 3D visualization of distributed brain dynamics in healthy subjects (Figure 5). The wireless EEG system is reliable and robust during the whole recording session. The cap placement is assisted by a live impedance check mechanism that works in parallel with data acquisition. Initial placements usually take 5 to 6 minutes with 90 to 100% of the array making successful contact (depending on head shape and hair type). During an experiment, few, if any, electrodes become disconnected since the headset is individually adjustable and secured.

Thus, combining ongoing development of the mobile brain/body imaging (MoBI) modality with the development of a new generation of wireless sensors and improved real-time data processing algorithms is expected to expand the range of possible realistic sensorimotor tasks and lead to a better characterization of the brain and body dynamics underlying sensory-motor control.

### 6.3 Adaptive control

Closed-loop BMI systems for noninvasive neurological rehabilitation should ideally provide better-tailored therapeutics for patients. Gaining further information about the ongoing patient's states via cognitive and motor monitoring would be beneficial in several ways. From a design perspective, an adaptive model learning to fit a given patient's states would be more efficient than heuristic adjustments and could account for individual variability. Moreover, an adaptive model will constantly adjust to a given patient and the fluctuations of his/her pathophysiological condition. The proposed brain-machine-body interface includes model-free<sup>67</sup> (Figure 1; upper loop) and model-based (Figure 1; lower loop) adaptive interfaces.

In BMI systems, patterns of ongoing brain activity are typically translated into control commands after several stages of signal processing. After amplification, artifact removal, and signal preprocessing, the EEG signal is transformed into features best matching the underlying neurological mechanisms employed by the user. In motor rehabilitation, this corresponds to the various cognitive and sensory-motor mechanisms used during relearning a given motor task (e.g. pointing, reaching, grasping, walking). Relevant features for BMIs using sensorimotor activity include event-related potentials (ERPs), power spectral density features (e.g. fluctuations in EEG power in a given frequency band), parametric modeling of the EEG data with autoregressive or adaptive autoregressive models, and time-frequency representations<sup>114</sup>. Others have used the raw EEG time series<sup>115</sup> or a combination of different feature extraction methods<sup>116,117</sup>. For example, Li *et al.*,<sup>117</sup> used ERPs and the EEG power in the theta and alpha bands in the posterior parietal cortex for decoding movement intention during a saccade-or-reach task. The authors used independent component analysis (ICA) as an unsupervised spatial filtering technique to remove artifacts arising from eye and muscle movements. This allowed them to estimate the location of source activities related to the intended movement direction by source localization of the two lateralized posterior parietal cortex components extracted by ICA.

Following the feature extraction stage, patterns of brain activity were then translated into control signals using decoding algorithms. Various popular linear methods such as linear discriminant analysis (LDA), support vector machine (SVM), Kalman filters and nonlinear models, such as neural networks, have been used successfully in numerous BMI applications (see review<sup>118</sup>).

Recent work has shown that the performance of BMI control can significantly be improved by adapting the decoding algorithm or decoder<sup>65,66,119,120,121,122</sup>. In these systems, adaptation takes place in the neural systems and at the algorithmic level, and is referred to as co-adaptive BMI or closed-loop decoder adaptation (CLDA). The goal is to produce a more accurate mapping between the ongoing pattern of brain activity and the user intended

movements. In invasive BMI in monkeys, different error signals have been used to adapt the decoding algorithms to include error signals from the nucleus accumbens<sup>65</sup>, by adopting of Bayesian classification methods<sup>119</sup> or use of behavioral metrics related to task goal<sup>121</sup>. Critical issues in the design of a CLDA algorithm concern the rate at which the algorithm is updated and the way the decoder is initialized, as both can influence its performance. This is particularly relevant for patients with movement disorders, as natural movements are often used to initialize such decoders. For movement disorder patients, less efficient decoder initialization methods must be used, resulting in lower initial performance. Orsborn *et al.*<sup>120</sup>, proposed a CLDA algorithm that updates parameters independently of decoder initialization, thereby improving performance at optimal<sup>123</sup> and intermediate time-scales (1-2 min.) relative to online<sup>124</sup> and batch<sup>125</sup> (10-15 min.) updates. Their algorithm allows a rapid and robust improvement of BMI performance and suggests that intermediate time-scale updates may be ideal for patients with movement disorders.

Another possible level of adaptation uses kinematic or kinetic information at the effector level<sup>72</sup> by using kinematic or kinetic information. By tuning control parameters based on online measurement of the patient's performance, this allows for adaptation to tune assistance from trial to trial as well as over the course of rehabilitation<sup>80</sup>, during which performance is expected to improve. These adaptive strategies are usually implemented according to:

$$P_{i+1} = fP_i - ge_i \quad (1)$$

where  $P_i$  is the control parameter that is adapted (e.g. the gain of the robot assistance force, the robot stiffness, the movement timing or the desired velocity),  $i$  is the  $i^{th}$  movement, and  $e_i$  is the performance error or metric, such as a measure of the patient's ability to reach a target. The constants  $f$  and  $g$  are defined as the forgetting and gain factors respectively. The forgetting factor  $f$  is meant to continuously engage and challenge patients. Without a forgetting factor (e.g. when  $f = 1$ ), the control parameter is held constant when performance error is zero. However, with a forgetting factor in the range  $0 < f < 1$ , the adaptive algorithm reduces the control parameter for small performance errors and thus continuously challenges the patient. Other similar adaptive laws<sup>126</sup> have been proposed of the form:

$$G_{i+1} = fG_i + ge_i \quad (2)$$

where  $G$  is the value of the robot impedance. Still others have used an optimization framework to adapt control parameters<sup>72</sup>.

Neuronal and behavioral markers can drive adaptation in the brain-machine-body interface framework and serve as error signals. Changes in oscillatory activity in the sensorimotor cortex, especially in the beta frequency band, can be used as biomarkers for PD patients<sup>127,128</sup>. Changes of oscillatory activity during movement execution can easily be identified by independent components analysis (ICA) (Figure 3). At the behavioral level, task-related markers will be used. For example, during a reach-to-grasp task, the peak tangential velocity is reduced in PD patients<sup>69</sup> (Figure 4) and could be used as error signal at the effector level. An alternative to unitary biomarkers would be to use a learning algorithm to extract nonlinear multidimensional personalized features from the patient's EEG as

available for BMI in the BCILAB software<sup>101,103</sup> (an extension of the EEGLAB software environment<sup>101</sup>). Finally, incorporating cognitive monitoring based on current BMI technology —an approach known as *passive BMIs*<sup>129</sup> — could potentially add a complementary and informative channel useful for constructing biomarkers. Passive BMI carries implicit information about the user state such as level of motivation or attention, which might be useful, for example, for tracking selective attention deficits in PD patients<sup>130</sup>.

#### 6.4 Sensory feedback

In rehabilitation, one typically provides extrinsic (or augmented) feedback in addition to intrinsic feedback – e.g. in the form of sensory-perceptual information available from various sensory modalities such as vision, audition and proprioception. The effectiveness of augmented sensory feedback strategies for motor learning in healthy subjects and motor relearning in rehabilitation, such as augmenting proprioceptive signals from the hemiparetic arm after stroke, have recently been systematically and exhaustively reviewed<sup>131,132</sup>, including categorization of different aspects and types of feedback. Aspects of feedback include its nature, timing and frequency. Feedback nature refers to information about the movement itself, which can either provide knowledge about movement performance or about movement outcome. Movement timing refers to the time when the feedback is delivered, either (concurrent) during or (terminal) after the execution of movements. The frequency can be summary (every  $n^{\text{th}}$  trial) or fading (reduced feedback frequency over time). The type of feedback concerns the modality to which it is delivered (visual, auditory, haptic and multimodal). Because most studies of motor learning and relearning use various aspects and types (or combinations) of augmented feedback and do not systematically compare their individual contributions, it is difficult to have a clear picture of their singular effectiveness. However, several trends are emerging. First, there is a general consensus appearing on the added value of augmented feedback for rehabilitation<sup>38,131,132</sup>. Second, concurrent visual, auditory and haptic (touch and force) feedback seems more effective for complex tasks than for single tasks, but should be switched to fading feedback as learning (or relearning) progresses. The switch is explained by the guidance hypothesis<sup>133,134</sup>, which states that invariably providing feedback during learning leads to a dependency on the feedback and encourages the learner to ignore their own intrinsic feedback signals. Third, adaptive feedback based on the subject's skill level appears promising to potentially involve and motivate the learner by adequately challenging the user, which is important for successful motor learning<sup>135</sup> and relearning<sup>38</sup>. Finally, multimodal feedback can enhance motor learning and relearning. This conclusion is supported by several observations including the resultant reduction of memory and cognitive load<sup>136</sup>, the optimization of neural activation and representations<sup>131</sup>, the fact that multimodal rather than unimodal stimuli are present in daily life, and the differential capabilities of the human senses – e.g. spatial information is better perceived using vision whereas temporal information is better perceived using hearing. Within the context of BMI control, multimodal feedback has been shown to significantly improve performance<sup>137,138</sup>. For example, monkeys trained to move an exoskeletal robot during a random target pursuit task reached targets faster and with better trajectories when visual and kinesthetic feedback were congruent compared with incongruent feedback conditions<sup>138</sup>.

The haptic sense is the only one that allows one to interact with the environment while simultaneously perceiving these interactions<sup>139</sup>. This unique ability is called the *bidirectional property* of the haptic sense and provides the basis for further enhancing motor learning and relearning through haptic interactions<sup>140</sup>. Thus, rehabilitation in movement disorders might greatly benefit from augmented haptic feedback. Preliminary experiments have been carried out using a noninvasive closed-loop system (model-free; upper closed-loop in Figure 1) with EEG, EMG, movement kinetics and force feedback modalities to test the feasibility of compensating tremor in PD patients using velocity-dependent force feedback<sup>141</sup>. Force feedback was implemented using two haptic robots with three degrees of freedom attached to the thumb and index fingers of one patient's hand. Four different force feedback conditions were tested: i) a no-force control mode (haptic robots compensated for their own weight), ii) a “low viscosity” mode (counterforce to movement proportional to the velocity), iii) a “high viscosity” mode (greater counterforce's scaling coefficient) and iv) a random noise mode (force with a constant magnitude but random direction). In these experiments, 60-channel EEG, EMG of the fingers and arm, and kinematics of the arm, shoulder and chest were also recorded simultaneously. Analysis of the EMG-EEG coherence revealed that a reduction of tremor amplitude was observed only in the “high viscosity” mode. These results suggest that, similarly to brain signals, kinematic signals can also be used as feedback channels in closed-loop paradigms for PD patients.

It is likely that different combinations of feedback modalities may work better for different motor relearning tasks. Rehabilitation of the upper limbs might benefit from visual and haptic feedback, whereas gait rehabilitation might better benefit from auditory and haptic feedback. Augmented haptic feedback can easily be integrated into the brain-machine-body interface framework using haptic or exoskeletal robots. In future work, we plan to test which optimal multimodal feedback combination leads to optimal motor relearning during rehabilitation of upper and lower extremity movements in PD patients.

## 7. Future developments

### 7.1 From spikes to behavior

Using a bottom-up perspective, detailed large-scale spiking neuron network models of the BG based closely on known anatomy and physiology could also be implemented on neuromorphic hardware. Similarly to the cortical organization of mammalian brains, these models should be hierarchical, modular, and map sensory and motor plan states to motor output. The design of several modules will take inspiration of computational models of action gating<sup>142</sup> and action selection<sup>143</sup>. Data from healthy and PD patients, on and off dopaminergic medication, will also provide constraints to the design of these BG models that will be used to test and verify hypotheses of action selection and sensory-motor learning and control. This approach is motivated by the recent efforts in PD research to integrate model-based control in closed-loop systems<sup>36,40,144</sup> (for a review, see Schiff<sup>63</sup>). Biologically based computational models of brain activity can improve our understanding of distributed brain networks in healthy and disease conditions, and should be considered as a complementary tool of experimental approaches for monitoring and regulating the time-varying fluctuations of network activity.

Networks of spiking neurons lead to efficient implementation in neuromorphic hardware<sup>145,146,147</sup>. Moreover, biological realism in the modeling and a choice of neuromorphic architecture ensures that these models lead to architectures that utilize current and future massively parallel neuromorphic chip technologies<sup>148,149,150</sup> that can be deployed in real-world applications<sup>151,152,153</sup> with a very low power consumption<sup>154,155</sup>. Moreover, neuromorphic architectures provide a natural medium to bridge spiking activity in BG models with the synchronous LFP-like activity recorded by surface EEG. The estimation of the LFP dynamics from spiking activity can be achieved by combining constraints from simultaneous recording of cortical oscillation and basal ganglia activity<sup>156</sup> with methods from signal estimation theory<sup>157</sup>, such as the Wiener-Kolmogorov filter. In the Macaque monkey primary visual cortex, this linear filter was successfully used to estimate the LFP time course from the spiking activity of a few neurons<sup>158</sup>. Neural mass models are another promising approach to bridge the different spatiotemporal scales of neural activity<sup>159</sup>, i.e. from spiking activity to cortical fields. Thus, these larger-scale network implementations in neuromorphic hardware make it feasible soon to reach spatial and temporal scales of interest to the top-down perspective, where both top-down and bottom-up perspectives meet.

## 7.2 Closed-loop systems for other movement disorders

Among the myriad neurologic disorders, dystonia may be one of the best suited for investigating closed-loop therapeutic interventions for at least two compelling reasons: 1) it exhibits exquisite task-specificity; and 2) the most common brain structure targeted in DBS intervention for dystonia, the globus pallidus interna (GPi), is one of the primary output nuclei of the basal ganglia and therefore in a direct position to modulate somatotopically-specific action selection. After PD and ET, dystonia is the third most common movement disorder. The clinical definition of dystonia has evolved over the past few decades and a recent consensus definition has only recently emerged<sup>160</sup>. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and postures. The movements are typically patterned and often initiated or worsened by voluntary action. For many dystonia patients, the abnormal motor function is present only during specific tasks. In fact, in one expert's view<sup>161</sup>, this feature is specific to dystonia. This "task-specificity" is clearly evident in the so-called "focal task-specific" dystonias, including for example writer's cramp and musician's dystonia. For many musician dystonia patients, the symptoms are present only while playing their instrument and sometimes only when playing specific passages of specific musical pieces<sup>162</sup>. This makes the measurement of abnormal motor control particularly challenging<sup>163</sup>. Although this task-specificity is most vivid in these kinds of dystonia, a wider class of dystonias exhibit a more broadly defined "state dependence", in which "state" is defined to encompass not only the motor program used in a specific task but also the current sensory and motor goal state. For example, a simple light touch of the chin may be sufficient for mitigating the abnormal neck muscle activity implicated in cervical dystonia. While not a "task", this change in "state" suggests that a state-dependent intervention can be useful.

For most of the focal dystonias, the main line treatments of anticholinergics and botulinum toxin injections are not, of course, state- or task-specific. One might envision, then, a real-

time, on-line, closed-loop therapy (such as DBS or the noninvasive rTMS, tDCS and tACS) that would modulate the appropriate brain networks only during specific states. The question then becomes how best to monitor states. While it may be opportunistic to think that it could be acquired by recording leads in a single-shaft DBS system, the brain structures best suited for modulation by the stimulating DBS leads may not also incorporate the best information about “state”. One might posit, however, that premotor and/or posterior parietal cortical areas contain more easily measurable “state” information that could then be used to modulate circuits including the GPi that mediate state-dependent action selection. Here again, dystonia may provide an ideal clinical scenario in which to develop closed-loop therapeutic approaches. The STN, the most common choice of DBS target for PD, has widespread projections primarily within the basal ganglia. In contrast, the GPi, the most common DBS target for dystonia, is a prominent output stage of the BG and therefore has more direct influence on subsequent action selection and the resultant motor outputs. Ultimately, in light of theories about the “use-dependent” factors in its pathogenesis<sup>164</sup>, the investigation of closed-loop therapies for dystonia may also provide novel clues about the pathophysiology of this perplexing disorder.

## 8. Conclusion

Closed-loop paradigms for BMIs represent a promising avenue of research for the invasive and noninvasive neurological rehabilitation of movement disorders. They allow monitoring and tightly regulating the brain dynamics and/or body movements of patients suffering from these disorders, in particular Parkinson's disease. Their adaptive power has improved traditional DBS protocols in monkeys and humans and showed encouraging progress towards an augmented-reality device helping to restore gait. Adaptive closed-loop paradigms have the flexibility required to cope with the progressive and/or dynamic nature of movement disorders such as PD, dystonia and ET, and provide a transformative way toward individually tailored rehabilitative therapeutics. Recent results of testing BMIs for people with tetraplegia<sup>165</sup> indicate that closed-loop systems are not limited to the rehabilitation of PD patients.

So far, most of the closed-loop BMIs act mainly on brain signals and largely ignore the body, which is however central to movement disorders. Moreover, as current invasive solutions for neurological rehabilitation are limited to a minority of patients suffering from movement disorders, there is an urgent need for further research for alternative solutions, particularly regarding noninvasive BMI approaches. With these limitations in mind, an integrated framework was presented. In this conception, a brain-machine-body interface (BMBI) senses signals from the brain and body and acts on the body to exploit the adaptive plastic sensory-motor loops, thereby assisting restoration of motor functions in patients with PD. This framework is versatile and flexible and could be applied to other imaging or stimulation modalities. For example, one could envision replacing the force feedback with a noninvasive technique for stimulating motor cortex using rTMS, tDCS or tACS. Finally, it is likely that incorporating the physician/clinician in the loop in rehabilitative solutions will add more flexibility to many therapeutic systems, especially those targeting at-home use, by allowing a continuous adaptation and optimal adjustments of the parameters and therapeutic strategies in place to cope with the progression and fluctuations of movement disorders, and

to further approach individualized therapies. The continuous monitoring of progress (or lack thereof) for a given therapy, and consequent adaptation, appears to be a prerequisite for dealing with the inherent variability of patients and the different degrees of severity of neurological disorders affecting body movements.

With the increase of the aging population, and consequently of the incidence of movement disorders, there is a societal demand for improving the quality of life of patients with movement disorders, as well as an economical need to reduce the overall costs related to health care. With the development of cheap, mobile, wireless BMI solutions in the near future, we can expect innovative and adaptive solutions for personalized neurological rehabilitation that take into account the individual variability of patients as well as the variability of movement disorders' symptoms and disease's degree of severity.

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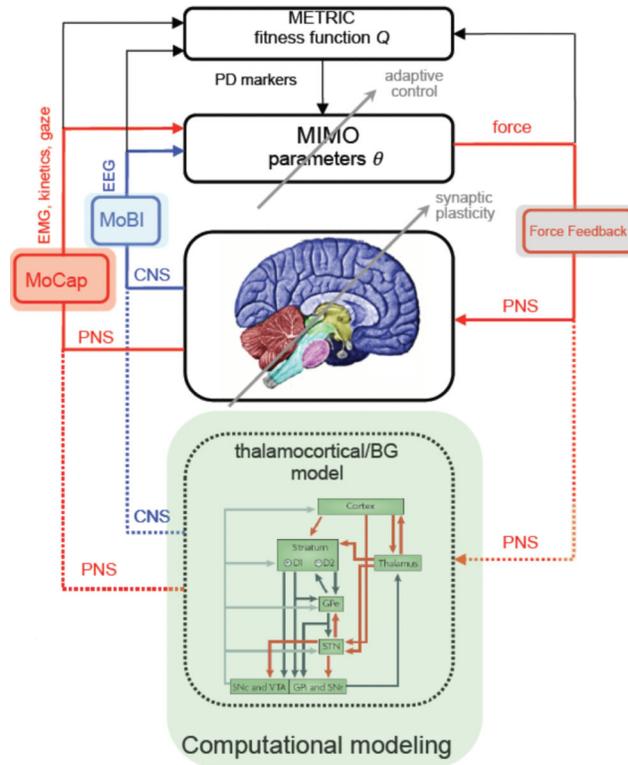
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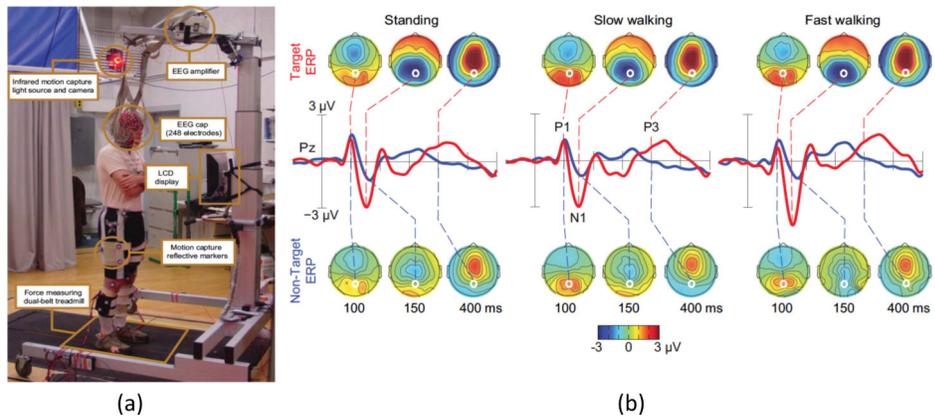
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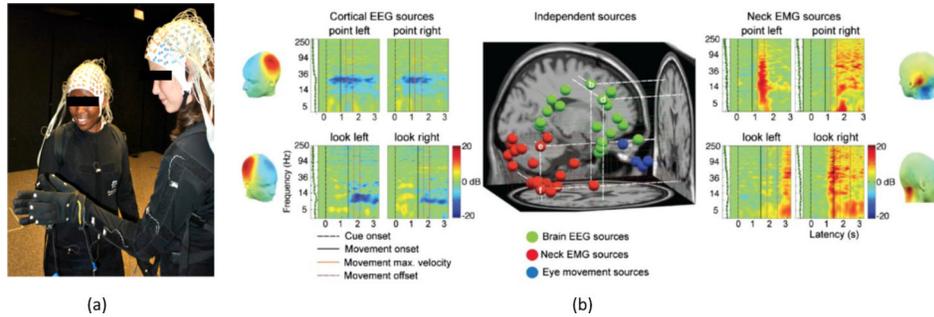
**Figure 1.**

A system framework towards neurofeedback noninvasive rehabilitation of movement disorders by means of closed-loop brain-machine-body interfaces. Signals from the central (CNS) and peripheral (PNS) nervous system are recorded and monitored by the mobile brain/body imaging (MoBI, [95]) and motion capture (MoCap) systems, respectively. Electroencephalography (EEG), electromyography (EMG), kinetics and eye-tracking signals provide inputs to the MIMO (multiple-input and multiple-output) module. The MIMO module outputs force feedback to external devices (haptic robots, cyber glove or exoskeleton) that is sensed by the brain via the PNS. The force is generated by adaptive control of the MIMO module's parameters ( $\theta$ ). The fitness function  $Q$  from the METRIC module is computed from the EEG, EMG and force signals, and outputs PD markers to the MIMO module. Oblique gray arrows indicate adaptive processes. Dashed lines indicate optional elements. Once tested and validated in the neurofeedback framework by comparing the forward modeling (see text for details) of its outputs with those monitored by MoBI and MoCap, the thalamocortical/BG model can be used as a model-based module providing additional inputs to the METRIC module helping constructing a better fitness function  $Q$ . Red and blue lines indicate information from the PNS and the CNS, respectively.



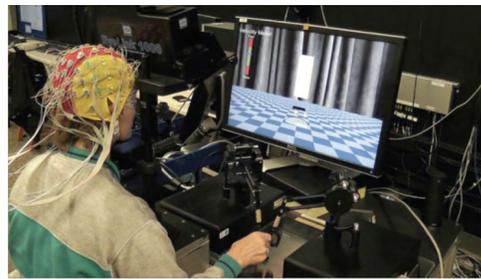
**Figure 2.**

(a) Mobile brain/body imaging (MoBI) setup for a participant on a treadmill and performing a visual oddball response task during standing, slow walking and fast walking. (b) Grand-average event-related potentials (ERPs) during standing, slow and fast walking. The ERP time course is represented in red for the target and blue for the non-target. Scalp maps show the grand-average ERP scalp distributions at 100, 150 and 400 ms after onsets of target (upper row) and non-target (lower row) stimuli. White dots indicate the location of electrode Pz. Note the scalp map similarities across conditions. Adapted from [97].

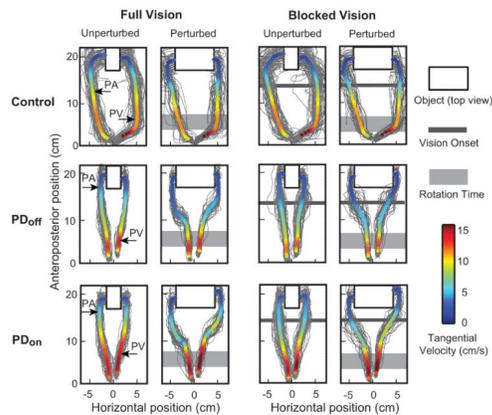


**Figure 3.**

(a) Participants are wearing a motion capture suit with infrared (IR) emitters and a high-density EEG cap (128 channels), allowing to monitor simultaneously the body kinematics and brain dynamics, respectively, during a hand mirroring task (one participant was instructed to follow the hand's movement of another participant). The position of the IR emitters is captured at 480 Hz by 12 cameras in the room. (b) Identification and localization of functionally distinct sources by independent component analysis (ICA) during a 3D object orienting task. The participant was cued to look forward, point to, or walk to and point to one of several objects present in the room. ICA allowed to separate the EEG data into a number of temporally and functionally independent sources from the brain and body that may then be localized (*middle*). *Top left*, an independent component (IC) source localized to in or near left precentral gyrus (BA 6) shows a decrease of high-beta band activity following cues to point to objects on the left or right. *Bottom left*, another right middle frontal (BA 6) IC source exhibits mean theta- and beta-band increases followed by mu- and beta-band decreases during and after visual orienting to the left or right. *Top right*, an IC source accounting for activity in a left neck muscle produces a burst of broadband EMG activity during left pointing movements and while maintaining a right pointing stance. *Bottom right*, a right neck muscle IC source exhibits an EMG increase during right head turns and during maintenance of left-looking head position. Data collected with a 256-channel EEG system. BA, Brodmann Area. Panel (b) modified from [95].



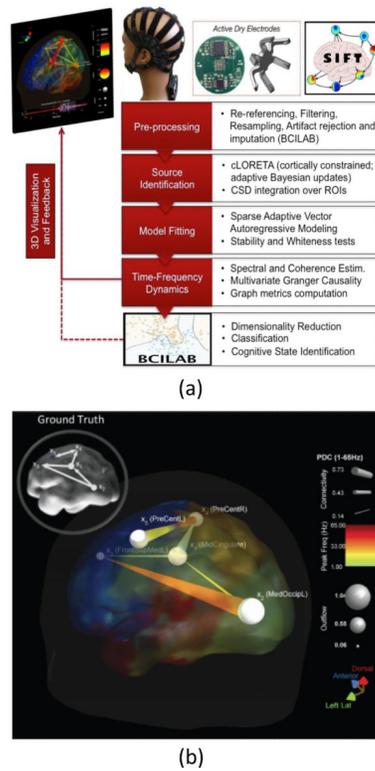
(a)



(b)

**Figure 4.**

Eye-hand coordination and corrective response control in PD during a reach-to-grasp task. (a) Experimental setup using eye-tracking hardware, haptic robots, EEG and a virtual reality environment. Participants reached to and grasped a rectangular object displayed on the screen with the thumb and index finger of their right hand fixed into thimble gimbals affixed to the left and right robot, respectively. Participants had haptic as well as visual feedback of the dock so that they felt their hands resting on a solid surface. The object's orientation was perturbed on 33% of the trials by rotating it 90 degrees in the frontal plane, thereby making the object appear horizontal. The perturbation occurred at a randomly jittered distance of 20-40% between the starting dock and the front of the object. The goal of the task remained the same regardless of the object orientation: to grasp along the left and right sides of the object. Therefore, participants had to adjust their grasp dynamically to a larger precision grip during perturbation trials. (b) Top view of reach to grasping movements in one representative PD patient on and off medications (PD ON vs. PD OFF) and his/her age-matched control. For the blocked vision conditions, visual feedback of finger position was removed during the first  $\sim 2/3$  of the reach, as depicted by a dark gray line. The average peak aperture (PA) and peak tangential velocity (PV) are marked along the thumb and index finger for each of the representative subjects during the unperturbed full vision condition. EEG data not shown. Adapted from [105].



**Figure 5.** 3D visualization of brain activity in real-time with a wireless EEG headset. (a) Real-time data processing pipeline using a Cognionics 64-channel system with flexible active dry electrodes, and the open source EEGLAB [64] extensions SIFT [65] and BCILAB [67]. (b) Temporal snapshot of online reconstructed source networks with Partial Direct Coherence (PDC estimator) displayed with the BrainMovie3D visualizer for simulated data. Node size indicates outflow (net influence of a source on all other sources). Cortical surface are colored according to their AAL atlas label (90 regions). Adapted from [113].