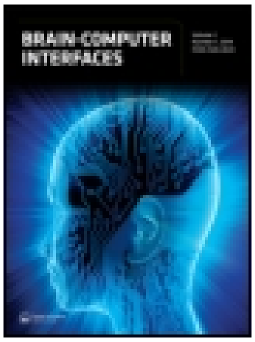

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ARTICLE

Brain-computer interfaces for stroke rehabilitation: summary of the 2016 BCI Meeting in Asilomar

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ABSTRACT
Brain-computer interfaces (BCIs) based on motor imagery have been gaining attention as tools to facilitate recovery from movement disorders resulting from stroke or other causes. These BCIs can detect imagined movements that are typically required within conventional rehabilitation therapy. This information about the timing, intensity, and location of imagined movements can help assess compliance and control feedback mechanisms such as functional electrical stimulation (FES) and virtual avatars. Here, we review work from eight groups that each presented recent results with BCI-based rehabilitation at a workshop during the 6th International Brain-Computer Interface Meeting. We also present major directions and challenges for future research.

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stroke rehabilitation; motor imagery; functional electrical stimulation; event-related desynchronization

1. Introduction

A brain-computer interface (BCI) can measure brain activity and generate a control signal in real time that can be used for different applications. BCI systems have used a variety of mental strategies and corresponding neural signals for this control, including (i) motor imagery (MI), (ii) the P300 evoked potential, (iii) steady-state evoked potentials (SSEP), and/or (iv) slow waves.

Stroke is the leading cause of long-term disability in the world, and 30–50% of stroke patients only attain very limited recovery. MI-based BCI systems are especially well suited for stroke rehabilitation, since (unlike other BCIs) the users imagine movement rather than other tasks, thereby activating motor areas. In this case, patients are asked to imagine a certain type of movement, which primarily affects their oscillations in the alpha or beta range of the EEG. Another approach with MI BCIs detects the motor-related cortical potential (MRCP) when the patient plans to perform a movement.

MI-based systems usually entail the imagination of right hand, left hand or foot movement. This imagined movement, like executed movement, produces an event-related desynchronization/synchronization (ERD/ERS) over the sensorimotor cortex, which the BCI can analyze to infer user intent. The electrodes are placed over sensorimotor regions, and people are trained with feedback paradigms to improve classification accuracy. MI BCIs require more training time than P300- or SSVEP-based systems, but can also yield high accuracies and are well suited for continuous control of prosthetic, orthotic or functional electrical stimulation (FES) devices.

Several groups have recently explored using MI BCIs to help persons with stroke improve motor function. For simplicity, we refer to this approach as 'BCI stroke rehab' in this paper. Patients are asked to imagine or attempt movements that are commonly used in stroke rehabilitation, such as wrist dorsiflexion, while a BCI monitors the patients' corresponding MI. The BCI then initiates rewarding feedback only when the correct MI is detected. This feedback also includes devices and methods that are commonly used, or gaining adoption, in conventional rehab, such as FES, virtual avatar movement, and rewarding images or sounds [35,37,42,47,65]. Thus, BCI stroke rehab does not wholly replace the methods and devices used in conventional therapy, but rather complements them.

Presumably, the closed-loop feedback increases central nervous system (CNS) plasticity, which leads to

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restoration of normal brain function or a rewiring of the CNS, although the mechanisms underlying functional improvement still require additional research. BCI stroke rehab systems may also help to engage the patient and provide therapists with a real-time tool to evaluate compliance.

The current article reviews a stroke rehabilitation workshop during the 6th International Brain-Computer Interface Meeting in Asilomar, Pacific Grove, USA which happened from 30 May 30 to 3 June 2016. This workshop was organized by the authors of this article, each of whom represents a different group. In this workshop, these eight groups each presented their work in this field, with questions and discussion of major issues. Five groups were from Europe (EPFL, Fondazione Santa Lucia (FSL), University Hospital Tübingen (UHT), Aalborg University (AAU), and g.tec medical engineering GmbH), one was from the USA (University of Wisconsin-Madison (UWM)) and two were from Japan (Keio University (KU) and Asahikawa Medical University (AMU)). All of them have a BCI-based stroke rehabilitation program on the international or national level, all of which entail collaboration with other groups. A ninth author (BZA) contributed to the introduction, discussion and some editing. In addition to reviewing the work presented at this workshop, the current article also presents some work from other groups, and discusses hypothetical issues and future research directions.

2. Stroke rehabilitation through g.tec

g.tec developed a new system for BCI stroke rehab called recoveriX, shown in Figure 1. This system was developed within the European Horizon 2020 framework project recoveriX and the FP7 ICT project VERE. It measures EEG activity with 16 electrodes over the sensorimotor cortex with active electrodes and a USB-based biosignal amplifier, and uses a computer to analyze the data in real time. The computer displays an avatar to the patient from a first-person perspective and instructs him/her to imagine either a left or right hand movement. The virtual avatar also acts as a feedback mechanism that is controlled by the output of the BCI system. This leads to a right hand movement of the avatar if the patient imagines right hand movement and vice versa for left hand movement. In addition to the avatar feedback, the muscles of the left or right hand are stimulated with a FES device to physically move the hand and thereby activate the proprioceptive system.

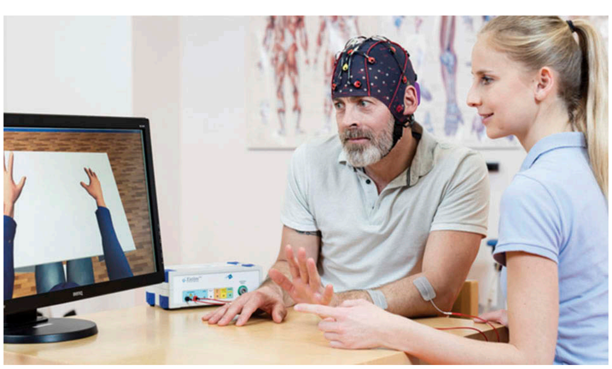
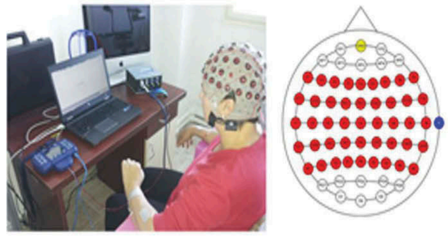


Figure 1. Components of the recoveriX system: computer screen with the 3D avatar in a first-person perspective, FES stimulator, EEG cap with active electrodes.

The BCI system uses common spatial patterns (CSP) and linear discriminant analysis (LDA) to automatically select the most important electrode positions and features to improve the classification accuracy [1–4]. During the first calibration session, the user always receives feedback equal to the cue (thus simulating 100% accuracy) regardless of the mental imagery. This is done to collect data to train the CSP and LDA weight vectors, and to help the user become familiar with the system. Subsequent sessions use a user-specific classifier. In each session after the first session, the CSP and LDA weight vectors are automatically updated after each run. Therefore, the system can adapt to changes in brain plasticity and patients' mental imagery within each rehabilitation session. The system operator can also manually select a classifier from an earlier run.

Three subjects used a variant of recoveriX with 64 electrodes and simpler visual feedback, shown in Figure 2. Subject 1 was a 61-year-old woman with right hand movement difficulty resulting from a recent stroke. Subject 2 was a 69-year-old man who could not move his right fingers at all due to a stroke about four months earlier. Subject 3 was a 64-year-old man who could only perform limited left arm movements due to a stroke about three months earlier. All three subjects were right-handed.

All three subjects performed an initial calibration session with two runs. All subsequent sessions contained six runs, each lasting about 6 minutes. Each run contained 40 trials that each lasted 8 seconds, interspersed with a 1 to 2 second inter-trial interval. Half of the 40 trials began with a cue to imagine left hand movement, and the other half cued right hand movement (chosen pseudorandomly). Subjects 1 and 3 each performed 24 training sessions, and Subject 2 performed 22 sessions. Subjects 1 and 3 each performed a common test of hand function called the nine-hole peg test (9-HPT) after every third session.



Sessions	Time [s] / dropped PEGs			
	Paretic hand		Healthy hand	
	P1	P3	P1	P3
0	65 / -	-	31 / -	-
3	54 / -	-	32 / -	-
6	45 / -	-	32 / -	-
9	42 / -	90 / 1	31 / -	26 / -
12	42 / -	77 / -	31 / -	26 / -
15	38 / -	94 / -	29 / -	26 / -
18	34 / -	60 / -	29 / -	25 / -
21	30 / -	61 / -	29 / -	25 / -
24	30 / -	52 / -	29 / -	26 / -
Time improvement	35	38	2	0

Figure 2. The left panel shows one patient using a prototype of the recoveriX system. The blue device to the left of the laptop manages the FES, and the larger device to the right of the laptop is an EEG amplifier. The right panel presents results from the 9-HPT for two of the patients.

Subject 3 was unable to perform this test prior to the ninth session, and Subject 2 could not perform it at all.

The preliminary results indicated that Patients 1 and 3 showed improvements in hand motor function. Patient 1's paretic hand could perform the 9-HPT about as well as her healthy hand after 21 sessions. Patient 3 was initially unable to perform the 9-HPT, and then showed modest improvement, although his impaired (left) hand did not attain the performance of his healthy hand. Subjects also attained high BCI classification accuracy [5]. We also explored classification accuracy in similar work with 64 electrodes in a BCI stroke rehab setting [6]. The classification accuracy was about the same with 64 electrodes and a simulated montage with 16 electrodes, and we have since been using a 16-channel montage in most new work with stroke patients. g.tec is still collaborating with this hospital partner in Iasi, Romania, and other hospital partners, to collect additional data to extend this initial report.

In collaboration with several external research universities and hospitals, g.tec is exploring several directions that could improve this system and/or BCI stroke rehab overall. These include new avatars and FES systems for lower-limb rehab, wireless electrode caps, dry electrodes, improved classifiers and classifier updating methods, brain stimulation, comparisons within patient groups (e.g. sub-acute vs. chronic), and new paradigms for interacting with end-users. Collaboration with hospital partners has been an effective way to explore new methods and devices across a wide variety of patients, and will remain a major part of g.tec's future research and development.

3. Stroke rehabilitation trials at EPFL

At the EPFL Defitech Chair on Brain-Machine Interface, we have been working towards BCI approaches to neurorehabilitation after stroke since the inception of the European project TOBI (http://www.tobi-project.org). In particular, we have designed *direct* BCI-based interventions for hand motor recovery [7–9] and for recovery of visuospatial attention deficits in spatial neglect patients [10], as well as *indirect* BCI methods for hand motor recovery [11]. In the direct approaches, our BCIs seek to foster activity-dependent brain plasticity by delivering therapy-relevant feedback contingent on the detection of neural correlates of the patient's intention to move the affected hand or to direct visual attention towards the neglected side of space. In the indirect approach, the BCI aims to confirm that patients are compliant with the behavioral intervention so that they are effectively engaged and attentive to the motor task, which play an important role in promoting plasticity [12,13]. These two approaches can be combined or used independently, depending on which one is the most suitable for each individual patient.

Regarding hand motor recovery, it has been shown that BCIs can be used in a BCI stroke rehab context to decode motor attempts from brain signals and to trigger movements of the paralyzed limb via a motorized orthosis [14]. As an alternative, the BCI could be coupled to neuromuscular electrical stimulation (NMES) of the affected arm, which activates both the body's natural efferent and afferent pathways (see Figure 3). In a recent clinical study, we validated this BCI-NMES approach using a MI BCI previously described in [15]. We enrolled 27 persons diagnosed with chronic stroke (minimum 10 months after the incident) suffering from a moderate-to-severe impairment of the upper limb in a randomized controlled clinical trial. Fourteen subjects were assigned to the BCI group and 13 to a 'sham' group. Patients in the BCI group received NMES of the extensor digitorum muscles triggered by the BCI detecting the intention of movement at the cortical level (modulation of the sensorimotor rhythms). For patients in the sham group, activation of the NMES was not correlated with their brain activity. All subjects were asked to attempt to open their paretic hand (full sustained finger extension), which was effectively achieved via NMES.

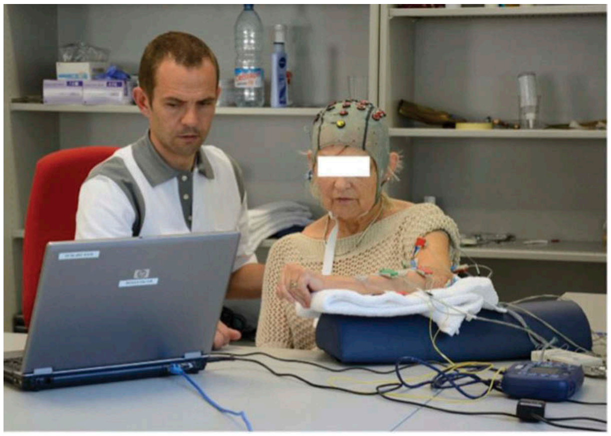


Figure 3. Clinical BCI-NMES setup with the patient and the physical therapist. The patient is wearing the EEG cap and NMES electrodes on the affected arm. The patient's attention is focused on the affected hand.

Subjects in the two groups (BCI and sham) performed 10 sessions (twice per week) and received a comparable amount of NMES. The primary clinical outcome metric of the study was the change in Fugl-Meyer assessment for impairment of the upper extremity (FMA-UE: from 0 to 66, plegic to normal). Preliminary results and findings of this study have been reported in [7–9].

This study included a remarkable preliminary result. Subjects in the BCI group significantly improved their motor function, which was above the 5.25 FMA points considered to be clinically important [16], while those in the sham group did not. Also notably, among other indicators of effective brain plasticity [17], connectivity in the mu and beta frequency bands inside the damaged motor cortex significantly increased for the BCI group, but not for the sham group. Moreover, the connectivity increase inside the damaged motor cortex was significantly correlated with the improvement of motor function of the upper limb for the chronic stroke patients.

Spatial neglect (SN) is a common consequence of stroke at the cortical and/or sub-cortical level, usually occurring in the right hemisphere [18]. One of the most accredited hypothesis is that SN is a consequence of unbalanced activity of the two cerebral hemispheres, translated behaviorally into a deficit of spatial attention orienting. Nevertheless, direct evidence of inter-hemispheric imbalance at the neurophysiological level is limited so far [18,19]. In this sense, BCIs might help the recovery of damaged networks by promoting task-related neural reactivation of the affected (right) hemisphere with respect to the unimpaired (left) hemisphere by means of a contingent real-time reward to SN patients. As in the case of hand motor recovery, such a BCI system needs to be based on a cognitive task strictly related to the attention deficit. For this reason, our EEG-based BCI approach exploits the covert visuospatial attention (CVSA) orienting paradigm [20–22]. CVSA represents the ability to focus attention in the visual space without eye movements [23]. Results of an exploratory study [10] with SN patients and healthy participants (HPs) provided preliminary evidence suggesting that (i) regardless of the severity of the attention deficit, SN patients were able to control the BCI; (ii) the introduction of the online BCI feedback reduced the initial inter-hemispheric imbalance for both HPs and SN patients; (iii) differences in connectivity between HPs and SN patients were attenuated; and (iv) SN patients reported a significant decrease in reaction times to the presented stimulus in the neglected spatial side once this stimulus moved towards the center of the visual field. These findings suggest that a CVSA BCI might help to foster re-activation of the damaged hemisphere in SN patients.

Finally, in our quest to uncover neurophysiological correlates of 'attentional' processes during the execution motor tasks [24,25], we have conducted a study involving 26 healthy participants [11] in a setting that bears a resemblance to motor rehabilitation therapies. Participants had to use a computer mouse to track a moving target along displayed trajectories while electroencephalographic (EEG) data and mouse/target positions were recorded. Importantly, in some blocks of visuomotor tracking trials, participants received some assistance, as is the case in robot-assisted therapies. We found a significant coupling between hand kinematics and a frontal network of theta frequency cortical oscillations during visuomotor tracking, which was attenuated during the condition of reduced attentional demand due to assistance. With further research, this could contribute to future systems that incorporate midline frontal EEG as a proxy to probe patients' cognitive engagement in rehabilitative motor tasks, which could be used to inform assistive rehabilitation therapies. Indeed, there is growing interest in increasing the efficacy of robot-assisted therapy through the adaptation of the amount of assistance on a trial-by-trial basis [26]. One of these adaptation strategies, 'assistance-as-needed', aims at providing patients with just the amount of assistance needed to perform the task, so as to keep a balance between effort and success. However, these adaptations are based on actual behavioral performance indicators, which are arguably not the best measures of participation or attentional processes. Thus, monitoring such processes directly at the brain level through BCI technology could have significant potential for improving future systems with real-time interaction.

4. Stroke rehabilitation at FSL

In 2008, the laboratory of Neuroelectrical Imaging and Brain-Computer Interface at Fondazione Santa Lucia began to explore the potential of EEG-based BCI technology in promoting functional hand motor recovery after stroke within the EU-funded TOBI project (http://www.tobi-project.org/welcome-tobi). A multidisciplinary team that included neuroscientists, bioengineers, and clinical rehabilitation experts was involved in all stages of the design, implementation, and clinical validation of our current BCI-assisted rehabilitative intervention.

The fundamental strategy stemmed from the assumption that MI entrains brain areas that govern movement execution, and thus the practice of specific MI tasks would influence brain plasticity and enhance post-stroke functional motor recovery [27,28]. Yet, the clinical benefit of MI as a rehabilitative intervention is hampered by the lack of quantitative task performance measures. Therefore, our hypothesis was that the combination of MI practice with BCI technology would allow the access of MI content under controlled conditions [29] and the monitoring of MI performances over time.

Based on this, we conceptualized and developed a BCI prototype to support hand MI training in subacute stroke patients during their admittance to the hospital for rehabilitation, as illustrated in Figure 3, right panel [30]. The system was developed with continuous involvement of rehabilitation experts and endowed with strong rehabilitation principles such as an ecological feedback consistent with the content of correct (kinesthetic as controlled via single pulse TMS) MI performance, selective reinforcement of ipsilesional EEG oscillatory activity (i.e. enhancement of affected hemisphere activation), and continuous assistance of an expert therapist during the BCI training.

Inputs on acceptability by patients and professionals were initially collected in the form of a proof-of-principle study, which found that our BCI approach was considered feasible as an add-on intervention in subacute severe stroke and was well tolerated by patients [31].

After proving the usability of our BCI prototype, a randomized controlled trial was run to prove the clinical efficacy of MI training assisted by our EEG-based BCI in improving hand motor function recovery in a cohort (28 patients) of subacute, first ever, severe stroke patients while admitted for rehabilitation at Fondazione Santa Lucia [32]. The study demonstrated clinically relevant benefit for upper-limb motor function and greater involvement (i.e. significant increase of EEG motor-related oscillatory activity after training) of the lesioned hemisphere in the target group undergoing BCI-supported MI training with respect to a matched control group of patients performing MI training without BCI. The association of functional improvement with changes in resting-state brain network organization further supports the use of our BCI technology to promote early post-stroke functional motor recovery.

These promising findings corroborated the idea that a relatively low-cost technique (i.e. EEG-based BCI) can be exploited to deliver a rehabilitative intervention (in this case MI) and prompted us to undertake a further translational effort by implementing an all-in-one BCI-supported MI training station with simplified hardware and software (see Figure 4, left panel). The Promotœr is currently employed as add-on to standard therapy in a rehabilitation ward. Training sessions are carried out with assistance of the same therapist in charge of the standard treatment for each patient, thus encouraging a further integration of our approach within the specific rehabilitation program of each patient.

Currently, 11 consecutively enrolled patients have completed the training with the Promotœr along with their standard care rehabilitation for a total of 141 sessions. Although restricted to our institution, this experience allows us, as a BCI laboratory, to be fully integrated in the clinic and receive input from rehabilitation experts that is fundamental for refining the approach and fostering synergies across neuroscience and rehabilitation medicine fields. These interactive synergies are the key to addressing the several issues still open before successful BCI-driven approaches can be part of the clinical armamentarium for stroke rehabilitation. From a clinical viewpoint, questions about delivering training remain open, in terms of both frequency and intensity (dose-response relationship). Longitudinal studies are needed to investigate the persistence of the BCI-induced clinical benefits. Furthermore, the variability in the nature and extent of upper-limb recovery is a well-recognized point [33]. In this respect, several systematic reviews have reported that, along with voluntary motor ability (i.e. severity of arm motor impairment), neurophysiological measures, such as the presence of an MEP early after stroke, are the strongest predictors of later recovery [27].

We are currently undertaking a large clinical trial, which includes consecutively admitted stroke patients who undergo a longitudinally functional and neurophysiological assessment (high-density EEG, TMS) before, at the end, and 3–6 months after BCI training. The leading idea is to retrospectively identify variables

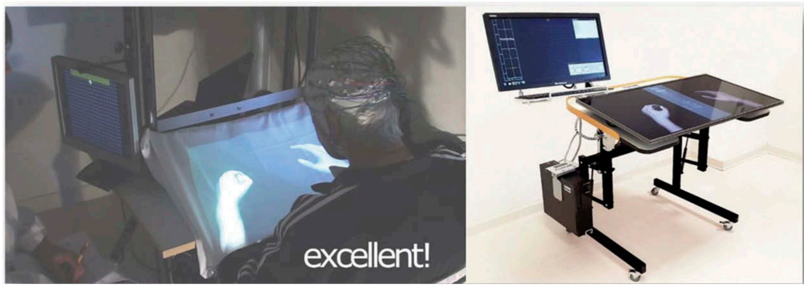


Figure 4. Left panel: during each session, the therapist can monitor the patient's brain activity, displayed on a dedicated screen. The degree of desynchronization in selected electrodes/frequencies over the ipsilesional hemisphere that are associated with motor imagery determines the vertical velocity of a cursor on the therapist's screen. Once the cursor reaches a target, the virtual hand performs the imagined movement (feedback to patients in successful trials). The therapist is also allowed to monitor the patient's extent of muscle relaxation based on the electromyographic signal, which is recorded from the hand and forearm muscles and displayed on a screen. Right panel: the Promotœr includes a computer, a commercial wireless EEG/EMG system, a screen for the therapist feedback (EEG and EMG activity monitoring) and a screen for the ecological feedback to the patient – a custom software program that provides a (personalized) visual representation of the patient's own hands. These components are assembled in an all-in-one BCI-supported motor imagery training station, which is currently available in the rehabilitation ward at Fondazione Santa Lucia.

that would allow for a reliable prediction of the best responders to our BCI-driven rehabilitative intervention. Such knowledge would be pivotal to resolve uncertainties surrounding the effectiveness of BCI training (especially at the level of brain plasticity induction), to optimize (ideally individualized) BCI-based rehabilitation, and to better clarify clinical outcomes of intervention. In addition, we expect that evidence of different patterns of responses to BCI training could lead to improved procedures to select the optimal control signals/patterns to re-establish a more physiological balance between ipsi- and contra-lesional sensorimotor cortex recruitment [34].

The expected advances will be also instrumental to foster synergy with industry and policy-makers, who play an essential role in the translation of BCI technology to clinical routine usage.

5. BCI rehabilitation at Keio University

Keio University has received funding through three brain-machine interface (BMI)-related national projects from the Japan Agency for Medical Research and Development (AMED). AMED is a recently established national funding agency inspired by the National Institutes of Health (NIH) in the United States, aiming to promote integrated medical R&D from basic research to practical applications, to smoothly achieve application of outcomes, and to achieve comprehensive and effective establishment/maintenance of an environment for medical R&D. Keio University also received funding from the Strategic Research Program for Brain Sciences (SRPBS), which aims to explore the fundamental mechanisms and efficacies of BMI-based treatment of neurological disorders, as evidenced by neuroscientific measures. The next fund is from Future Medicine, which aims to bring neuroscientific BMI discoveries into the clinical setting by developing commercially available medical products through collaboration with world-wide industry makers/suppliers, such as Panasonic Corp. and Nihon Kohden Corp. The last supplementary fund from Future Medicine has supported the cost for investigator-initiated clinical trials. Through this strategic activity that spans fundamental, translational, and regulatory sciences, our research group, in collaboration with the Department of Rehabilitation Medicine, Keio University School of Medicine (PI: Meigen Liu), has been intensively developing BMI-based neurorehabilitation for stroke patients with severe hemiplegia.

We have so far constructed the scientific portfolio that evidences the clinical efficacy and neurophysiological relevance of EEG-based BMI for motor rehabilitation in stroke patients with severe hemiplegia. Harmonizing with other publications outside Keio University [35], our joint industry-university collaboration team is designing the GCP (good clinical practice)-certified randomized control protocol of clinical trials with the GMP (good manufacturing practice)-certified BMI product. This regulatory process has been addressed by the Pharmaceuticals and Medical Devices Agency (PMDA), which is a medical regulatory agency within Japan.

Treatment is not omnipotent. Therefore, the therapeutic effect size of the current ERD-based BMI motor rehabilitation is limited. As a result, inclusion criteria and expected outcome of the treatment should be finely defined as the standards, and the next treatment option for the patients with a good prognosis (and a bad prognosis as well) should also be designed. In Keio University, for BMI-based motor rehabilitation, stroke survivors suffering severe motor deficit even without voluntary EMG were recruited. Their sensory deficits, however, are either none or moderate, since somatosensory feedback may play a key role in functional recovery through interaction with BMI. Cognitive impairment should also be moderate to ensure task compliance. The target motion of the training was finger extension, since it is the primary endpoint to increase the use of a paralyzed upper extremity in the basic activity of daily living. The target muscle in training was therefore the extensor digitorum communis muscle. After a 2-week intervention (except Saturday and Sunday) of 1-hour BMI-related motor rehabilitation, 21 out of 29 patients began to generate volitional EMG. Following our clinical pathways, these patients who displayed a good prognosis received HANDS therapy as the next treatment. HANDS is a closed-loop, EMG-triggered, functional electrical stimulation approach that entails powered assistance of muscle contraction in an electrophysiological fashion. Combination with a soft brace constrains the thumb position in the opposite position from the fingers, which facilitates both grasping/releasing movement and spasticity reduction. HANDS is more convenient in practical use; thus, 8 hours of intensive daily use were successfully administered. After 3 weeks of training, progressive increases in Fugl-Meyer test upper-extremity motor score and Motor Activity Log Amount of Use score were confirmed [36].

Making a scientific portfolio in both fundamental, translational, and regulatory sciences may lead to successful fund-raising for sustainable development, and connect a new rehabilitative technology (BMI-based motor rehabilitation in this case) to existing treatment which is essential for practical use.

6. Stroke rehabilitation at the University Hospital Tübingen

Currently, two main strategies are pursued for restoration of motor function using BMIs at the University Hospital in Tübingen, Germany. The first strategy aims at bypassing damaged motor pathways, establishing direct control of an orthotic exoskeleton to assist in performing activities of daily living, e.g. grasping a cup and drinking, or holding a fork and eating, while the second strategy aims at facilitation of neuroplasticity and motor learning to enhance motor recovery [37]. After first indications that conditioning of ipsilesional SMR might be beneficial in chronic stroke [38], and data suggesting a relationship between ipsilesional cortical function and stroke severity [39–41], we conceptualized and developed a first-generation SMR-based BMI for severely affected stroke patients. These patients could control an orthotic device to open and close their paralyzed hand using ipsilesional brain activity [42]. It was hypothesized that, by re-establishing contingency between ipsilesional cortical activity related to planned or intended motor activity and proprioceptive/haptic feedback, the ipsilesional sensorimotor loop becomes strengthened, resulting in facilitation of motor recovery [37,41,43]. After some promising case studies [44,45], a larger controlled clinical study involving 32 severe chronic stroke patients without residual hand mobility and without any available treatment option was pursued [14]. This study provided evidence that combining BMI training with behaviorally oriented physiotherapy could result in functional improvements in motor function. In contrast to the widely accepted view that motor function after severe stroke cannot substantially improve once motor deficits are chronic, these results demonstrate the opposite, and underline the importance of effective learning environments for patients who have suffered a stroke. Other groups have used BMI without haptic feedback. In these systems, visual feedback of SMR is used to monitor and train MI [46], as previous studies suggested that MI might represent an important element in training-based stroke rehabilitation. From a neurophysiological view, such systems primarily strive to return abnormal brain activity closer to normal [47].

While these studies strongly suggest that BMI technologies are powerful tools in stroke neurorehabilitation, larger clinical studies and studies that investigate the exact underlying mechanisms of action are needed. Clearly, the required effort to train stroke survivors daily with expensive research equipment and under supervision of specialized scientists, physicians, and physiotherapists, as carried out in the described studies, makes it hard to establish BMI training as a standard therapy in stroke at present. Thus, new means to make BMI training more effective or lowering the costs for such BMI training are required.

Currently, we see mainly two approaches that can improve BMI effectiveness: (1) full implantation of a wireless BMI capable of bridging weakened or non-existent cortico-spinal pathways, or refining existent non-invasive systems by e.g. implementation of brain stimulation shown to improve BMI learning [48], and (2) BMI paradigms that are more effective in strengthening the thalamocortical sensorimotor circuit. Yet, many questions related to BMI training in stroke neurorehabilitation remain unanswered, for instance dose-

Figure 5. Illustration of the Tübingen hybrid brain/neural hand exoskeleton (B/NHE) for home-based stroke neurorehabilitation. The brain's electrical activity from the ipsilesional hemisphere is recorded and transmitted to a tablet computer detecting sensorimotor rhythm (SMR) desynchronization associated with the attempt to open the paralyzed fingers. Hand closing motions are either performed by the patient or (in case of flaccid paralysis) by horizontal eye movements detected by electrooculography (EOG). After specific training periods, in which B/NHE-supported hand opening and closing is learned, patients use the system in their daily-life environments to perform activities of daily living, fostering generalization of learned skills.

response relationships or the influence of BMI training on other brain functions, e.g. the cognitive domain.

While assistive and rehabilitative BMIs follow different rationales, they serve the same purpose: integration of both strategies in a hybrid brain/neural hand exoskeleton system (Figure 5) that can be used in daily-life environments for daily life actions helping stroke survivors to generalize learned grasping motions might pave the way for broader application of BMI technology in the near future. Such a system, used in rehabilitation facilities and then in the patient's home environment, would also allow the collection of large amounts of (neuro)physiological data, which would facilitate addressing some of the above-mentioned questions.

Recent developments of hybrid brain/neural computer interaction (BNCI) systems that integrate different bio-signals have demonstrated sufficiently robust and reliable control of simple exoskeletons or robots [49,50], e.g. to perform activities of daily life (ADL), such as the example in Figure 5. It is clear that the stepwise implementation and distribution of such BMI systems will require broader commercialization of these systems at some point, an enterprise which currently can only be started as a collective effort in a partnership between public and private stake-holders. Beyond decisive political commitment on national and international levels associated with sufficient funding, involvement and tight interactions between academia, hospitals, rehabilitation centers, and the industry will be necessary.

7. BCI rehabilitation at AAU

The Brain-Computer-Interface (BCI) group at Aalborg University, together with Dario Farina's group at the University of Göttingen, have developed a BCI system that could be adapted to stroke rehabilitation based on movement-related cortical potentials (MRCP) [51]. The MRCP is a negative potential that commences 1–2 seconds prior to a movement being performed or imagined, reaching its peak negative phase at movement execution, followed by a rebound phase. Our paradigm is composed of two phases: a training phase and a testing phase. During the training phase, patients attempt 30 dorsiflexion movements and the time of peak negativity (PN) of the MRCP is quantified offline. In the subsequent testing phase, patients attempt the same number of movements while a single electrical stimulus of the deep branch of the common peroneal nerve is applied at motor threshold and timed so that the generated afferent volley coincides with the PN of the MRCP. In this way, the patient learns to make a direct association between motor intent and the artificial reproduction of the intended movement. This associative BCI directly follows the principle of Hebbian learning [52] that hypothesizes that neural assemblies activated in a correlated manner will strengthen synaptic connections that we tested in healthy participants [53]. Figure 6 depicts the schematic of the associative BCI.

To date we have tested the system on both chronic [54] and acute stroke patients. In the former case, patients participated in three intervention sessions within 1 week, spaced at least 48 hours apart. The excitability of the cortical projections to the target muscle (tibialis anterior) was significantly increased in all patients following each session of the $\text{BCI}_{\text{associative}}$ intervention while no such changes were observed for the $\text{BCI}_{\text{non-associative}}$ control group (here the artificially generated afferent feedback was randomly applied in relation to the different phases of the MRCP). All chronic patients in the $\text{BCI}_{\text{associative}}$ group significantly improved on functional

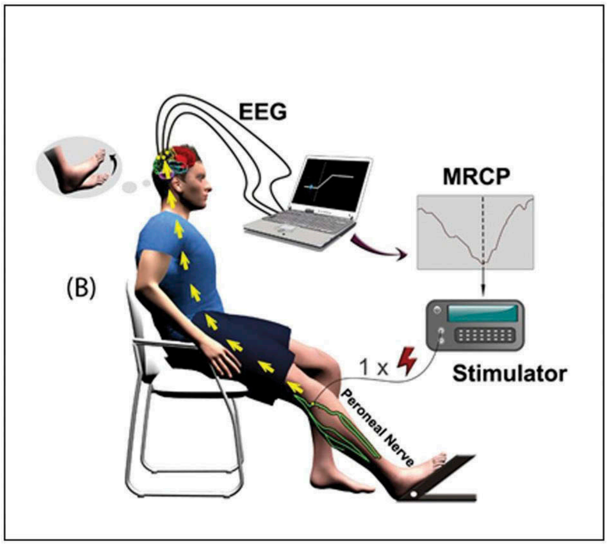


Figure 6. Schematic of the brain-controlled electrical stimulation of the target muscle.

measures such as the 10 m walk test. We are currently running a randomized control trial in acute stroke patients, who participate in three sessions per week across four weeks. Data to date reveal, in addition to the alterations in the excitability of the cortical projections to the TA, significant functional improvements on the typical clinical scales such as the LE-FM and Ashworth scale.

The system described here requires no user training and each intervention lasts approximately 20 minutes, ideal for the clinical setting where patients, particularly in the acute phase following stroke, have a schedule filled with various other rehabilitation interventions such as cognitive training. The precise coupling between the brain command and the afferent signal is critical in our BCI, and this association may become the driving principle for the design of BCI rehabilitation in the future.

8. Stroke rehab at Asahikawa Medical University (AMU)

Asahikawa Medical University (AMU) hospital and a nearby rehabilitation hospital have both installed recoveriX and are using it with patients. AMU treats patients with acute stroke with re-vascularization treatments until the subchronic phase (3–4 weeks after onset). All patients undergo functional MRI examination with both executed and imagined grasping before and after rehabilitation with recoveriX. Each rehabilitation session consists of three runs of 80 hand motor imaginations, and rehabilitation sessions are performed every other day for a month, as shown in Figure 7.

In addition to EEG mapping results and BCI classification accuracy, a 9-hole PEG test is used to assess functional improvements. The left panel of Figure 8 presents initial results showing that both BCI classification accuracy and right hand motor function improved with training. We also evaluated fMRI results to assess the changes in cortical motor areas in both hemispheres, because we are interested in the bilateral changes resulting from BCI stroke rehab. The right

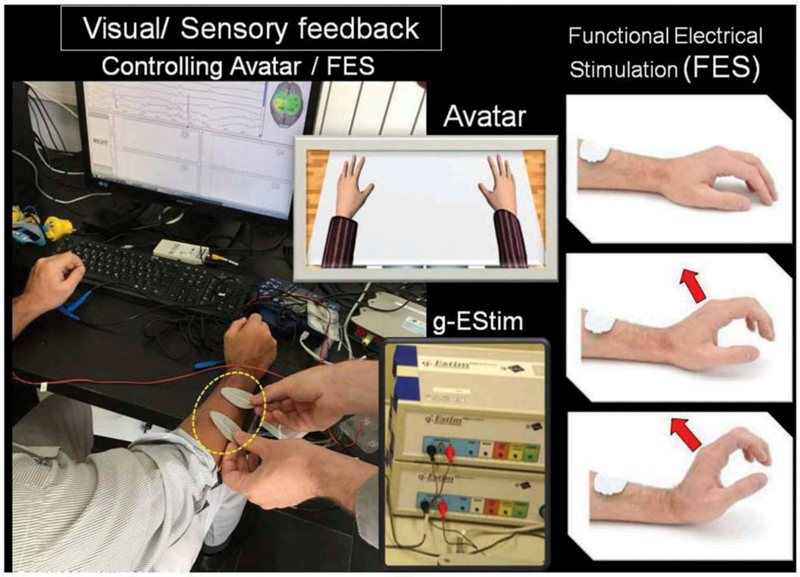


Figure 7. recoveriX rehabilitation. The patient is seated in front of a computer screen to see instructions from the avatar, and two bipolar FES channels are mounted on each arm to stimulate the arm with the FES stimulator (g-EStim). The movement due to the stimulation is shown on the right side of the figure.

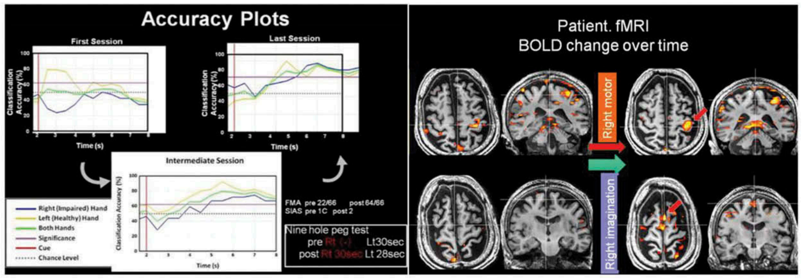


Figure 8. The left panel shows the changes that occurred over training with a stroke patient. The patient initially could not perform the 9-HPT with his impaired (right) hand. After training, he could complete the 9-HPT with his right hand in 30 seconds, about the same time required for his unimpaired left hand. The BCI classification accuracy was initially below significance and close to chance level, but improved during training and ultimately reached over 80%. The right panel shows fMRI activation during motor execution and imagery, both before training (left images) and after training (right images). The small red arrows in the right images reflect noteworthy areas of increased activation.

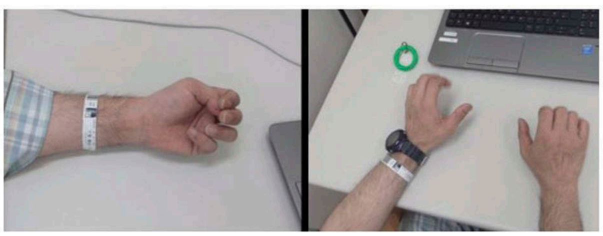


Figure 9. Rapid functional improvement in one patient at AMU using the recoveriX system. Left: before beginning BCI rehab, the patient could only open the hand as shown in the picture. Right: the next day, after a single BCI rehab session, the patient could completely open and close the hand.

panel of Figure 8 shows that motor execution and imagery caused broader activation of primary and supplementary areas after training.

Figure 9 presents an example of very rapid recovery of hand function. This result is from a single patient, like the results from AMU presented above. We are conducting further experiments to validate the rehabilitation procedures and outcomes, including the rapid functional improvement and the neurophysiological changes associated with improved motor function during BCI rehab.

9. Stroke rehabilitation at University of Wisconsin-Madison (UWM)

Stroke patients with UE impairments were recruited as part of an ongoing pilot study using EEG-BCI-facilitated FES at UWM. Potential subjects were excluded from study participation if they had additional neuropsychiatric diagnoses (e.g. epilepsy, Alzheimer's, schizophrenia) or if they were allergic to electrode gel, tape, or metal against the skin. Potential subjects were also excluded if they were receiving treatment for any infectious diseases, if they were pregnant or likely to become pregnant during the course of study participation, if they had any contraindications for MRI, or were unable to provide informed consent. This study was approved by the local Health Sciences Institutional Review Board. All subjects provided written informed consent upon enrollment. Data from 16 stroke patients (average age = 62 years, 10 males, average time since stroke onset = 33 months) with upper-limb impairment and receiving up to 15 sessions of intervention using the active FES method were included in this analysis. Subjects were assessed at four time points relative to the administration of BCI therapy: pre-therapy (no more than 1 week before the first BCI therapy session), mid-therapy (after completion of at least five BCI therapy sessions), post-therapy (within 1 week after completing the last BCI therapy session), and 1 month after completion of all BCI therapy. Behavioral assessments and MRI scans were obtained on each assessment day. Total ARAT scores for the subject's impaired hand were examined for this study. Scores for the 9-HPT were calculated as the average time (in seconds) needed to complete the task between two attempts both using the impaired hand. SIS domain scores were transformed independently to reflect the percent possible points obtained by each subject for each domain. There was improvement in ARAT (1 month post), and in SIS strength (significantly greater scores suggest improvement immediately post and 1 month post) and 9-HPT scores (significantly lesser scores suggest improvement immediately post and 1 month post) (Figure 10) [55].

We examined the relationship between fMRI activation measures and upper-limb motor outcomes in 11 stroke patients (average age = 56 years, median time since stroke 13 months) who received intervention using the active FES technology [55]. Laterality Index (LI) values during finger tapping of each hand were

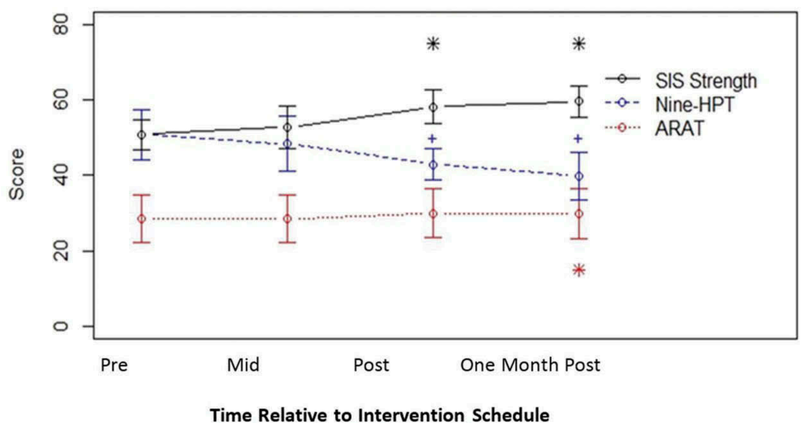


Figure 10. Change over time in behavioral outcomes following BCI therapy. Linear mixed-effect analysis identified significant differences or trends across the four time points with BCI therapy on the affected hand for ARAT, 9-HPT, and SIS Strength (*significant at $p < .05$; +trending to significance $0.05 < p < .1$).

calculated for each time point and assessed for correlation with behavioral outcomes. Brain activity during finger tapping of each hand shifted over the course of BCI therapy, but not in the absence of therapy, to greater involvement of the non-lesioned hemisphere (and lesser involvement of the stroke-lesioned hemisphere) as measured by LI (Figure 11). Moreover, changes from baseline LI values during finger tapping of the impaired hand were correlated with gains in both objective and subjective behavioral measures (Figure 12).

LI can be used as a measure of functional brain organization and has been used to examine functional brain reorganization in stroke patients with motor deficits using other therapy modalities [56]. Relative utility for hemispheric lateralization of different clinical fMRI activation tasks within a comprehensive language paradigm battery in brain tumor patients was assessed by both threshold-dependent and threshold-independent analysis methods [56]. In order to examine the specific patterns of brain change induced in stroke patients following EEG-BCI therapy, we examined lateralization patterns associated with a finger-tapping task in the same group of patients reported above.

Subjects performed a block-design finger-tapping task during fMRI scans that consisted of alternating 20-second blocks of tapping versus rest. Subjects were cued to rest or to tap the fingers of one hand sequentially on a button box using either visual or tactile cues. Visual cues consisted of the word 'TAP' alternating with the word 'REST' projected on a screen. MRI data were collected using one of two 3 tesla GE MR750 scanners equipped with high-speed gradients (Sigma GE Healthcare, Milwaukee, Wisconsin) using an eight-channel head coil. Functional scans were run using a T2*-weighted gradient-echo echo planar imaging (EPI) pulse sequence sensitive to BOLD contrast. Technical parameters used to acquire these EPI scans are as follows: field of view 224 mm, matrix 64 × 64, TR 2600 ms, TE 22ms, flip angle 60 degrees, and 40 axial plane slices of 3.5 mm thickness. During each fMRI scan, 70 sequential whole-brain acquisitions were recorded. These scanning parameters allowed for complete mapping of the cortex. A T1-weighted

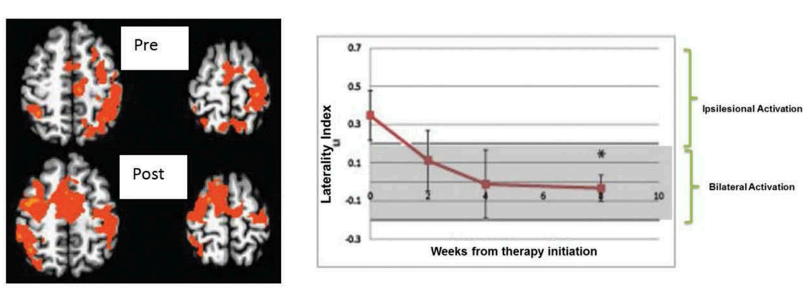


Figure 11. Left: group map showing shift in left-lateralized activity at pre-therapy (top of panel) to bilateral activation post-therapy (bottom of panel). This image is shown in radiological convention with the left of the brain or the ipsilesional side on the right. Right: shift in LI from ipsilesional to bilateral pattern over time following BCI therapy, *$p < .05$.

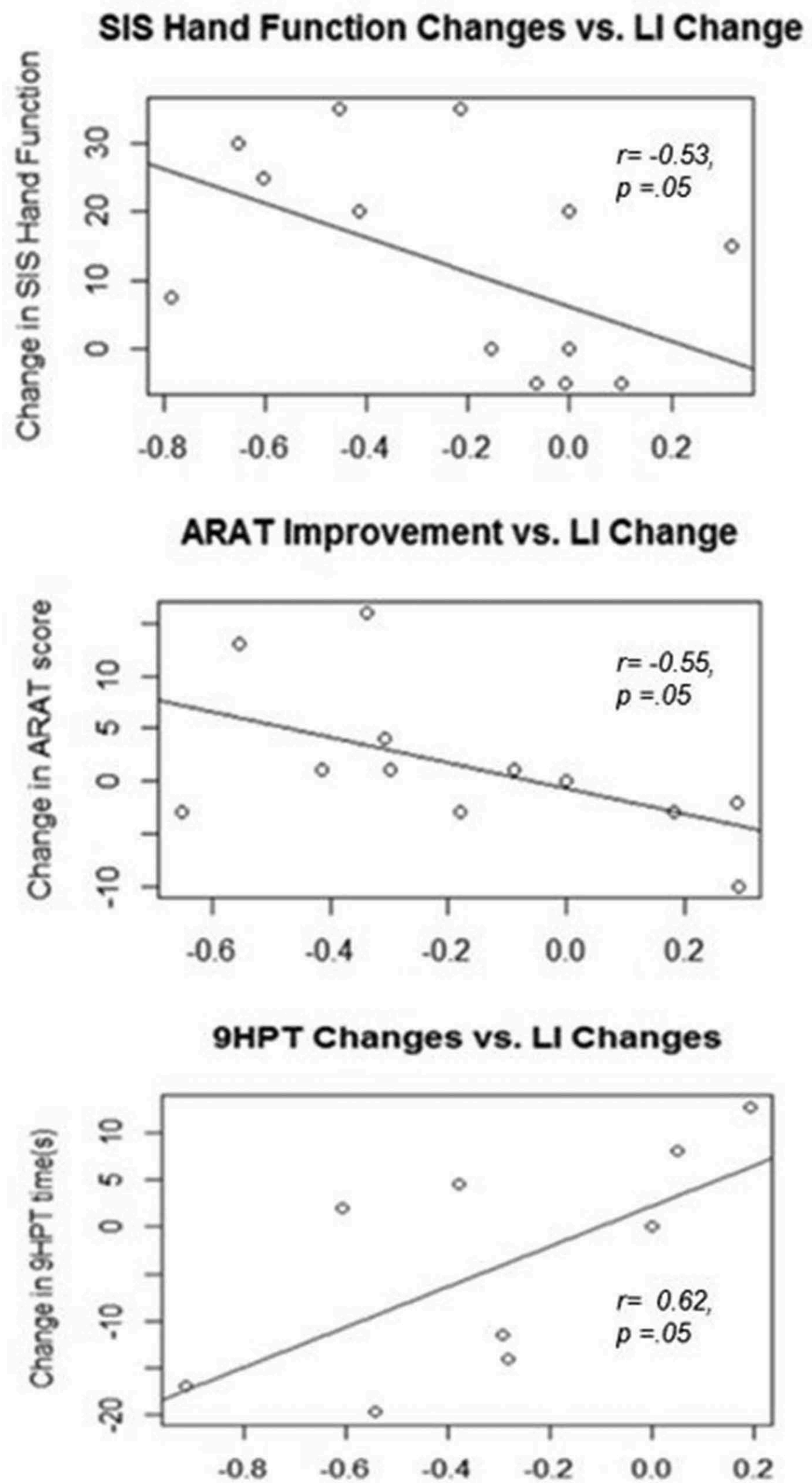


Figure 12. Change in LI (*x*-axis) vs. change in SIS hand function, ARAT, and 9-HPT.

high-resolution anatomical image was also obtained for each subject using a BRAVO FSPGR pulse sequence during each MRI scanning session. Technical parameters used to acquire these scans are: field of view 256 mm, matrix 256 × 256, TR 8.16ms, TE 3.18 ms, flip angle 12 degrees and 156 axial plane slices of 1 mm thickness with 1 mm spacing between slices.

All pre- and post-processing of MRI data was performed using the AFNI software package. The first four volumes of each functional sequence were discarded to allow for signal stabilization. EPI data sets were motion-corrected and then spatially smoothed at 6 mm with a full width at half maximum Gaussian kernel. Each voxel time-series was scaled to a mean of 100, and AFNI's 3dDeconvolve was used to perform a voxel-wise regression analysis with six motion parameters regressed out.

9.1. *fMRI activation maps of pre and post intervention*

When considering group-level activation patterns observed during finger tapping of the impaired hand, a progression from more ipsilesional activity at pre-therapy to bilateral activation post-therapy at the group level (Figure 11, left) was observed. This suggests that the EEG-BCI therapy has facilitated use of both ipsi- and contra-lesional hemispheres to attempt the desired hand movement. This is consistent with the underlying mechanism of BCI which facilitates the unmasking of latent pathways or the recruitment of hitherto unused brain regions in the performance of a task that was previously exclusively done by selected regions predominantly in the ipsilesional hemisphere. This bilateral activity persisted 1 month after the cessation of BCI therapy.

9.2. *fMRI measures and behavior correlation*

We examined the relationship between fMRI activation measures and upper-limb motor outcomes in 13 stroke patients (median 20-month post-stroke) who completed up to 15 sessions of intervention using the active FES technology [55,57]. Upper-limb motor outcomes included objective measures of ARAT and the nine-hole peg test (9-HPT) and subjective measures included the hand function domain on the SIS. Laterality Index (LI) values during finger tapping of each hand were calculated for each time point and assessed for correlation with behavioral outcomes. For calculating LI, a mask for each side of the motor network was constructed based on motor network regions identified from an independent component analysis of whole-brain resting-state fMRI scans [58]. LI was calculated using the formula (VI − VC)/(VI + VC), where VI is the number of voxels in the ipsilesional hemisphere mask with significant activation at the preset statistical threshold and VC is the number of voxels in the contralesional hemisphere mask with significant activation at the same threshold. Using this system, LI values above 0.2 are considered to represent left-lateralized, those below −0.2 represent right-lateralized activity, and those between −0.2 and 0.2 correspond to bilateral activity [59]. Note that, given the known effect of different statistical thresholds on LI calculations [56], we calculated LI values at different statistical thresholds and found the overall results reported below to be consistent.

Brain activity during finger tapping of each hand shifted over the course of BCI therapy, but not in the absence of therapy, to greater involvement of the non-lesioned hemisphere (and lesser involvement of the stroke-lesioned hemisphere) as measured by LI (Figure 11, right). Moreover, changes from baseline LI values during finger tapping of the impaired hand were correlated with gains in both objective and subjective behavioral measures (Figure 12).

10. Discussion

Recent work showed that BCI systems based on ERD/ERS and MRCP are effective in stroke rehabilitation. UHT developed an ERD/ERS-based BMI system that triggers a real hand movement with an orthosis and was able to show significant improvements in a group study [48]. FSL uses a virtual avatar in front of the patient that is controlled with the BCI to give visual feedback and showed improvements [29]. EPFL uses a BCI-FES device to produce motor movements [7]. g.tec uses a combination of a first-person-view avatar with FES stimulation of the corresponding body parts (hand or leg) in a system called recoveriX [60]. KU uses a BCI-robotic device to generate movements and showed its effectiveness in a group study [61]. AMU uses the BCI system for recovery after stroke as well as after neurosurgery in acute patients. Mrachacz-Kersting and colleagues showed improvement with an MRCP-based system with peripheral nerve stimulation [54]. UWM presented work exploring LI and motor movement via a BCI-FES device [55].

The studies confirmed that patients with stroke can effectively control MI BCIs in a BCI stroke rehab paradigm. Functional outcomes did improve, although some studies did not employ matched controls, or have not been published in a peer-reviewed journal. BCI stroke rehab remains a new field, with numerous unanswered questions that require future research. The need for additional research is currently a major weakness of the field. Some of the most pressing directions are presented below, along with some commentary, based on our discussion at our workshop and issues raised in this paper.

Neurophysiological basis: we believe that functional improvement resulting from BCI rehab training stems largely from improved plasticity. Controlling feedback devices through MI in real time should lead to tighter coordination between relevant sensorimotor activation and feedback (including tactile and proprioceptive feedback), which is critical for Hebbian learning. However, the neurophysiological basis for improvements resulting from BCI rehab requires further study. This is an ongoing effort from many of our groups, with a variety of methods including EEG, fMRI, TMS, and peripheral stimulation. Several studies described here have utilized fMRI as a tool to explore neurophysiological issues relating to BCI stroke rehab, and real-time fMRI (probably in combination with other methods) may become useful for influencing feedback as well.

Task and procedure: the phrasing and other presentation of task instructions could influence the activities that patients attempt or imagine, and thus influence outcomes. Research has shown that BCI accuracy is worse when users are asked to imagine observing a movement, instead of attempting or performing movement [62]. Instead of 'motor imagery', some patients might attain better results if they are asked to visualize, plan, attempt, or execute movement. Further research should explore timing issues such as the duration of each trial, run, and session and the rest periods between them. Most of the work presented here involves sessions on separate days, with less than 1 hour of data recording each. Longer and/or more frequent sessions could provide more intensive training, but could also cause patients to become fatigued or annoyed. This dose-response relationship could depend largely on patients' engagement.

Feedback and motivation: we believe that BCI rehab helps to engage patients in at least two ways. First, feedback is only provided when the patient performs the correct motor imagery task (during ideal operation). Patients should quickly learn that they do have control over the system, and that correct task performance provides rewarding feedback. Second, therapists have a means to assess compliance. Therapists can use different means to engage patients, such as by encouraging them if classification accuracy is high or providing advice otherwise.

However, our speculations regarding motivation will require further study. Most BCI rehab studies do not parametrically assess motivation, engagement, or other subjective factors. This is a weakness of the field. Short questionnaires should be employed in future studies to learn more about patients' experiences throughout the process of BCI rehab, along with controls. EEG measures that go beyond motor imagery could further assess patients' engagement. In addition to frontal midline theta activity [11], other signals such as the P300 complex, contingent negative variation (CNV), and other free-running signals could be useful. The resulting information could not only bolster our knowledge of patient engagement but also improve user interaction, such as by providing a warning if a patient doesn't notice a cue to begin a trial.

The tight coupling between task performance and rewarding feedback relies on high classification accuracy. Thus, new research to improve classification accuracy while reducing training time within the context of BCI rehab is important. The relationship between accuracy and functional improvement also merits further study. Unlike ideal operation, many BCI rehab efforts will attain only low or modest accuracy with some users, especially during initial training.

Additional devices: the work presented here has explored several devices that could become common components of future BCI rehab systems. Orthoses, tongue stimulators, peripheral nerve stimulators, different FES systems, and other devices might catalyze improved outcomes. Noninvasive brain stimulation, exoskeletons, advanced treadmills and systems for lower-limb rehab, and (for patients whose need justifies the surgery) invasive sensing and stimulation also merit further research. Upgraded versions of existing devices, such as dry electrodes and smaller, wireless amplifiers, could be combined with these additional devices to reduce preparation time and inconvenience.

Standards and policies: if BCI-based rehab for stroke and/or other conditions moves further toward patient applications, appropriate standardization of both practitioners and systems will be vital to ensure safety, quality, and the lowest risk of accidents. In some cases, existing standards and guidelines are adequate. For example, certification procedures regarding device emissions or claiming to be a licensed physical therapist are already in place and widely followed. In other cases, new or revised standards may be needed. Physical therapists who claim to be experts in BCI stroke rehab might be expected or required to present some certificate or other proof of their expertise, such as completion of a training course and examination. Recommendations for new standards, guidelines, and related framework conditions should be developed in a peer-reviewed paper spanning multiple groups. Implementing these recommendations, as well as other policy issues such as funding, will require engaging policy-makers and involvement of industry, academia, and medicine.

Other patient groups: some of the concepts, methods, and devices used in BCI stroke rehab might be extended to help other patient groups. While this is currently a speculative possibility, it could effectively broaden BCI stroke rehab into ‘BCI rehab’. Persons with other motor disabilities involving the CNS, such as spinal cord injury (SCI) or brain injury, might benefit from BCI motor rehab training for the same fundamental reasons that seem to support CNS improvement in BCI stroke rehab. More broadly, advances in BCI stroke rehab might influence work for persons with different cognitive, psychiatric, and emotional disorders, such as spatial neglect.

These and other research issues should be explored in real-world settings, with matched controls and consideration of different patient features (e.g. time since stroke, stroke location and severity, functional impairment). Developing new methods, devices, systems, policies, and research directions will require strong collaboration between academic, medical, and commercial entities, ideally with further support from national and international funding entities. Although many future directions need to be explored, the recent and ongoing progress reported here, as well as results from other groups, provides modest hope for next-generation therapies that can provide improved recovery for patients.

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