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Post-stroke Rehabilitation of Severe Upper Limb Paresis in Germany – Toward Long-Term Treatment With Brain-Computer Interfaces

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Severe upper limb paresis can represent an immense burden for stroke survivors. Given the rising prevalence of stroke, restoration of severe upper limb motor impairment remains a major challenge for rehabilitation medicine because effective treatment strategies are lacking. Commonly applied interventions in Germany, such as mirror therapy and impairment-oriented training, are limited in efficacy, demanding for new strategies to be found. By translating brain signals into control commands of external devices, brain-computer interfaces (BCIs) and brain-machine interfaces (BMIs) represent promising, neurotechnology-based alternatives for stroke patients with highly restricted arm and hand function. In this mini-review, we outline perspectives on how BCI-based therapy can be integrated into the different stages of neurorehabilitation in Germany to meet a long-term treatment approach: We found that it is most appropriate to start therapy with BCI-based neurofeedback immediately after early rehabilitation. BCI-driven functional electrical stimulation (FES) and BMI robotic therapy are well suited for subsequent post hospital curative treatment in the subacute stage. BCI-based hand exoskeleton training can be continued within outpatient occupational therapy to further improve hand function and address motivational issues in chronic stroke patients. Once the rehabilitation potential is exhausted, BCI technology can be used to drive assistive devices to compensate for impaired function. However, there are several challenges yet to overcome before such long-term treatment strategies can be implemented within broad clinical application: 1. developing reliable BCI systems with better usability; 2. conducting more research to improve BCI training paradigms and 3. establishing reliable methods to identify suitable patients.

Keywords: brain-computer interface, severe upper limb paresis, neurorehabilitation, long-term treatment, neurotechnology

INTRODUCTION

Stroke is a leading cause for long-term disability and often results in poor quality of life (1). In 2017, there were around 260,000 in-patient cases of stroke registered in German hospitals (2). While the incidence in Germany mostly remained constant (3), the probability to survive an acute stroke significantly improved over the last two decades (4). With a growing number of stroke survivors, the number of patients facing post-stroke impairments is increasing. Besides impairments in cognition, speech, mood regulation or sexual function, loss of motor function, especially in the upper extremity, is a severe burden after stroke.

Upper limb impairment occurs in approximately 80% of stroke survivors (5). Here, the initial severity of motor impairment often predicts chances for recovery (6). While there is a good chance for full recovery from mild paresis, this is less likely for severe upper limb paresis (7). In 30–50% of all stroke survivors, the affected arm is still severely impaired 6 months after stroke (8, 9). This group face immense difficulties in performing activities of daily living (ADLs) and must often rely on family support or caregivers (10). Given the rising burden of stroke, there is a pressing need for innovative tools that foster successful restoration of motor function.

REHABILITATION OF SEVERE UPPER LIMB PARESIS

Constraint-induced movement training (CIMT) represents an effective motor intervention in upper limb rehabilitation (11–13). However, as voluntary wrist and finger extension is a minimum requirement for CIMT, it is only applicable in a limited number of stroke patients, usually excluding those with severe upper limb paresis (14). The treatment repertoire for patients with severe motor impairment is small. Classical physiotherapy is often applied as standard therapy. Mirror therapy has shown to improve arm and hand function (13, 15, 16). In mirror therapy, the unimpaired hand is observed in a mirror projected onto the side of the impaired hand. Since such training does not require remaining motor function in the paretic limb, it is recommended as a complementary approach for stroke survivors with severe arm paralysis (17). Arm-BASIS-Training (ABT) is a method of impairment-oriented training that aims at restoring motoric innervation by selectively training specific arm movements (e.g., shoulder joint movements, elbow joint movements, wrist joint movements), exclusively designed for the rehabilitation of severe upper limb paresis (18). In a systematic review by Urton et al. (19), ABT was the only intervention that improved arm mobility in addition to standard physiotherapy, receiving recommendation grade A. The use of external devices (robotics) allows to train movements with high repetition rates which cannot be performed by the patient independently. It was shown that robotic-aided therapy can improve arm function, force and mobility in stroke patients with severe upper limb paresis (20, 21).

While there are well-evidenced motor interventions for mild paralysis, successful rehabilitation of severe upper limb paresis is still an unsolved problem: For classical physiotherapy, evidence of efficacy is not convincing (12, 22, 23). Impairment-oriented training was shown to improve selective arm mobility, but not arm function (18). Robotics-guided therapy is useful in the subacute stage, but there is still a controversy whether also chronic patients benefit from this therapy. Furthermore, it is not clear yet whether it can also improve ADL skills and thus reduce or prevent the necessity of long-term care (24, 25). The same has also not been conclusively clarified for mirror therapy (16, 26). With the lack of standardized and convincing treatment options, there is high demand to find new strategies to restore severe upper limp paresis in stroke survivors.

BRAIN-COMPUTER INTERFACE AND BRAIN-MACHINE INTERFACE

Brain computer interfaces (BCIs) use the modulation of neurometabolic or neuroelectric signals to control external devices (27). By analyzing changes in brain activity, BCI technology can convert the user's intention into control commands of digital devices or tools usually delivering some form of sensory feedback. A sub-form of BCI systems enabling volitional control of machines, e.g., exoskeletons or prostheses, are usually termed brain-machine interfaces (BMIs). The most established BCI paradigms are based on electroencephalography (EEG), due to its low cost and easy handling (28). In BCI and BMI applications for motor rehabilitation, EEG is typically used to record the sensorimotor rhythm (SMR), generated by neuronal cell populations of the sensorimotor cortex (29). During motor attempt or imagination, power of SMR decreases and this modulation, called event-related-desynchronization (ERD), can be translated into a control command for an external device. Since even stroke survivors with severe chronic motor deficits can modulate their SMR (30), and no actual physical movement is required to control BCI-based devices, they represent a promising rehabilitation strategy for stroke patients with severe upper limb paresis.

BCI technology addresses important physiological fundamentals of neurorehabilitation. Based on Hebbian learning principles, such systems can induce neuroplasticity by effectively coupling efferent brains signals to afferent input (e.g., caused by a closing exoskeleton) (31). This way, neural assemblies are activated in an associative manner, strengthening cortical connections, as evidenced by increased motor evoked potentials (MEP) in stroke survivors using a BCI (32). Linking central motor output to peripheral input in real-time closes the sensorimotor feedback loop, which can promote the integration of affected corticospinal connections (33) and foster voluntary motor control (34). Moreover, BCIs improve the ability to activate affected brain areas by visualizing changes in brain activity in real-time (a paradigm termed neurofeedback) (34). This was shown to result in greater involvement of the ipsilesional hemisphere compared to random feedback (35). Apart from influencing neurophysiological parameters reflecting neuroplasticity, BMI applications also showed to induce functional improvement (36–39).

Although BCI-based approaches appear to be promising for upper limb rehabilitation, sufficient evidence for broad clinical application is still lacking and more research is needed. However, conducting studies according to principles of evidence-based medicine (EBM) is often difficult due to the heterogeneity of stroke patients. Further, BCI-based motor therapy involves far more variables than just dose and timing, and double blinding is difficult to implement. Therefore, Coscia et al. (40) suggest investigating BCI applications in personalized longitudinal studies in contrast to randomized controlled trials (RCTs). In such a design, patients receive specific treatment until a functional plateau is reached, before continuing with another intervention. The primary aim of such approach is to improve the individual outcome in patient populations that usually have poor prospects for recovery and rarely show spontaneous remission (40). In this context, it is crucial to find long-term treatment strategies that can be well integrated throughout the different phases of neurorehabilitation. Beyond research, such strategies are of great importance for clinicians who apply BCI-based therapy as early-adopters to expand treatment options. Since BCI-based therapy addresses several aspects of motor learning (neurofeedback, training of repetitive tasks, active behavior in therapy), this provides good reason for early application (41) – especially as there are only few alternatives for restoring severe upper limb paresis in stroke patients.

BCI-BASED LONG-TERM TREATMENT STRATEGIES IN GERMANY

Thanks to its various applications, BCI-based therapy can be embedded in many stages of stroke rehabilitation. Here, based on a literature review, we derived the best strategies to facilitate and accelerate the integration of BCI-based therapy into the German process of neurorehabilitation. We include studies that assess the impact of BCI-based interventions on motor recovery of stroke patients with severe upper limb paresis, either in the subacute (<6 months) or chronic stage (>6 months). Study outcomes were either functional scores and/or neurophysiological parameters. Case studies and studies with small sample size (<10 participants) were not included. In Germany, the process of neurological rehabilitation is divided into 6 phases (A to F): Phase A represents the emergency care on a stroke unit, followed by phase B which is equivalent to early rehabilitation. In Phase C, patients can actively participate in rehabilitation interventions, however, there is still high demand for medical treatment. In Phase D, patients receive medical rehabilitation in specialized rehabilitation centers (Phase D), which corresponds to the concept of post hospital curative treatment. In Phase E, outpatient occupational reintegration is pursued and, in case long-time care is necessary, Phase F is initiated to support and maintain function (42).

In acute care and early rehabilitation (Phase A and B), BCI-based applications often cannot be applied due to patient's reduced vigilance and impaired cooperativity (43). However, as soon as active participation is possible (Phase C), BCI-based training can be started. At the beginning, it is advisable to familiarize patients with BCI technology by providing neurofeedback on SMR modulation related to motor imagery (MI). As shown by Pichiorri et al. (35) and Mihara et al. (44), BCI assisted neurofeedback on MI can contribute to functional recovery and enhance neural connectivity on the affected brain hemisphere in subacute stroke patients. Compared to visual feedback, somatosensory and/or proprioceptive feedback seems advantageous in rehabilitation (45). Furthermore, daily MI-based neurofeedback training has been shown to improve SMR control (46), facilitating the control of BMI motor interventions later on. Since patients do not have to be mobilized for neurofeedback training, this can be applied on bedside, increasing accessibility. In phase C, the patient's state of health is often still unstable, and exhaustion caused by intensive motor therapy could do more harm than good.

Although there are no RCTs comparing early vs. late onset, a general recommendation is that the earlier motor interventions start, the better (17). Thus, BCI therapy should advance once SMR control is well established, and the patient's clinical condition allows. In a next step, EEG-based BMI systems can be used to control robotic therapy devices to effectively link repetitive exercise training with cortical motor output. Ang et al. (36) showed that such a BMI system coupled with the MIT-Manus, a robotic arm that initiates and guides upper limb movements, enhances arm and hand function in stroke patients with severe upper limb paresis. It was reported that such therapy is well tolerated by patients and no adverse effects occur, making it an effective and safe method for upper limb rehabilitation. As BMI robotic training requires expensive equipment and specialized staff, it seems best to apply such therapy in specialized rehabilitation centers (Phase D). Here, subacute stroke patients come together in large numbers, guaranteeing maximum capacity utilization and effective use. Besides brain controlled robotic therapy, BCIs can be applied for exoskeleton control and FES. Exoskeletons are portable devices that support or completely imitate movement, while FES uses electrical pulses to stimulate muscle contractions, enabling the movement of paralyzed limbs. Biasiucci et al. (37) showed that BCI-driven FES can reduce severe upper limb impairment in subacute stroke patients. Most notably, functional improvement prevailed 6 months after therapy, making it a promising strategy for a curative treatment approach (Phase D).

There are good reasons to continue BCI therapy in chronic stroke patients that already showed some degree of motor recovery. In patients with initial hemiparesis but returning arm control, EEG-based hand exoskeletons can be used to restore hand function. It was shown that the application of a BCI-driven hand exoskeleton in chronic stroke patients reduces complete finger paralysis (39), improves grip function (47) and results in an increased use of the paralyzed hand in ADL tasks (48). A major advantage of BCI-based exoskeleton control is that it allows patients to perform grasping movements with their paralyzed hand and enables them to perform bimanual tasks in training sessions (e.g., eating with cutlery), counteracting the learned non-use of the paralyzed limb. The high relation of such exercises to everyday life situations promotes patient's motivation to continue therapy. This is especially important as depression and reduced drive are severe complications following stroke (49). Considering the reduced effort needed in comparison to robotic-guided therapy, the applicability in chronic patients and the practicability in bimanual tasks, BMI hand exoskeleton training is well suited for outpatient occupational therapy (Phase E). This way, a continuous treatment is pursued even after medical rehabilitation (Phase D) is completed.

In case no sufficient improvement can be achieved, nursing or family care (Phase F) is often unavoidable for patients with remaining severe upper limb impairment. Although the rehabilitative potential might be exhausted in these cases, the BCI approach can be used to compensate for lost function by controlling assistive devices, e.g., exoskeletons or robotic prostheses (assistive BCIs). Bundy et al. (50) have demonstrated the feasibility of a BCI-based hand exoskeleton for home use in chronic stroke patients, using EEG signals of the unaffected hemisphere. Applied in a home-based setting, assistive BCIs allow patients to perform important ADLs such as eating and drinking independently (51). This way, patients become less reliant on family or caregiver support and can regain quality of life.

CURRENT CHALLENGES AND LIMITATIONS

Attaching and calibrating BCI systems currently requires the support of specially trained personnel and takes considerable amount of time (52). Since time is a scarce commodity in clinical practice, preparation for BCI-based therapy must become quick and easy, e.g., through intuitive graphical user interfaces and fast automatic calibration systems. For assistive BCIs applied in a home-based setting, the need of a supervisor contradicts the idea of giving back independency. Although improvements have been made to enhance practicability by implementing veto commands (53), establishing hybrid control paradigms (54) and developing user-friendly EEG systems (55, 56), assistive BCI systems that can be applied by the user without any external help are still missing. Another drawback of BCI-based interventions lies in the high acquisition costs of the technical devices. BCI-based therapy must yet prove its clear effectiveness to justify the high expenses, otherwise it will not find entrance in clinical practice. Consequently, efforts need to be made to drive technical development, lower cost of production and conduct studies that thoroughly investigate the benefit of BCI technology (33).

BCIs can fail to detect modulation of brain activity in up to 20% of individuals (57). While some speak of BCI-illiteracy, Vidaurre et al. (58) showed that machine learning approaches can considerably reduce the number of BCI "illiterates." This should encourage researchers to improve BCI classification and paradigms rather than to attribute the fault to the user (59). Current training approaches for brain modulation often seem inappropriate, e.g., lacking clear instructions, specific learning objectives and meaningful feedback. This affects BCI robustness and requires new training procedures (60). Stroke patients in particular may have difficulty modulating their cortical activity due to the brain lesion, potentially leading to frustration when trying to control BCI-based devices (61). In this context, it may be advantageous to individually adapt session time of BCI-based therapy since fatigue and lack of concentration can affect BCI control substantially (62, 63). While heart rate variability (HRV) (64) and task-related theta-band activity (65) have been proposed as possible biomarkers to monitor patient's mental capacity during BCI sessions, there is still much work needed to establish parameters that reliably anticipate mental workload and fatigue. Overall, more research assessing user experience with BCIs needs to be conducted, especially considering hedonic quality aspects such as motivation and frustration since they play an important role in stroke rehabilitation (66). Also, neuroplasticity mechanisms induced by BCI-based application need to be better understood, with regards to so far less studied aspects such as wide-spread neural networks and cortical excitability (67, 68).

For motor interventions to be most effective, it has been suggested to move from a "one-fits-all" approach toward customized rehabilitative interventions (69). In this context, identification of stroke patients that will benefit most from BCI therapy needs to be realized. So far, it has been shown that functional connectivity assessed by functional magnetic resonance imaging (fMRI) predicts motor recovery and outcome of sensorimotor function scores (70, 71). In this light, it may be reasonable to use fMRI to determine patient's potential for motor recovery and his/her eligibility to benefit from BCI therapy (33). Sannelli et al. (72) suggested to group BCI users according to their calibration and feedback performance to select subjects and allow customized training. Overall, however, it is not yet possible to precisely estimate how many stroke survivors can directly benefit from BCI-based therapy. Only largescale, longitudinal clinical studies will provide the necessary data to infer the underlying mechanisms of BCI-related recovery and to identify predictors of individual BCI-training response.

CONCLUSIONS

With its capability to advance motor recovery, BCI-based motor interventions provide a good argument to be implemented in stroke rehabilitation in Germany. BCI-based neurofeedback training is well suited to promote neural and functional recovery in early rehabilitation. BCI-based motor interventions showed efficiency in both subacute and chronic stroke patients, making them suitable for post hospital curative treatment and outpatient occupational therapy. Once a plateau in motor recovery is reached, assistive BCI-based devices can be applied in a home setting to improve quality of life. Put together, BCIs represent a promising approach for long-term treatment of severe upper limb paresis in stroke patients. Nevertheless, there are still some obstacles to overcome before BCI-based therapies can be applied in routine clinical practice.

AUTHOR CONTRIBUTIONS

CA and SRS conceived the topic. CA conceptualized the manuscript. CA took the lead in writing the manuscript and was supported by AC, MV, VH, and SRS. All authors provided critical feedback and helped shape the research idea and manuscript, reviewed the results, and approved the final version of the manuscript.

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