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Brain–machine interfaces in neurorehabilitation of stroke

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ABSTRACT

Stroke is among the leading causes of long-term disabilities leaving an increasing number of people with cognitive, affective and motor impairments depending on assistance in their daily life. While function after stroke can significantly improve in the first weeks and months, further recovery is often slow or non-existent in the more severe cases encompassing 30–50% of all stroke victims. The neurobiological mechanisms underlying recovery in those patients are incompletely understood. However, recent studies demonstrated the brain's remarkable capacity for functional and structural plasticity and recovery even in severe chronic stroke. As all established rehabilitation strategies require some remaining motor function, there is currently no standardized and accepted treatment for patients with complete chronic muscle paralysis. The development of brain–machine interfaces (BMIs) that translate brain activity into control signals of computers or external devices provides two new strategies to overcome stroke-related motor paralysis. First, BMIs can establish continuous high-dimensional brain-control of robotic devices or functional electric stimulation (FES) to assist in daily life activities (*assistive* BMI). Second, BMIs could facilitate neuroplasticity, thus enhancing motor learning and motor recovery (*rehabilitative* BMI). Advances in sensor technology, development of non-invasive and implantable wireless BMI-systems and their combination with brain stimulation, along with evidence for BMI systems' clinical efficacy suggest that BMI-related strategies will play an increasing role in neurorehabilitation of stroke.

1. Introduction

Stroke is the leading cause of disability worldwide (Lopez et al., 2006). The global burden of stroke reflecting the total number of stroke survivors and loss of disability-adjusted life years (DALY) is increasing, with most of the burden in low- and middle-income countries (Feigin et al., 2014). At the same time, the number of people that depend on assistance in their daily life has drastically increased and will further accumulate in the coming decades due to demographic factors (Birbeck et al., 2014). Besides disturbances in the cognitive and affective domains, loss of motor function represents the heaviest burden of disease after stroke. While acute loss of motor function can significantly improve in the first months after stroke, further recovery is often slow or non-existent (Langhorne et al., 2011). The neurobiological reasons for this slowdown are incompletely understood and subject of intensive investigation (Burke and Cramer, 2013; Buma et al., 2013).

Currently, three main mechanisms are thought to contribute to stroke recovery. The first mechanism relates to the reduction in edema and a process termed diaschisis, i.e. a sudden loss in function with reduced blood flow and metabolism of brain areas connected to an irreversibly damaged injury core that may in part reverse in the early phase after stroke (Feeney and Baron, 1986). The second mechanism relates to functional recovery due to compensation (Lang et al., 2006; Cirstea and Levin, 2000) based on improved use and refinement of remaining motor functions. The third postulated mechanism assumes "real" recovery, i.e. restoration of lost brain functions due to homeostatic and learning-dependent reorganization of the brain (Nudo and Milliken, 1996). To different degrees, the latter two mechanisms involve or may lead to changes in neurotransmitter concentrations, neuro- and synaptogenesis, dendritic branching and axonal sprouting (Buma et al., 2013). This makes interpretation of neurophysiological or neuroimaging measures that strive for a strict differentiation of these different mechanisms and their dynamic interaction across stroke recovery rather challenging.

The conventional clinical wisdom used to be that by six months to a year after stroke, the potential for recovery has substantially diminished

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(an opinion reflected in many health insurance policies). This view was challenged by a meta-analysis providing an evidence base for stroke rehabilitation even in the "chronic" stage of stroke (Teasell et al., 2014). Clinical studies showed that e.g. constrained induced movement therapy (CIMT) can be effective even in the rehabilitation of chronic stroke (Sirtori et al., 2009). In CIMT, the healthy arm is constrained, which forces the patient to use the non-used paralyzed limb (Taub et al., 2002). The success of such a strategy indicates that the degree of neural plasticity and motor learning does not entirely depend on the time after stroke, but depends in large part on learning and environmental conditions.

However, many stroke survivors (about 30–50%) do not qualify for CIMT (Wolf et al., 1989; Taub et al., 1999) as it requires remaining residual movement. For these patients, there is currently no standardized or accepted treatment strategy.

Recent advances in neurotechnology have led to the development of brain–computer or brain–machine interfaces (BCIs/BMIs) that translate electric, magnetic or metabolic brain activity into control signals of computers or machines, e.g. neuroprosthetic or robotic devices (Venkatakrishnan et al., 2014). Recent studies suggest that BMIs will become an important component of several new strategies that strive to overcome severe stroke-related motor impairments.

2. Brain–machine interfaces (BMIs)

Currently, there are two main strategies pursued to restore function after stroke using BMIs. The first strategy aims at bypassing non-functional cortico-spinal pathways to allow for continuous and permanent control of robotic devices (Collinger et al., 2013) or functional electric stimulation (FES) of paralyzed muscles (Moritz et al., 2008; Pohlmeyer et al., 2009; Ethier et al., 2012; McGie et al., in press; Pfurtscheller et al., 2003). By substituting for lost motor functions, such *assistive BMIs* have demonstrated recovery of versatile motor control in daily life activities (Hochberg et al., 2006; Collinger et al., 2013). The second strategy aims at facilitation of neuroplasticity and motor learning to enhance motor recovery (*rehabilitative BMIs*) (Dobkin, 2007; Soekadar et al., 2011a) (Fig. 1a).

While deriving from different research traditions, both strategies probably involve the same neural mechanisms for BMI learning and control, mainly operant conditioning and feedback learning independent of the invasiveness of the approach and both involve the cortico-striatal loop (Koralek et al., 2012). In non-invasive BMIs, six types of brain signals have been tested: 1. sensori-motor rhythms (SMR, 8–15 Hz, also termed rolandic alpha or mu-rhythm depending on the context) (McFarland et al., 1993, 2006; Pfurtscheller et al., 2006; Soekadar et al., 2011a, in press-a), 2. slow cortical potentials (SCP) (Birbaumer et al., 1999), 3. event-related potentials (ERPs) (Farwell and Donchin, 1988) and 4. steady-state visually or auditory evoked potentials (SSVEP/SSAEP) (Sakurada et al., 2013), 5. blood-oxygenation level dependent (BOLD)-contrast imaging using functional MRI (Weiskopf et al., 2003), and 6. concentration changes of oxy/deoxy hemoglobin using functional near-infrared spectroscopy (fNIRS; Sitaram et al., 2009; Mihara et al., 2013; Rea et al., 2014). Implantable BMIs, in contrast, require surgical implantation of epidural, subdural, or intracortical electrode arrays. In order to make assistive BMIs reliable in daily life environments, stable decoding of brain activity for controlling a high degree-of-freedom (DOF) output is necessary, an issue currently only achievable using invasive recordings. Implantable BMIs have successfully used local field potentials (LFPs) inside the cortex (Hwang and Andersen, 2009; Flint et al., 2013) or on the surface (Leuthardt et al., 2004; Schalk et al., 2008; Wang et al., 2013) and action potentials (spikes) (e.g., Taylor et al., 2002; Serruya et al., 2002; Carmena et al., 2003).

The first clinically relevant assistive BCI was used by patients suffering from locked-in syndrome, a condition in which patients are awake and cognitively aware of their environment, but unable to move or to speak. An EEG-based BCI translated purposeful modulation of SCP into binary selections of letters or words on a screen (Birbaumer et al., 1999, 2014). Recently, such system was successfully used in a tetraplegic patient with brainstem stroke (Sellers et al., 2014). While restoration of communication was the only relevant BMI application for a long time, the impact and relevance of both non-invasive and implantable assistive BMIs for restoration of movement were negligible. However, recent demonstrations of reliable control of a robotic arm after intracortical electrode array implantation allowing tetraplegic individuals, e.g. after brain stem stroke, to perform skillful and coordinated reaching and grasping movements (Hochberg et al., 2012; Collinger et al., 2013) generated considerable enthusiasm (see video demonstrations 1 & 2). Still, surgical implantation of hardware entails relatively low but substantial risk of infection and hemorrhage that many stroke survivors may not be willing to accept. At the same time, hybrid systems merging EEG with other biosignals, e.g. electrooculograms (EOG) and electromyograms (EMG) (Millán et al., 2010), termed brain/neural computer interaction (BNCI) systems, have provided some remarkable examples of restored motor function, e.g., driving a wearable

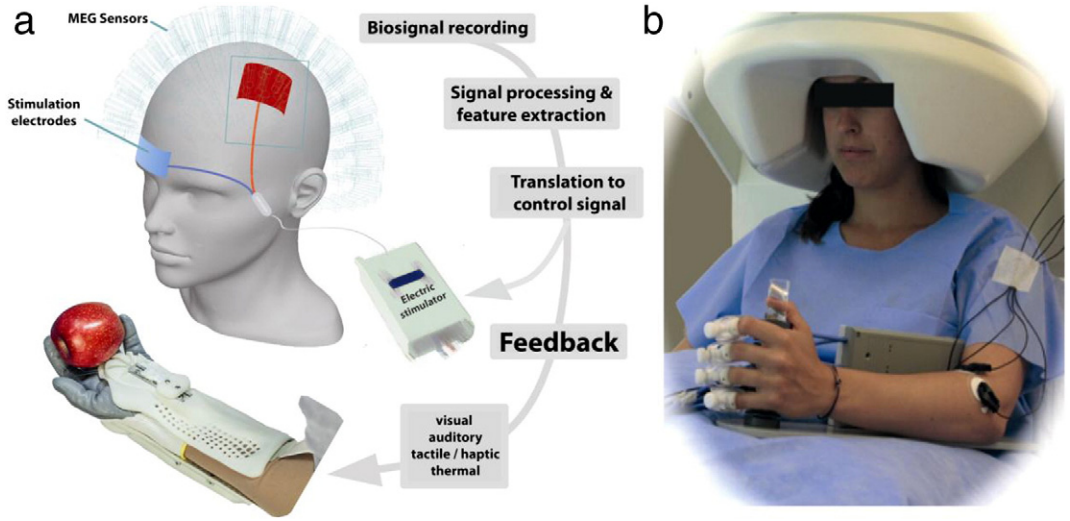

Fig. 1. a: Illustration of a brain–machine interface (BMI) system for stroke neurorehabilitation training. Bio-signals associated with attempted movements of the paralyzed hand and fingers are translated into online feedback and/or brain-state dependent transcranial electric stimulation to augment neuroplasticity facilitating motor recovery. b: Illustration of the setup used in Soekadar et al. (in press-b) to investigate Hebbian learning to control brain oscillatory activity.

exoskeleton opening and closing the paralyzed hand and fingers (Soekadar et al., in press-a) to perform activities of daily living (ADLs).

These impressive demonstrations suggest that assistive BMIs will become a realistic option to improve living conditions of patients with paralysis once the associated costs and risks of these systems can be balanced with long-term benefits for the patients.

The theoretical concept of *rehabilitative* BMIs, also termed *biofeedback* or *restorative* BMI (Soekadar et al., 2011a), is based on the early work of Barry Sterman et al. (1969), and postulates that operant conditioning of neural activity can alter behavior. Sterman showed that operant conditioning of sensorimotor rhythms (SMRs) in patients with severe epilepsy can reduce frequency of grand-mal seizures (Sterman and Macdonald, 1978). The relevance for other neurological and psychiatric disorders of such approach was later demonstrated in controlled clinical studies, e.g. for attention deficit and hyperactivity disorder (Lubar and Shouse, 1976; Monastra et al., 2005; Strehl et al., 2006) or depression (Linden et al., 2012).

3. BMIs in stroke neurorehabilitation

An early case study suggested that operant conditioning of ipsilesional SMR may be beneficial after stroke (e.g., Rozelle and Budzynski, 1995). Further studies indicated that ipsilesional cortical function early after stroke predicted subsequent motor recovery (Platz et al., 2002; Calautti et al., 2010). Motivated by these results as well as previous work by Basmajian (1981), Basmajian et al. (1982), Birbaumer and Cohen (2007) developed a SMR-based BMI enabling severely affected stroke patients to control an orthotic device and thereby open or close their paralyzed hand. This system provided immediate sensory feedback contingent upon their ipsilesional brain activity (Buch et al., 2008). They hypothesized that by re-establishing contingency between ipsilesional cortical activity related to motor planning of, or attempted execution of, finger movements and proprioceptive (haptic) feedback, such a BMI might strengthen the ipsilesional sensorimotor loop and foster neuroplasticity that facilitates motor recovery (Dobkin, 2007; Birbaumer and Cohen, 2007). The hypothesized mechanism behind such plasticity involves simultaneous activation of inputs and outputs to motor cortices, thus triggering Hebbian plasticity (Fig. 2). Other groups have also tried BMI without haptic feedback using SMR as a method to monitor and train motor imagery (Prasad et al., 2010). The mechanism by which such BMIs might improve motor function is less clear, possibly involving attempts to return brain activity "closer to normal" (Daly and Wolpaw, 2008).

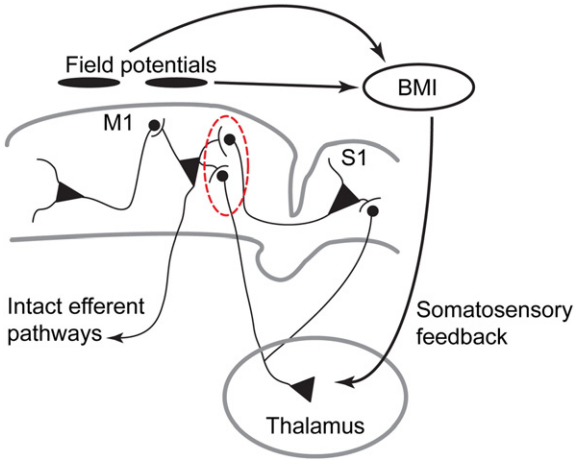

Fig. 2. Schematic of hypothesized mechanism of plasticity generated using a BMI. Brain signals (field potentials) are used by the BMI to control a prosthetic device or neuromuscular stimulation, which provides somatosensory feedback to primary motor cortex (M1) via both somatosensory cortex (S1) and direct thalamic input. The simultaneous activation of presynaptic inputs to M1 with postsynaptic M1 activation causes Hebbian potentiation analogous to spike-timing dependent plasticity.

Although known for many decades, the functional role of sensorimotor cortex oscillations is still not well understood. While generated by LFP within the motor cortical areas of non-human primates (Sanes and Donoghue, 1993), SMR and beta rhythms showed no specific contingency to an actual motor output suggesting a functional relatedness with rather unspecific sensorimotor integration (Murthy and Fetz, 1996). But due to its relatedness to motor activity, accessibility by EEG and high signal-to-noise ratio, SMR seemed an ideal candidate for non-invasive BMI-training in stroke neurorehabilitation (Soekadar et al., 2011a,b).

An initial study indicated that the majority of chronic stroke patients can learn to control ipsilesional SMR (Buch et al., 2008), but a few weeks of training did not result in any significant motor function improvement or generalization of the skill into activities of daily living. However, daily BMI training coupled with goal-directed behavioral physical therapy over a longer period led to remarkable improvements of motor and cognitive capacities of a stroke survivor with severe chronic paralysis after a thalamic hemorrhage (Broetz et al., 2010) as measured by the Fugl-Meyer Assessment (FMA), Wolf Motor Function Test (WMFT) and Goal Attainment Score (GAS). While the participant was unable to use his hand or arm for any relevant activities of daily living and entirely depended on assistance for personal hygiene and dressing, all parameters of motor function improved over the course of the training. Furthermore, the patient became independent of any walking aid or assistance for personal hygiene, and concentration and attentiveness improved significantly. A longitudinal fMRI study indicated that clinical improvements were associated with an increased activation of the ipsilesional hemisphere (Caria et al., 2011). Another study that applied combined BMI and functional electric stimulation (FES) of paralyzed finger muscles in a chronic stroke survivor reported restored individual finger extension (measured as degrees of isolated index finger joint extension) after nine sessions (Daly et al., 2009; Wang et al., 2010). Encouraged by these findings, a larger clinical trial with 32 chronic stroke survivors without residual finger movements (12.22 ± 1.51 out of 54 points according to a combined hand and modified arm FMA, cFMA, indicating severe upper-limb motor impairment) was conducted and showed that motor improvements after 20 sessions of ipsilesional BMI training combined with goal-directed behavioral physiotherapy were superior to motor improvements in a sham BMI-group who received random BMI-feedback (Ramos-Murguialday et al., 2013). cFMA improvements in the BMI-group were associated with changes in fMRI laterality index and paretic hand EMG activity. Importantly, neurophysiological assessment indicated that motor recovery was correlated with the presence of upper-limb motor evoked potentials (MEPs) elicited from the ipsilesional hemisphere (Brasil et al., 2012), underlining the importance of the descending corticospinal tract's integrity for training-related recovery (Jung et al., 2012). Integrity of the ascending sensory pathways showed similar relevance for successful BMI control and learning (Shaikhouni et al., 2013). A more recent clinical study comparing conventional robot-assisted therapy with BMI-controlled robotic training in chronic stroke survivors found similar results (Ang et al., in press). While patients improved under both training conditions, re-assessment of motor function three months later indicated that more participants in the BMI-training group attained motor gains (as measured by FMA) than in the group that received conventional robot-assisted training. Other less controlled studies with smaller samples further corroborate this finding (Várkuti et al., 2013; Mukaino et al., 2014).

While these first results need confirmation through larger clinical trials, the reported outcomes are remarkable and underline the capacity of chronic stroke patients with severe motor deficits to regain motor function under effective learning conditions. As some of the reported studies included individuals with residual voluntary motor function, it is unclear how much residual function and motor pathway connectivity are needed for improved rehabilitation outcomes. Also, many

commonly used instruments for clinical evaluation of motor function after stroke are not optimal for assessing motor recovery after severe forms of stroke as they cannot reliably differentiate minimal residual hand function (Broetz et al., 2014). This may in part explain the heterogeneity in clinical tests that were used to investigate efficacy of BMI in neurorehabilitation of stroke making direct comparisons between study results difficult (for overview see Table 1).

Based on the same principle as MEG/EEG-based BMI training, real-time fMRI (rt-fMRI) and fNIRS neurofeedback have also been used to increase the activity of ipsilesional motor cortical areas (Sitaram et al., 2012; Mihara et al., 2013). Allowing feedback of deeper brain structures, e.g. dopaminergic mid-brain regions, rt-fMRI may become an effective non-invasive tool to study the role of sub-cortical brain structures in the context of stroke recovery (Sulzer et al., 2013). Also, multisite rt-fMRI BMI feedback could be used to increase the connectivity between functionally associated brain regions (Ruiz et al., 2014).

While the majority of stroke patients, particularly those with subcortical lesions, were able to learn SMR-based BMI control (Buch et al., 2008, 2012), such BMI learning is often slower after stroke compared to healthy controls (Soekadar et al., 2011b). Thus, development of strategies aiming at enhancement of BMI learning may further increase applicability of BMI training protocols for stroke neurorehabilitation. A particularly promising tool in this context is the application of non-invasive brain stimulation (NIBS) (Dayan et al., 2013; Liew et al., 2014).

4. Combination of BMIs and brain stimulation in neurorehabilitation of stroke

While it was shown that the application of electric currents to the brain can modulate mood, cognition and behavior, only the recent development of neurophysiological and neuroimaging tools allows systematic investigation of the mechanisms underlying these effects (Bolwig, 2014). Besides invasive stimulation techniques, such as deep brain stimulation or motor cortex stimulation, non-invasive forms of brain stimulation (NIBS), including transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) are increasingly used (Liew et al., 2014) and their effects on brain physiology are being investigated (Dayan et al., 2013). For instance, it was shown that tDCS, i.e. the application of weak electric direct currents (DC) of 1–2 mA through saline soaked sponges or electrodes, can improve learning and consolidation throughout different domains (Reis et al., 2008; Marshall et al., 2004). When applied over the ipsilesional motor cortex of chronic stroke patients, reaction time and pinch force of the affected hand improved (Hummel et al., 2006). Similarly, facilitatory repetitive TMS (rTMS) applied to the ipsilesional hemisphere (Khedr et al., 2010) and inhibitory rTMS targeting the contralesional hemisphere (Takeuchi et al., 2005) or their combination (Sung et al., 2013) showed effects on motor functions in stroke, but more studies with larger sample sizes are needed (Hao et al., 2013).

Recently, it was shown that tDCS can enhance learning to control an SMR-based BMI (Soekadar et al., in press-b). In this study, healthy participants engaged in SMR-BMI control directly after receiving 20 min of anodal or cathodal tDCS over their primary motor cortex (M1) (Fig. 1b). After one week of daily training, improvement of SMR control was superior in those participants who received anodal tDCS compared to those who received cathodal or sham stimulation. One month after the end of the training, the newly acquired skill remained superior in the group that received anodal tDCS.

Several studies indicated that timing of tDCS relative to training can influence stimulation effects (Pirulli et al., 2013; Stagg et al., 2011; Galea and Celnik, 2009; Volpato et al., 2013). Thus, development of new strategies allowing for simultaneous or state-dependent brain stimulation during BMI control promised to improve applicability and effectiveness of BMI training protocols in patients with brain lesions. Recently, successful combination of simultaneous tDCS and EEG-based BMI control was demonstrated (Soekadar et al., 2014). However, this setup allows placing the stimulation electrode only as close as 1 cm near the EEG electrode used for BMI control to avoid direct contact resulting in amplifier saturation by stimulation currents entering the EEG system. This limits the possibility of applying electric currents near electrodes used for BMI control. Another strategy, however, uses neuromagnetic brain signals (MEG) that can pass through the stimulation electrode. This new strategy allows for in vivo assessment of neuromagnetic brain oscillations in brain regions immediately underneath the stimulation electrode (Soekadar et al., 2013a). Soekadar et al. (2013b) showed for the first time that a BMI utilizing SMR of the primary motor cortex (M1) could control an orthotic device while this region, the ipsilesional M1 of a chronic stroke survivor without residual movements, underwent anodal tDCS (Fig. 1a). This new strategy may lead to the refinement of existing stimulation protocols to improve their effectiveness and shed light on the relationship between brain physiology, cognition and behavior.

5. Current challenges and future developments

Thus far, almost all BMIs used for rehabilitation of stroke have been non-invasive. Yet having provided remarkable results, non-invasive measures limit the possibility to use brain signals from small generator volumes that oscillate at high frequencies due to the distance of the electrodes or sensors from the signal source. While low-frequency rhythms, such as SMR, showed limited correlation and contingency with intended movements (Schalk et al., 2007; Mehring et al., 2004; Stark and Abeles, 2007; Flint et al., 2012a), decoding of high gamma band and action potentials (single- or multi-unit) (Mehring et al., 2004; Stark and Abeles, 2007; Flint et al., 2012b) allowed for control of high degree of freedom prosthetic limbs (Hochberg et al., 2012; Collinger et al., 2013) or FES (Ethier et al., 2012).

Since the basis for neural plasticity in BMIs is hypothesized to be Hebbian plasticity involving simultaneous activation of pre- and post-synaptic neurons (Fig. 2), this contingency may be critical to driving functional connectivity optimally. Therefore, the use of other brain signals, such as high gamma/broadband power (70 to ~300 Hz) may prove equally or even more effective than lower frequency signals such as SMR. Recently, it was shown that high gamma signals can be used to decode highly fractionated movements, for example in biomimetic BMIs (Flint et al., 2013). Such signals are most effectively obtained using invasive recordings with intracortical, subdural or epidural electrodes (Mehring et al., 2004; Stark and Abeles, 2007; Zhuang et al., 2010; Slutzky et al., 2010, 2011; Flint et al., 2014). While intracranial electrodes require implantation, epidural or subdural electrodes could ultimately be implanted through a burr hole instead of a craniotomy reducing the perioperative risk and cost.

A substantial barrier here is the lack of fully implantable (and ideally, wireless) intracranial devices. One helpful development may be the recent approval of a recording and stimulation system for epilepsy (Heck et al., 2014), although this device only uses a small number of electrodes for recording. Once fully internalized systems are available, the risk–benefit ratio may change considerably. Similarly, as non-invasive brain recording technology advances, other means of providing comparable functional improvement without surgery may change the risk–benefit ratio. Ultimately, the decision to implant and apply such BMI system will be highly individual and dependent upon the patient's circumstances.

A recent study showed effective use of an implantable neural interface to bridge damaged neural pathways to restore function and promote recovery after brain injury in a rat model (Guggenmos et al., 2013). In this study, the primary motor cortical area of a rat was injured leading to a disruption of communication between motor and somatosensory areas. An implanted neural prosthesis translated action potentials in premotor cortex into contingent electrical stimulation in somatosensory cortex. After continuous application over 2 weeks,

Table 1
Clinical studies that investigated brain–machine interfaces (BMIs) in stroke neurorehabilitation. Only those studies are listed that assessed motor function or electromyographic (EMG) activity before and after BMI training. EEG: electroencephalography, MEG: magnetoencephalography, fNIRS: functional near-infrared spectroscopy, fMRI: functional magnetic resonance imaging, EMG: electromyography, SMR: sensorimotor rhythm, ERD: event-related desynchronization, FES: functional electric stimulation, rBSI: revised brain symmetry index, LI: laterality index, FCC: functional connectivity correlate, FMA: Fugl-Meyer Assessment, cFMA: combined hand and modified arm FMA, MAL AOU: Motor Activity Log Amount of Use, TUG: Timed Up and Go test, SIAS: Stroke Impairment Assessment Set, ARAT: Action Research Arm Test, HWC: Holden Walking Classification, MAS: Motor Assessment Scale for stroke, 9-HPT: 9 Hole Peg Test, WMFT: Wolf Motor Function Test, GAS: Goal Attainment Score, GS: grip strength, MRC: Medical Research Council Scale for Muscle Strength, MI: motor imagery, ME: motor execution.

Study	Number of stroke patients included	Stroke severity at inclusion	BMI methodology	Feedback	Clinical scores/neurophysiological measures
Ang et al. (in press) (upper extremity)	n = 11 n = 15	*Moderate to severe* FMA: 26.4 ± 14.8 (out of 66)	EEG (SMR, beta), MI	Visual, proprioceptive/haptic (robot)	FMA, rBSI
Ono et al. (2014) (upper extremity)	n = 6 n = 6	*Severe* SIAS finger score: 0–1 (out of 5)	EEG (SMR), ME	Visual, proprioceptive/haptic (orthosis)	EMG activity, ERD
Young et al. (2014) (upper extremity)	n = 8 n = 6	*Mild to severe* ARAT: 23.71 ± 25.68 (out of 57)	EEG (SMR, beta), ME	Visual, FES-related muscle contraction	Stroke Impact Scale, ARAT, 9-HPT, LI, fMRI
Ramos-Murguialday et al. (2013) (upper extremity)	n = 16 n = 16	*Severe* cFMA: 12.15 ± 8.8 (out of 54)	EEG (SMR), ME	Visual, proprioceptive/haptic (orthosis)	FMA
Mihara et al. (2013) (upper extremity)	n = 10 n = 10	*Severe* FMA_{hand}: <5.0 (out of 12)	fNIRS, MI	Visual	FMA, ARAT
Várkuti et al. (2013) (upper extremity)	n = 6 n = 3	*Moderate to severe* FMA: 22.57 ± 15.2 (out of 66)	EEG (SMR, beta), MI	Visual, proprioceptive/haptic (robot)	FMA, FCC based on fMRI
Takahashi et al. (2012) (lower extremity)	n = 1	*Severe* SIAS foot tap score: 0–1 (out of 5)	EEG (beta), ME	Visual, FES-related muscle contraction	EMG activity, maximum range of motion (ROM)
Shindo et al. (2011) (upper extremity)	n = 8	*Severe* SIAS finger test: 1a–2 (out of 5)	EEG (SMR), MI	Visual, proprioceptive/haptic (orthosis)	SIAS, MAL AOU, MAS
Caria et al. (2011) (upper extremity)	n = 1	*Severe* FMA: 13.0 (out of 66)	EEG/MEG (SMR), MI	Visual, proprioceptive/haptic (orthosis)	FMA
Broetz et al. (2010) (upper extremity)	n = 1	*Severe* FMA: 13.0 (out of 66)	EEG/MEG (SMR), MI	Visual, proprioceptive/haptic (orthosis)	FMA, WMFT, Ashworth Scale, GAS
Ang et al. (2010) (upper extremity)	n = 11 n = 14	*Severe* FMA: 14.9 (out of 66)	EEG (SMR, beta)	Visual, proprioceptive/haptic (robot)	FMA
Prasad et al. (2010) (upper extremity)	n = 5	*Mild to severe* ARAT: 22.6 ± 22.6 (out of 57)	EEG (SMR), MI	Visual	ARAT, GS, motoricity index, 9-HPT
Sun et al. (2011) (lower extremity)	n = 20	*Moderate to severe* HWC: 2.5 ± 0.51 (out of 6)	EEG (SMR, beta), MI	Visual	HWC, Berg Balance Scale
Ang et al. (2009) (upper extremity)	n = 6 n = 7	*Moderate to severe* FMA: 29.7 (out of 66)	EEG (SMR, beta), MI	Visual, proprioceptive/haptic (robot)	FMA
Daly et al. (2009) (upper extremity)	n = 1	*Moderate to severe* Volitional partial movement of mass finger and thumb extension, no isolated finger movement	EEG (SMR), MI	Visual, FES-related muscle contraction	Degrees of isolated finger extension
Buch et al. (2008) (upper extremity)	n = 8	*Severe* Finger extension weakness rated as 0 out of 5 on the MRC scale	MEG (SMR), MI	Visual, proprioceptive/haptic (orthosis)	MRC

reaching and grasping functions have improved to a degree indistinguishable from pre-lesion levels. Similarly, ECoG signals could be linked to direct stimulation of the spinal cord's anterior horn (Nishimura et al., 2013), e.g. in rehabilitation of sub-cortical stroke.

Although there is increasing evidence for the efficacy of BMI-related tools to improve rehabilitation strategies in stroke or other neurologic disorders, more and larger clinical studies are needed. In particular, it is critical to investigate the underlying mechanisms of BMI-induced functional recovery. For example, does such functional improvement result from functional or structural brain reorganization, or is it merely due to compensatory mechanisms? Understanding the mechanisms of recovery could also lead to identification of biomarkers that could predict treatment response (e.g., Buch et al., 2012; Brasil et al., 2012). In addition, as true with most rehabilitative paradigms, the optimal dosage (frequency and intensity) of BMI training needs to be investigated. Advances in the field of telerehabilitation allowing for monitoring physiological parameters and treatment course may facilitate application of BMIs in home-based rehabilitation programs. In cases in which ipsilesional BMI training is not feasible due to the absence of brain signals to be trained and where the possibility to augment such signal by brain stimulation or other means is unavailable, training of contralesional, ipsilateral brain activity might be a possible alternative (Bundy et al., 2012; Carmena, 2013).

Another challenge is to identify and provide optimal frameworks for generalization of skills learned in the lab or hospital to daily life environments. Full implantation or hybrid systems combining features of rehabilitative and assistive BMIs may facilitate generalization and stabilize regained motor function. This could reduce the necessity of physiotherapy or other means to increase generalization.

Finally, an important aspect of stroke that is crucial to recovery, but often neglected, is the prevalence of depression and sustained learned helplessness. Early after stroke, over 30% of all stroke victims exhibit symptoms of depression, anxiety, fatigue and apathy (Hackett et al., 2014) impeding their motivation and capacity to engage in rehabilitation measures. It was shown that these symptoms relate to cortico-striatal connectivity (Shepherd, 2013) and disruption of the cortico-striatal thalamocortical loop (Terroni et al., 2011). Besides application of antidepressants (e.g. fluoxetine) that showed to significantly improve clinical outcome when administered early after stroke (Chollet et al., 2011, 2014; Mead et al., 2013), techniques aiming at purposeful modulation of this circuit's activity, such as rt-fMRI or DBS targeting subcortical activity, or BMIs targeting cortical activity, may fill the current gap and help restore motor, cognitive and affective function in these stroke survivors.

6. Conclusions

Brain machine interfaces are powerful tools that can enable stroke survivors to regain movement. While larger clinical studies are needed to understand BMI-related stroke recovery mechanisms, predictors of treatment response, as well as reliability and safety of implantable systems, BMI technology is evolving towards a potentially broadly applied and important component in rehabilitation strategies for stroke survivors for whom no other treatment options exist. Combination of BMIs with invasive and non-invasive brain stimulation (NIBS) promises to provide a better understanding of mechanisms underlying brain recovery and to improve efficacy of BMIs in stroke neurorehabilitation.

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Further reading

Link to video 1: https://www.youtube.com/watch?v=ogBX18maUiM.Link to video 2: https://www.youtube.com/watch?v=76lIQtE8oDY.