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REVIEW ARTICLE

Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke

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Upper limb motor deficits in severe stroke survivors often remain unresolved over extended time periods. Novel neurotechnologies have the potential to significantly support upper limb motor restoration in severely impaired stroke individuals. Here, we review recent controlled clinical studies and reviews focusing on the mechanisms of action and effectiveness of single and combined technology-aided interventions for upper limb motor rehabilitation after stroke, including robotics, muscular electrical stimulation, brain stimulation and brain computer/machine interfaces. We aim at identifying possible guidance for the optimal use of these new technologies to enhance upper limb motor recovery especially in severe chronic stroke patients. We found that the current literature does not provide enough evidence to support strict guidelines, because of the variability of the procedures for each intervention and of the heterogeneity of the stroke population. The present results confirm that neurotechnology-aided upper limb rehabilitation is promising for severe chronic stroke patients, but the combination of interventions often lacks understanding of single intervention mechanisms of action, which may not reflect the summation of single intervention's effectiveness. Stroke rehabilitation is a long and complex process, and one single intervention administrated in a short time interval cannot have a large impact for motor recovery, especially in severely impaired patients. To design personalized interventions combining or proposing different interventions in sequence, it is necessary to have an excellent understanding of the mechanisms determining the effectiveness of a single treatment in this heterogeneous population of stroke patients. We encourage the identification of objective biomarkers for stroke recovery for patients' stratification and to tailor treatments. Furthermore, the advantage of longitudinal personalized trial designs compared to classical double-blind placebo-controlled clinical trials as the basis for precise personalized stroke rehabilitation medicine is discussed. Finally, we also promote the necessary conceptual change from 'one-suits-all' treatments within in-patient clinical rehabilitation set-ups towards personalized home-based treatment strategies, by adopting novel technologies merging rehabilitation and motor assistance, including implantable ones.

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Abbreviations: BCI = brain-computer interface; BMI = brain-machine interface; FM = Fugl-Meyer; tDCs = transcranial direct-current stimulation; TMS = transcranial magnetic stimulation

Introduction

Stroke constitutes a major public health problem affecting millions of people worldwide with considerable impacts on socio-economics and health-related costs. It is the second cause of death (Langhorne *et al.*, 2011), and the third cause of disability-adjusted life-years worldwide (Feigin *et al.*, 2014): ~8.2 million people were affected by stroke in Europe in 2010, with a total cost of ~€64 billion per year (Olesen *et al.*, 2012). Due to ageing societies, these numbers might still rise, estimated to increase 1.5–2-fold from 2010 to 2030 (Feigin *et al.*, 2014).

Improving upper limb functioning is a major therapeutic target in stroke rehabilitation (Pollock *et al.*, 2014; Veerbeek *et al.*, 2017) to maximize patients' functional recovery and reduce long-term disability (Nichols-Larsen *et al.*, 2005; Veerbeek *et al.*, 2011; Pollock *et al.*, 2014). Motor impairment of the upper limb occurs in 73–88% first time stroke survivors and in 55–75% of chronic stroke patients (Lawrence *et al.*, 2001). Constraint-induced movement therapy (CIMT), but also standard occupational practice, virtual reality and brain stimulation-based interventions for sensory and motor impairments show positive rehabilitative effects in mildly and moderately impaired stroke victims (Pollock *et al.*, 2014; Raffin and Hummel, 2018). However, stroke survivors with severe motor deficits are often excluded from these therapeutic approaches as their deficit does not allow easily rehabilitative motor training (e.g. CIMT), treatment effects are negligible and recovery unpredictable (Byblow *et al.*, 2015; Wuwei *et al.*, 2015; Buch *et al.*, 2016; Guggisberg *et al.*, 2017).

Recent neurotechnology-supported interventions offer the opportunity to deliver high-intensity motor training to stroke victims with severe motor impairments (Sivan *et al.*, 2011). Robotics, muscular electrical stimulation, brain stimulation, brain computer/machine interfaces (BCI/BMI) can support upper limb motor restoration including hand and arm movements and induce neuro-plastic changes within the motor network (Mrachacz-Kersting *et al.*, 2016; Biasiucci *et al.*, 2018).

The main hurdle for an improvement of the status quo of stroke rehabilitation is the fragmentary knowledge about the physiological, psychological and social mechanisms, their interplay and how they impact on functional brain reorganization and stroke recovery. Positive stimulating and negatively blocking adaptive brain reorganization factors are insufficiently characterized except from some more or less trivial determinants, such as number and time of treatment sessions, pointing towards the more the better (Kwakkel *et al.*, 1997). Even the long accepted model of detrimental interhemispheric inhibition of the overactive contralesional brain hemisphere on the ipsilesional hemisphere is based on an oversimplification and lack of differential knowledge and is thus called into question (Hummel *et al.*, 2008; Krakauer and Carmichael, 2017; Morishita and Hummel, 2017).

Here, we take a pragmatic approach of comparing effectiveness data, keeping this lack of knowledge of mechanisms in mind and providing novel ideas towards precision medicine-based approaches to individually tailor treatments to the characteristics and needs of the individual patient with severe chronic stroke to maximize rehabilitative outcome.

Search strategy and selection criteria

The purpose was to identify, for each of the four neurotechnologies (robotics, muscular electrical stimulation, brain stimulation, and BCI/BMI) and their combination, recent (published between January 2014 and June 2017) and relevant (including large samples of patients) reviews/meta-analyses, randomized controlled trials or clinical studies reporting about neurotechnology-aided treatments' effectiveness.

We searched for references in PubMed and Cochrane Library under the terms 'effect' + 'robotic', 'brain computer/machine interface', 'functional electrical stimulation', 'brain stimulation' + 'stroke' + 'upper limb' + 'motor rehabilitation' in the above indicated time interval. In addition, reference lists of retrieved articles were reviewed to identify relevant studies.

From the studies found, publications not in English, and reporting small pilot and proof of concepts studies (less than seven individuals) deviating from the above mentioned study's typology were excluded. Studies addressing neglect, aphasia and somatosensory deficits only were also excluded because this article is focused on motor rehabilitation. Studies where neurotechnologies were used as assessment tools or biomarkers without treatment, or if the aim was to investigate basic mechanisms only, were also excluded. Virtual reality, home-based treatments, treatments including pharmacological agents were not included, because the focus of this article was on novel neuro-technological approaches that can offer promising solutions for the treatment of patients with severe chronic stroke.

The number of papers found and retained is reported in Table 1. The list of the retained studies and their features is reported in Supplementary Table 1.

For detailed insights about the application and effectiveness of the neurotechnological treatments, studies including acute to chronic and mild to severe patients were screened (Table 1), but discussion and conclusions are focused on severe chronic stroke survivors (Table 2). To identify which studies focused on severe post-stroke patients, we considered the level of motor impairment of the patient population in those studies stating to include moderate to severe chronic stroke patients. We reported the level of motor impairment of the patient population in these studies as the average upper extremities Fugl-Meyer (FM) scores at baseline before the treatments (Supplementary Table 1). The attribution of the level of severity (moderate and severe) was variable across studies: indeed, the level of severity can be attributed according to different factors, such as an arbitrary cut-off of FM scores, or a significantly smaller recovery in comparison to the proportional recovery rule (Prabhakaran *et al.*, 2008; Winters *et al.*, 2015), not allowing one to compare homogenous populations across studies. For this reason, in our analysis, we identified as a population of severe post-stroke individuals one having an average score of the upper limb section of the FM scale (maximum score 66) lower than 30, and we considered as a population of moderate to severely affected individuals, one having an average score of the upper limb FM scale between 30 and 45 (extremes included) (Table 2). We also defined treatment effectiveness with the upper limb section of the FM scale (Fugl-Meyer *et al.*, 1974). We used the FM score as metric to define the severity of the impairment and treatment effectiveness because it was the most adopted clinical outcome across the studies we included (Supplementary Table 1). The

Table 1 Summary of the features of the studies included in the review

Neurotechnology	Total studies found	Number of studies retained	Number of patients	Patient population	Mean difference in upper limb FM pre-post intervention (min–max)	Number of sessions (min–max)
General	-	4	59 186	-	-	-
Robotics	38	8	1612	Subacute–chronic Moderate–severe	2.0–18.0	10–40
Electrical stimulation	38	11	1296	Acute–subacute–chronic Moderate–severe	4.9–14.8	10–120
Invasive brain stimulation	10	2	94	Chronic–moderate–severe	4.3–10.0	15–30
tDCs	42	14	1334	Acute–subacute–chronic Moderate–severe	5.2–11.4	2–200
TMS	9	6	648	Subacute–chronic Mild–moderate–severe	3.0–13.7	1–100
BCI/BMI	13	10	823	Subacute–chronic Moderate–severe	6.3–13.2	1–30
tDCs + robotics	55	5	295	Subacute–chronic Moderate–severe	3.0–10.3	10–30
Electrical stimulation + robotics	55	2	50	Chronic–moderate	3.9–11.0	20
Electrical stimulation + TMS/tDCs	55	3	60	Acute–subacute–chronic Moderate–severe	4.3–12.7	5–24
BCI/BMI + tDCs + robotics	52	2	37	Chronic Moderate–severe	5.0–6.0	10

The upper limb FM score is between 0 and 66. Min = minimum; max = maximum.

Table 2 Summary of the features of the studies including chronic moderate to severe and severe stroke patients

Chronic stroke patients level of impairment	Number of studies retained	Treatment	Mean upper limb FM difference pre-post intervention as min–max (number of patients in the study)	Number of sessions (min–max if multiple studies)
Moderate to severe $30 \leqslant$ mean FM $\leqslant 45$	2	Invasive brain stimulation	4.3 (94)–10.0	15–30
	2	Anodal tDCs	11.4 (21)–11.4 (24)	9–12
	1	BCI/BMI (robot shoulder-elbow)	7.2 (21)	18
	3	Combination: BCI/BMI + tDCs (dual mode or anodal) + robotics (shoulder-elbow or orthosis for finger extension) and neuromuscular electrical stimulation	3.9 (39)–11 (11)	10–20
Severe Mean FM < 30	4	Robotics (shoulder-elbow)	3.4 (77)–7.7 (39)	12–60
	2	Functional electrical stimulation (upper limb tasks)	6.5 (11)–14.8 (23)	10–20
	1	tDCs (bilateral)	6.0 (25)	24
	2	BCI/BMI (shoulder-elbow robot and functional electrical stimulation)	6.3 (26)–7.8 (30)	18–20
	3	Combination: TMS (repetitive inhibitory) + robotics (shoulder-elbow) or neuromuscular electrical stimulation wrist and BCI, anodal tDCs and othosis for finger extension.	3.0 (17)–6 (18)	10–24

The upper limb FM score is between 0 and 66. Min = minimum; max = maximum.

definition of severity and impairment was based on the FM scale because, in general, the FM is recognized as a sensitive, reliable, valid and frequently-used measure of recovery at the impairment level and most other measures cannot be used in very severe cases, which constitute the focus of our review (Prabhakaran *et al.*, 2008). To estimate the effectiveness of each intervention, we considered an effect size of 6 FM points in agreement with what is generally reported in the literature for assessing a minimal clinically important difference between groups of stroke patients [5.25 points (Page *et al.*, 2012) or 7 points (Sivan *et al.*, 2011)].

Robot-aided rehabilitation

Rehabilitation robots are interactive motorized devices allowing fine-graded limbs mobilization and its precise measurement. They are generally divided into exoskeletons that assist limb movement by controlling the displacement of each segment, and end-effector devices enabling the mobilization of a limb from a distal application point. Both can work in two or three spatial dimensions and in different modes: simple passive, assisted-as-needed ones, providing resistance training or error-augmentation (Marchal-Crespo and Reinkensmeyer, 2009). Despite this variability, motor function gains obtained during robot-assisted therapy seem independent from the type of robot, when the training is provided with a robotic device of the same category (e.g. end effector devices) (Colombo *et al.*, 2017), highlighting the importance for stroke rehabilitation of the use and control of the device over its specific design. Robot-based treatment acts on peripheral nervous system mechanisms by enhancing the (impaired) afferent input to support stroke recovery. Together with the generated motor commands, it drives reorganization in the sensorimotor system, most likely due to Hebbian-like plasticity mechanisms. Furthermore, robot-based treatment allows high task and context-specific training able to stimulate, reactivate and reintegrate the afferents of the somatosensory system involved in the motor control loop, another important component strongly impacting on recovery (Langhorne *et al.*, 2011).

Eight studies (Hesse *et al.*, 2014; Klamroth-Marganska *et al.*, 2014; Orihuela-Espina *et al.*, 2016; Wu *et al.*, 2016; Colombo *et al.*, 2017; Shin *et al.*, 2017; Tomi *et al.*, 2017; Veerbeek *et al.*, 2017) reporting just robot-aided rehabilitation, and nine studies (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015; Lee *et al.*, 2015; Triccas *et al.*, 2015*a*,*b*; Di Lazzaro *et al.*, 2016; Straudi *et al.*, 2016; Rong *et al.*, 2017; Simonetti *et al.*, 2017) including robots combined with other neurotechnologies were compliant with the defined inclusion requirements (Table 1).

Diverse clinical trials have suggested that robotics alone provides intense and safe motor rehabilitation (Klamroth-Marganska *et al.*, 2014; Veerbeek *et al.*, 2017), and phase II trials are appearing (Veerbeek *et al.*, 2017). Current meta-analyses and works including large groups are in agreement with previous older studies (Hesse *et al.*, 2005; Lo *et al.*, 2010), reporting significant, small but marginally clinically meaningful upper limb improvement (e.g. ~2 FM points) and no effects on upper limb capacity and activity of daily living in stroke patients (Veerbeek *et al.*, 2017). Studies including smaller groups positively report differences up to 18 FM points for mild to moderate impaired individuals (McCabe *et al.*, 2015; Tomi *et al.*, 2017), and up to 8 FM points for severely impaired individuals after an intensive upper limb training (McCabe *et al.*, 2015). Task-oriented training with robotic devices might improve upper limb motor functions in subacute (Orihuela-Espina *et al.*, 2016) and especially chronic severe stroke patients (Klamroth-Marganska *et al.*, 2014) more effectively than physical therapy.

Studies' results are difficult to compare and summarize because of the lack of common classification in the essential parameters implied in the robotic treatment, such as the amount and type of support and assistance or resistance, the number of joints involved, the features of motor tasks, and the dose (Veerbeek *et al.*, 2017). Therefore, it is currently not possible to draw clear guidelines for this type of intervention except the notion that, in order to achieve clinically significant outcomes, especially in patients with severe stroke, robotic-aided treatments have to be sustained and intense—such as 5 days a week for 12 weeks (Klamroth-Marganska *et al.*, 2014)—and probably personalized.

Muscular electrical stimulation

Electrical stimulation was proposed more than 30 years ago as a rehabilitative technology for hemiparetic/hemiplegic patients. Muscular electrical stimulation also acts on partly similar mechanisms of stroke recovery as robotics, generating force in the affected muscles and respective movements of the paralysed limb stimulating the afferents of the somatosensory system involved and integrated in the motor control loop. Especially, brain-controlled functional electrical stimulation strengthens the brain's connections to the paretic muscles. Functional electrical stimulation-induced action potentials travel antidromically to the motor cortex with its motor neurons, which may coincide systematically with descending or sensory spinal cord inputs, impacting on their connectivity to motor neurons. Furthermore, functional electrical stimulation-induced afferent activity may coincide with the central motor cortical activity related to the voluntary efforts leading for neuroplastic changes and respective functional reorganization in the respective motor-cortical networks (for review see Ethier *et al.*, 2015). Electrical-induced contractions of paretic musculature lead to reciprocal inhibition of spastic antagonists through the stimulation of spinal interneurons (Robinson, 1995). In particular, depending on the kind of stimulation, it is possible to elicit an inhibitory effect on spasticity through influencing the excitability of the alpha motor neurons and triggering sensorimotor reorganization (Peurala *et al.*, 2002). The simple use of currents has been enriched by elaborated stimulation protocols, such as coupling detection and stimulation of motor synergies (Laffont *et al.*, 2014), allowing the coordination of muscle activity and synergies during functional tasks towards a physiological pattern (Vafadar *et al.*, 2015) and brain-controlled application leveraging the interplay of the respective motor command with the electrical stimulation-induced afferent input.

Here, 11 studies reporting muscular electrical stimulation effectiveness for stroke upper limb rehabilitation were selected (Dorsch *et al.*, 2014; Kim *et al.*, 2014; Quandt and Hummel, 2014; Knutson *et al.*, 2015*a*, *b*; Liu *et al.*, 2015; Vafadar *et al.*, 2015; Wilson *et al.*, 2016; Carda *et al.*, 2017; Eraifej *et al.*, 2017; Schick *et al.*, 2017), and seven where muscular electrical stimulation was used in combination with other treatments (Koyama *et al.*, 2014; Lee *et al.*, 2015; Sattler *et al.*, 2015, Jang *et al.*, 2016; Kim *et al.*, 2016; Rong *et al.*, 2017; Tosun *et al.*, 2017) (Table 1). In almost all of these studies, the muscular electrical stimulation elicits a movement and only in few cases, it is used solely for sensory stimulation (Wilson *et al.*, 2016). It is applied mainly to treat shoulder subluxation (Vafadar *et al.*, 2015) or to allow hand opening (Knutson *et al.*, 2015*a*; Wilson *et al.*, 2016; Carda *et al.*, 2017; Schick *et al.*, 2017), but also wrist dorsiflexion (Liu *et al.*, 2015) or multiple joints actuation (Dorsch *et al.*, 2014). Depending on the muscles stimulated, the task and individual sensitivity, the stimulation parameters are highly variable: the stimulation frequency can be set between 10 and 50 Hz, the pulse amplitude from 0 to 100 mA and pulse width from 0 to 300 µs (Knutson *et al.*, 2015*b*; Vafadar *et al.*, 2015).

A Cochrane review with a meta-analysis indicates functional electrical stimulation as an effective treatment for shoulder subluxation especially early after stroke (Vafadar *et al.*, 2015). In this case, functional electrical stimulation is used to stimulate the muscles responsible to maintain the head of the humerus in the glenoid fossa (supraspinatus and posterior deltoid) to prevent or restore subluxation, reduce pain, and improve function (Vafadar *et al.*, 2015). However, for pain and functional improvement, it does not have superior effects to physical therapy (Vafadar *et al.*, 2015). In all cases, evidence shows short-term effects, inconclusive in long-term studies (Vafadar *et al.*, 2015).

For hand and finger function, strong evidence of the advantage of muscular electrical stimulation over physical therapy or no therapy is still missing (Dorsch *et al.*, 2014; Quandt and Hummel, 2014; Eraifej *et al.*, 2017). It has been suggested to be effective if combined with other approaches such as mirror therapy (Schick *et al.*, 2017), motor imagery (Liu *et al.*, 2015), intensive goal-oriented (Carda *et al.*, 2017) and BCI-based motor training (Biasiucci *et al.*, 2018). This might indicate that the modality of administration of muscular electrical stimulation, and in particular the task contingent sequence of the stimulation, is an important factor as much as the appropriate stimulation parameters. Interestingly, variations of muscular electrical stimulation, such as cyclic neuromuscular electrical stimulation (NMES), switch-triggered NMES, EMG-triggered NMES, and sensory stimulation on paretic upper-extremities might have comparable effects, with no advantages of complex stimulation over the simple one (Wilson *et al.*, 2016). For chronic severe patients, evidence is limited, but muscular electrical stimulation seems to favour significant clinical improvements, even when it is administrated in low dose (10 sessions) (Carda *et al*., 2017), and when dose is increased, it seems to favour larger improvements (McCabe *et al*., 2015).

Except for shoulder subluxation, guidelines cannot be derived from this intervention since the optimal dose and administration of muscular electrical stimulation has not been established yet. Protocols across studies are heterogeneous (Knutson *et al*., 2015*a*) and optimal stimulation parameters are highly individual and influenced by the pathology (Quandt and Hummel, 2014).

Brain stimulation

Brain stimulation uses local magnetic fields or electric currents to facilitate or inhibit targeted brain areas. Among non-invasive brain stimulation techniques, transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCs) are the most adopted (for review, see Hummel and Cohen, 2005). Non-invasive brain stimulation is used to modulate the excitability of the stimulated neuropil. The mentioned techniques act on different specific central mechanisms: TMS most likely stimulates axons at their bends and can induce action potentials (Maccabee *et al*., 1993); TDCs polarize neuronal elements (somas, dendrites, axons) based on their orientation and polarity of the induced electric field (Rahman *et al*., 2013). Both can produce changes in cortical excitability in healthy subjects and stroke patients (Hummel and Cohen, 2005; Nitsche *et al*., 2008; Triccas *et al*., 2016). They can stimulate or inhibit according to the applied parameters, for instance, pulse frequency, stimulation-train timing, or stimulus intensity for TMS, and current polarity, current intensity, and stimulation duration for tDCs (Hummel and Cohen, 2005; Nitsche *et al*., 2008; Laffont *et al*., 2014; Rossini *et al*., 2015). When net effects are measured via TMS-induced motor-evoked potentials, anodal tDCs increases, whereas cathodal tDCs decreases cortical excitability (Nitsche and Paulus, 2000). It is important to note that this simple dichotomy oversimplifies the complex interactions within the brain, especially of non-motor areas (Hummel *et al*., 2008; Morishita and Hummel, 2017). More complex inhibition and excitation patterns have been identified, via investigations of cortical gyration, microstructural properties of neurons (e.g. orientation of the somato-dendritic axis), or higher-order behavioural functions (Rahman *et al*., 2014).

Brain stimulation in stroke is aimed at enhancing adaptive brain plasticity during rehabilitative training, by locally modifying cortical excitability, enhancing focal and remote neuroplastic properties and/or correcting maladaptive brain plasticity induced by the cerebrovascular accident (Lefaucheur *et al*., 2014). Its use in stroke rehabilitation was initiated more than 10 years ago (Hummel *et al*., 2005; Khedr *et al*., 2005; Hummel and Cohen, 2006), and its efficacy is still under investigation with several studies conducted in the past 3 years. We included evidence from 19 publications, where brain stimulation is used alone (Fusco *et al*., 2014; Lefaucheur *et al*., 2014; O'Shea *et al*., 2014; Plow and Machado, 2014; Elsner *et al*., 2015; Tretriluxana *et al*., 2015; Allman *et al*., 2016; Chang *et al*., 2016; D'Agata *et al*., 2016; Del Felice *et al*., 2016; Ilić *et al*., 2016; Kubis, 2016; Levy *et al*., 2016; Rocha *et al*., 2016; Triccas *et al*., 2016; Cho *et al*., 2017; Figlewski *et al*., 2017; Koh *et al*., 2017; Lefaucheur *et al*., 2017), and 10 studies (Koyama *et al*., 2014; Ang *et al*., 2015*b*; Kasashima-Shindo *et al*., 2015; Sattler *et al*., 2015; Triccas *et al*., 2015*a*, *b*; Di Lazzaro *et al*., 2016; Straudi *et al*., 2016; Simonetti *et al*., 2017; Tosun *et al*., 2017) where brain stimulation is used in combination with other interventions (Table 1).

Guidelines for use in stroke rehabilitation have been provided for repetitive TMS (rTMS) (Lefaucheur *et al*., 2014; Rossini *et al*., 2015). Probable efficacy (Level B) has been reported for low-frequency rTMS applied to the contralesional motor cortex (M1) to improve motor performance in the chronic phase by downregulation of excitatory tone in the contralesional hemisphere. Additionally, high-frequency rTMS stimulation of the ipsilesional M1 reached a Level C recommendation (possibly useful) for improving motor function for the acute and post-acute, and maybe the chronic phase. Active stimulation modes (dual M1 tDCs 1.5 mA versus low-frequency rTMS at 1 Hz) might lead to comparable results in chronic stroke patients using the Action Research Arm Test as functional outcome (D'Agata *et al*., 2016). Task-complexity is relevant for the effectiveness of the stimulation, for example low-frequency rTMS (1 Hz) applied to contralesional M1 facilitated reach-to-grasp action only for small objects (1.2 versus 7.2 cm cylindrical dowels (Tretriluxana *et al*., 2015), as well as patient characteristics (such as functional integrity of the corticospinal tract and the brain-derived neurotrophic factor genotype), which may influence the response to a high-frequency rTMS (10 Hz, ipsilesional M1) (Chang *et al*., 2016).

Recent evidence-based guidelines for the therapeutic use of tDCs found heterogeneous evidence for motor recovery after stroke (Lefaucheur *et al*., 2017) and some meta-analyses reported small not significant effects on upper limb impairments and activities of daily living post-intervention (Kang *et al*., 2016; Triccas *et al*., 2016). Recent publications discussed some of the issues underlying this result, including which modality to use, how the stimulation should be coupled with the motor training, which are the underlying mechanisms, how clinical stroke characteristics affect the efficacy of the different stimulation protocols and which 'biomarkers' might help to predict outcome and the magnitude of treatment response (for reviews see Morishita and Hummel, 2017; Raffin and Hummel, 2018).

Concerning the preferential stimulation modality, O'Shea *et al*. (2014) could show, using a simple reaction time task, that anodal, facilitatory ipsilesional M1 tDCs (1 mA) and cathodal, inhibitory contralesional M1 tDCs (1 mA) improved reaction time in chronic stroke, when compared to sham. However, bilateral tDCs had no effect. Additionally, in a recent randomized controlled trial investigating the effect of anodal ipsilesional M1 tDCs (1 mA) or cathodal contralesional M1 tDCs (1 mA) coupled with modified constraint-induced therapy, anodal stimulation had a more lasting impact on the motor outcomes than cathodal stimulation in chronic stroke patients (Rocha *et al.*, 2016). Figlewski *et al.* (2017) provided additional evidence for the additive value of ipsilesional M1 anodal tDCs (1.5 mA) when coupled with CIMT. Focusing on post stroke spasticity, Del Felice *et al.* (2016) showed a superior effectivity for cathodal contralesional M1 tDCs (1 mA), when compared to dual M1 tDCs (1 mA). For the selection of the best time window for application of tDCs, Fusco *et al.* (2014) found that anodal ipsilesional M1 tDCs (1.5 mA) when applied before motor rehabilitative training, improved hand dexterity but not rehabilitation effectiveness in a cohort of patients with subacute stroke. This is in line with data from healthy subjects pointing towards enhancement of learning, when anodal tDCs (1 mA) is applied during motor training and rather disturbance, when applied before motor training (Stagg *et al.*, 2011).

Currently, there is limited knowledge on which mechanisms mediate the tDCs effects (Fritsch *et al.*, 2010). Allman *et al.* (2016) provided new insights using structural and functional MRI. In their study, anodal ipsilesional M1 (1 mA) tDCs was paired with motor training in chronic stroke patients. Patients in the anodal stimulation group showed increased activity during movement of the paretic hand in the ipsilesional motor and premotor cortex. In addition, patients had intervention-related increases in grey matter volume of ipsilesional motor and premotor areas.

Because of their different mechanistic properties, TMS and tDCs can be used in combination to achieve synergistic effects. Cho *et al.* (2017) hypothesized that cathodal contralesional M1 tDCS (2 mA) can balance interhemispheric interactions and hereby enhance effects of high-frequency ipsilesional M1 rTMS (10 Hz). In their study, combined stimulation had a synergistic effect being more effective than TMS alone (Cho *et al.*, 2017).

Stroke characteristics such as lesion site or type of stroke determine the responsiveness to a brain stimulation interventional protocol. For instance, high-frequency rTMS (10 Hz) applied to ipsilesional M1 only improved finger- and hand-movement kinematics in patients with subcortical, but not with additional cortical stroke (Ameli *et al.*, 2009). Patient stratification for treatment protocols may maximize effects in future trials (Morishita and Hummel, 2017; Raffin and Hummel, 2018). Currently, there is insufficient evidence to draw final conclusions on the potential benefit of stratification for the treatment protocol; however, the identification of potential biomarkers constitutes one of the core future areas in the field (Guggisberg *et al.*, 2019). Potential biomarkers are based on neuroimaging, such as lesion location, structural, functional information and connectivity parameters (Ameli *et al.*, 2009; Lindenberg *et al.*, 2012; Diekhoff-Krebs *et al.*, 2017; Koch and Hummel, 2017; Schulz *et al.*, 2017; for reviews see Koch and Hummel, 2017; Guggisberg *et al.*, 2019) ipsilesional intracortical inhibition (GABAergic) (Liuzzi *et al.*, 2014), and clinical characteristics (Stinear, 2010; O'Shea *et al.*, 2014).

The use of invasive implants to deliver brain stimulation could overcome some limitations of non-invasive brain stimulation, e.g. only superficial areas can be reached, topographic resolution and the long-term chronic use are limited. Invasive interventions will allow the application of brain stimulation with high temporal and spatial resolution, sufficient intensity and continuous stimulation throughout task-oriented long-term motor training for home-based use. The first larger trial in this direction, the 'Everest' trial, evaluated safety and efficacy of epidural cortical electrical stimulation in clinic rehabilitation (Levy *et al.*, 2016). The epidural brain implant was tested on 94 moderate to severe chronic stroke patients and compared to standard rehabilitation administered for 6 weeks. The primary efficacy endpoints (4.5 points in the upper FM and 0.21 points in the Arm Motor Ability Test) at 4 weeks post-treatment were not accomplished. However, *post hoc* comparisons showed that a greater proportion of experimental (39%) than control (15%) patients maintained or achieved the primary endpoints at 24 weeks post-treatment.

Despite the fact that guidelines are available for upper limb rehabilitation (Lefaucheur *et al.*, 2014, 2017), knowledge and evidence of brain stimulation for stroke rehabilitation in patients with severely impaired upper extremity function is still not sufficient. This also raises the unsolved question, which patient population might benefit most from brain stimulation. A review focused on mechanisms of synaptic and functional reorganization after stroke suggesting a bimodal balance–recovery model that links interhemispheric balancing and functional recovery to the structural reserve spared by the lesion that could enable brain stimulation to be tailored to the needs of individual patients (Di Pino *et al.*, 2014). This is still quite a simplified model (Hummel *et al.*, 2008). As the functional relevance of secondary motor areas become more and more clear, novel stimulation targets gain attention (Koch and Hummel, 2017; Morishita and Hummel, 2017). In a recent case study, deep brain stimulation of the dentate nucleus resulted in reduced tremor and ataxia in a patient with cerebellar stroke (Teixeira *et al.*, 2015). A clinical trial (EDEN trial) is evaluating if deep brain stimulation in the dentate nucleus area is safe for the treatment of stroke. It will include 12 chronic stroke patients with estimated termination in 2019. Additionally, novel non-invasive stimulation techniques are developed, like non-invasive deep brain stimulation via temporally interfering electric fields (Grossman *et al.*, 2017), which is an exciting development with the potential that stroke patients might benefit in future.

As with many treatment modalities used for stroke, knowledge of the neurophysiological basis of non-invasive brain stimulation (rTMS, tDCS) effects and mechanisms of action, especially in patients compared to healthy subjects, is still limited. Thus, crucial steps towards larger treatment effects and personalized patient-tailored applications are to understand heterogeneous responses (from responders to non-responders) to brain stimulation, and parameters, which determine and predict the treatment response.

Brain computer/machine interfaces

BCI/BMIs activate or deactivate assistive or rehabilitative devices directly by brain activity of the user (usually neuroelectric or neurometabolic) without a motor output. The non-invasive recording of brain activity for a BCI can be achieved with different imaging techniques: for their relative portable nature and low cost, EEG and near-infrared spectroscopy are mostly applied for stroke rehabilitation (van Dokkum *et al.*, 2015), with EEG used more frequently (Pfurtscheller *et al.*, 2008), but other techniques have also been adopted, such as a magnetoencephalography-based or real-time functional MRI-based BCI (Buch *et al.*, 2008; Sitaram *et al.*, 2008). A pattern change in one EEG feature (amplitudes of a particular evoked oscillation, composition of slow cortical potentials or spectral features) can be used to trigger an external device to display real-time feedback or to execute the intended action (van Dokkum *et al.*, 2015). Indeed, BCI/BMI systems are used in stroke to restore the lost motor functions acting on central and peripheral mechanisms: they reactivate and reorganize the central command structures and through their feedback-based learning close the interrupted central-peripheral loop leading to Hebbian-like plasticity-based cortical mechanisms. They are used to train 'healthy' brain activity and/or to operate assistive devices (van Dokkum *et al.*, 2015). In the first case, BCI/BMIs are coupled to an auditory or visual feedback system to visualize the effects of brain activity changes, facilitate and enhance the learning of recruiting brain areas and their activation (Laffont *et al.*, 2014): these approaches are often termed neurofeedback. In the second case, BCI/BMIs control passive or active limb mobilization through an external device (such as robots or muscular electrical stimulation) to help patients to improve brain plasticity, based on associative Hebbian learning principles (Soekadar *et al.*, 2015), 'closing the sensorimotor loop' and thus promoting the relearning of voluntary motor control (Laffont *et al.*, 2014). Further details about its mechanisms of action are reported in Soekadar *et al.* (2015) and Biasiucci *et al.* (2018).

The application of BCI/BMIs for stroke rehabilitation is relatively recent; the number of studies in the field is limited and mostly restricted to single cases or case reports. We included 10 studies reporting its effectiveness when it is used alone (Ang *et al.*, 2014, 2015*a*; Li *et al.*, 2014; Ono *et al.*, 2014; Morone *et al.*, 2015; Soekadar *et al.*, 2015; van Dokkum *et al.*, 2015; Jang *et al.*, 2016; Kim *et al.*, 2016; Remsik *et al.*, 2016) (Table 1), and two when used in combination with other treatments (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015). The type of actuator used to provide feedback varied among studies, with three using robotic or orthotic devices (Ang *et al.*, 2014, 2015*a*; Ono *et al.*, 2014), three using muscular electrical stimulation alone or with visual feedback of a virtual gaming instructing about what to imagine during motor imagery tasks (Li *et al.*, 2014; Jang *et al.*, 2016; Kim *et al.*, 2016), one using visual feedback of the movement of a virtual hand during a motor imagery task only (Morone *et al.*, 2015), and two using robotic and tDCS (Ang *et al.*, 2014; Kasashima-Shindo *et al.*, 2015). Both self-guided (motor imagery and neurofeedback) and assistive movements (using orthotics and muscular electrical stimulation) show significant effects with a limited effect size. The enhancement of treatment effects is achieved when BCI/BMIs are coupled with robots and muscular electrical stimulation (Li *et al.*, 2014; Ang *et al.*, 2015*a*) with results comparable to conventional physiotherapy or with an improvement of up to 9.4 FM points in moderate to severe patients (Morone *et al.*, 2015). BCI/BMIs seem particularly suitable for the severe cases (Morone *et al.*, 2015), as also shown by a previous study (Ramos-Murguialday *et al.*, 2013) and a recent report (Biasiucci *et al.*, 2018) with evidence of restoration of individual finger extension in severe chronic stroke survivors using the detection of motor intention with BCI to drive electrical stimulation in hand muscles (Soekadar *et al.*, 2015).

There is currently insufficient evidence to suggest guidelines about BCI/BMIs administration and effectiveness. Few sessions (a minimum of 18) seem enough to provide clinical significant improvements (Ang *et al.*, 2015*a*), but it is necessary to perform larger randomized controlled trials to have further evidences about its administration, its effectiveness and which stroke population might mostly benefit from this intervention. Enlarging size, neurological and demographic range of participants, adopting novel neuroimaging measures such as near-infrared spectroscopy, functional MRI and real-time functional MRI and invasive and/or hybrid brain-body computer/machine interfaces, developing portable systems for in-home use and increasing personalized treatments have been already identified as the next steps for BCI/BMI-aided rehabilitation (Remsik *et al.*, 2016).

Combinations of interventions

As single interventions' effect size might not be large enough, combination of interventions might enhance significantly the magnitude of functional improvement and recovery by additive or even supra-additive effects (Laffont *et al.*, 2014; Hatem *et al.*, 2016) conceptually combining to target central and peripheral mechanisms of stroke recovery. However, this statement needs experimental-clinical verification because a combination of effective strategies does not necessarily lead to more effective functional improvement: combining two effective treatment modalities may potentially worsen outcome, as it was found frequently in psychotherapy research. For this reason, we review post-stroke upper limb rehabilitation based on the combination of neurotechnologies. Twelve papers were selected (Koyama *et al.*, 2014; Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015; Lee *et al.*, 2015; Sattler *et al.*, 2015; Triccas *et al.*, 2015*a*, *b*; Di Lazzaro *et al.*, 2016; Straudi *et al.*, 2016; Rong *et al.*, 2017; Simonetti *et al.*, 2017; Tosun *et al.*, 2017) (Table 1).

Robotics is the treatment most frequently combined with others (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015; Triccas *et al.*, 2015*a*, *b*; Di Lazzaro *et al.*, 2016; Jang *et al.*, 2016; Straudi *et al.*, 2016; Rong *et al.*, 2017). As shown, its combination with BCI/BMI is promising, probably because of optimal learning conditions, where a brain-driven voluntary movement is paired in time with visual and proprioceptive feedback of that movement and its intention facilitating adaptive motor reorganization. A similar positive synergy has been observed also for BCI/BMI with muscular electrical stimulation (Soekadar *et al.*, 2015).

The effectiveness of the addition of muscular electrical stimulation to robotic training has been addressed in a study using the Bi-Manu-Track robot to target wrist flexion-extension and forearm pronation-supination (Lee *et al.*, 2015). In one group, muscular electrical stimulation was contingent to wrist extension and forearm pronation-supination with symmetrical biphasic square waveform, a frequency of 30 pulses per second, a pulse duration of 200 μs and intensity at muscle contraction level. In the other group (sham group), the intensity of stimulation was zero and the participants were notified that it was set below sensory threshold (Lee *et al.*, 2015). Both groups significantly improved their motor impairment (3.9 versus 3.8 FM points on average) and motor functions, but without significant group differences that were only found for muscle spasticity of wrist flexors, in hand functions and in the quality of life measures. In a more complex design, robotics and neuromuscular electrical stimulation have been combined to provide multi-joint coordinated upper limb physical training, assisting elbow, wrist and fingers to achieve reaching, hand opening and grasping (Rong *et al.*, 2017). An exoskeleton with two modules for the elbow and wrist was combined with neuromuscular electrical stimulation of biceps brachii, triceps brachii, flexor carpi radialis, extensor carpi ulnaris and extensor digitorum communis to control elbow and wrist flexion/extension, and of the extensor carpi ulnaris and extensor digitorum communis for hand opening/closing. In this case, the pre-post training improvement was on average of 11 FM points (Rong *et al.*, 2017), indicating that relevant clinical results might be achieved if the combination of interventions is provided in a learning principles based context, and if the functionality of the whole limb and not just of a single joint is practiced.

An interesting approach is the combination of brain stimulation to enhance neuroplasticity with robotics and electrical stimulation, which has been done so far in few studies with few patients. The combination of robotics and tDCs is currently evaluated (Simonetti *et al.*, 2017); however, the heterogeneity of methodology and patients, and the restricted number of studies and patients do not allow a specific statement about efficacy, but rather a general one regarding feasibility. Indeed, studies adopt 20 min to 1 h of robotic treatment, with devices assisting only wrist, wrist and elbow, or shoulder and elbow, with the combination of tDCs administered in the first 7–20 min of the robotic treatment as anodal, cathodal or bilateral stimulation, with the number of sessions also varying from one to 30. Overall, single studies share the same conclusions of the review (Triccas *et al.*, 2015*a*, *b*; Di Lazzaro *et al.*, 2016; Simonetti *et al.*, 2017). Small significant changes are observable only after adjusting statistical analysis for lesion site (cortical versus subcortical), timing from the stroke onset (chronic versus subacute) and type of stroke (ischaemic versus haemorrhagic) (Simonetti *et al.*, 2017). Patients with subacute stroke show on average almost double the improvement compared to chronic stroke patients (10.3 versus 5.8 FM points), after receiving 20 min anodal tDCs before 1 h of training with an upper limb exoskeleton for 18 sessions (Triccas *et al.*, 2015*a*, *b*). This might point to the importance of tailoring this treatment to the individual patient, but also it has to be considered that spontaneous remission in acute and subacute patients may carry treatment effects. Bilateral tDCs administrated for 30 min of therapy with a shoulder-elbow robot for 10 sessions seems more effective in the chronic stage and in patients with subcortical lesions (Straudi *et al.*, 2016). Given the heterogeneity in the administration, effectiveness of tDCs and robotics might improve with the best differential choice of interventions' setup. For example, prolonging their simultaneous presentation (>15 sessions) might enhance effects (Di Lazzaro *et al.*, 2016), as well as choosing the optimal duration and location to apply tDCs (Triccas *et al.*, 2015*a*, *b*; Di Lazzaro *et al.*, 2016) or determining the temporal relationship between brain stimulation and robotic therapy (Simonetti *et al.*, 2017). Improvements might be better retained when anodal tDCs is delivered before practice of robotic treatment rather than during or after it. Similar considerations are valid for the combination tDCs and electrical stimulation (Sattler *et al.*, 2015).

The combination of TMS and muscular electrical stimulation appears to have higher efficacy than each intervention alone. Koyama *et al.* (2014) tried 12 sessions including 880 repetitions of neuromuscular electrical stimulation of wrist extensors (frequency 50 Hz, pulse width of 250 μs, stimulation cycle of 500 ms and intensity matching the level to induce 10° wrist extension, maximum 30 mA) in combination with inhibitory repetitive TMS (biphasic magnetic stimuli at 1 Hz) on the contralesional hemisphere in moderate to severe stroke patients. The results show a pre-post treatment improvement on average of 4.3 FM points. Tosun *et al.* (2017) showed in a larger group of stroke patients that low frequency repetitive TMS alone and with neuromuscular electrical stimulation of wrist extensors significantly enhance motor recovery in the paretic hand more than conventional therapy.

Finally, first evidence was provided that tDCs (anodal 1 mA over M1 motor cortex of the ipsilesional hemisphere) applied 20 min before motor imagery BCI with a motor feedback provided by a robotic device assisting either shoulder-elbow or finger extension showed that the addition of tDCs elicited significant motor improvement only after long term application (3 months) (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015). However, tDCs enhanced BCI/BMI features by increasing event-related desynchronization (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015) and improved online accuracies of the BCI (Ang *et al.*, 2015*b*). This facilitation may enhance the efficacy of BCI (Ang *et al.*, 2015*b*), reinforcing adaptive brain plasticity and inhibiting maladaptive reorganization (Laffont *et al.*, 2014).

In general, the combination of neurotechnologies for post-stroke upper limb rehabilitation is still in its infancy with few studies comparing the various possibilities of administration of two or more treatments; therefore, no guidelines or indications can be provided so far. In patients with moderate and severe chronic stroke, the combination of interventions seems effective in reducing motor impairments, but not more than single interventions (Table 2), as it has been also shown in a recent study where repetitive peripheral nerve sensory stimulation of the median nerve was provided in combination with anodal tDCs as add-on interventions to training wrist extension with functional electrical stimulation (Menezes *et al.*, 2018). Severe chronic patients might benefit more than moderate ones from the combination of interventions (Ang *et al.*, 2015*b*; Kasashima-Shindo *et al.*, 2015). The often limited efficacy of the combination of interventions (Table 2) might be also related to a deficient learning context to maximize synergistic effects of single interventions, but also reflects our limited understanding of the physiological mechanisms of brain reorganization after stroke (Fig. 1).

Conclusions and future directions

Neurotechnology-aided upper limb rehabilitation has a very promising potential especially for patients with severe stroke, who have very limited opportunities of classical rehabilitative treatments. However, experimental

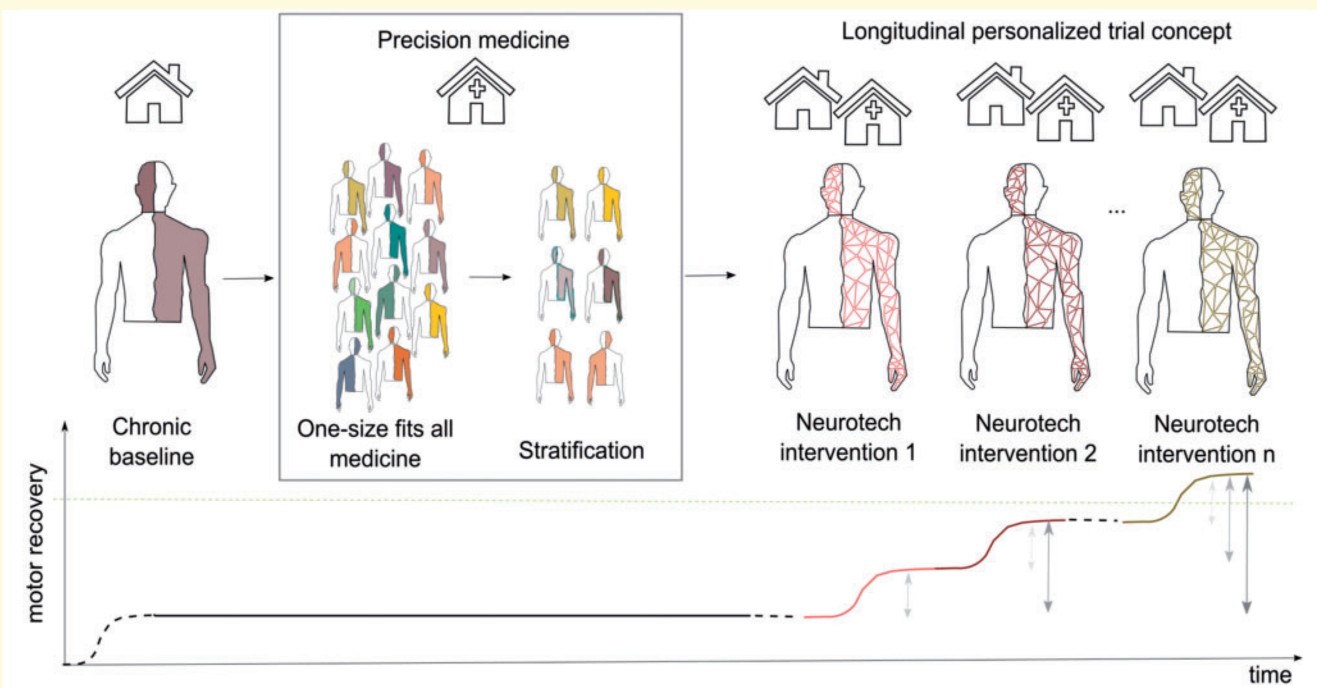

Figure 1 Conceptualization of longitudinal personalized rehabilitation-treatment designs for patients with severe chronic stroke. Ideally, each patient with severe chronic stroke with a stable motor recovery could be stratified based on objective biomarkers of stroke recovery in order to select the most appropriate/promising neurotechnology-aided interventions and/or their combination for the specific case. Then, these interventions can be administered in the clinic and/or at home in sequence, moving from one to another only when patient's motor recovery plateaus. In this way, comparisons of the efficacy of each intervention (grey arrows) are still possible, and if the selected interventions and/or their combination are suitable, motor recovery could increase.

evidence of exclusive benefits of a particular treatment over the others (McCabe *et al.*, 2015), and differential indication of the various treatments (which treatment for which patient), is still lacking (Miller *et al.*, 2010; McCabe *et al.*, 2015). Moreover, the combination of neurotechnology-aided interventions for upper limb stroke rehabilitation does not show cumulative, but rather comparable efficacy to the one achieved with single interventions. A limitation of the present review is that the results are based only on the FM score, which represents a measure of impairment. However, for stroke recovery and the effects of treatment interventions also other aspects like compensation, adaptation or relearning are relevant influential factors. As most of the studies provide mainly data from the FM score (~59%, Supplementary Table 1) allowing a comparison of the studies, a systematic estimation of the effects of interventions on other relevant parameters such relearning to compensate or adapt for deficits for daily life was unfortunately not possible. In the future, it would be favourable in neuro-rehabilitative treatment studies to have a clinical evaluation, which represents several factors critical for recovery ranging from impairment, adaption, and compensation to quality of life. Compound measures, created out of these parameters, might represent best the individual patients' recovery or treatment effects.

All the discussed neurotechnology-based interventions for upper limb rehabilitation after stroke and their combination seem to suffer from comparable limitations such as: small sample size, lack of understanding of underlying mechanisms, no patient stratification or tailored-approaches, 'one-suits-all' concept applications in a clinical or laboratory environment only, performed in a limited time, with a lack of attention to the motor task that might often be meaningless and far from activities of daily living. In future clinical-scientific efforts, it is mandatory to address these crucial points.

Large homogeneous controlled studies tackling the influence of impairment, timing of intervention and dosage for each intervention are desirable. However, non-invasive technology-aided stroke rehabilitation trials differ from pharmacology and implantable medical device trials. In non-invasive technology-aided stroke rehabilitation, each intervention includes multiple parameters in addition to the variability of dose and timing, and it acts on multiple systems (such as central, peripheral nervous system and muscles) and functional domains. As a result, each intervention is highly variable, especially when it is a combination of multiple interventions. Remarkably, despite generally larger patient numbers and fewer parameters to control than in the case of neurotechnologies, pharmacological treatments also show heterogeneous, and in part, contradictory findings, similar to those found in neurotechnology-aided treatments, leading to insufficient evidence, not allowing one to draw strong and clear conclusions in regard of favourable treatment effects to enhance neurorehabilitation and stroke recovery (Scheidtmann *et al.*, 2001; Sprigg *et al.*, 2007; Berends *et al.*, 2009; Clark, 2009; Chollet *et al.*, 2011; Chen *et al.*, 2013; Cramer, 2015; Tran *et al.*, 2016; Graham *et al.*, 2017; Kraglund *et al.*, 2018; Viale *et al.*, 2018). Heterogeneity is an irreducible feature of stroke patients and already many factors have been suggested to possibly influence treatment effectiveness or impact recovery, such as age, gender, type of stroke (ischaemic or haemorrhagic), side of lesion, cortical or subcortical lesion, time since stroke onset, presence of the BDNF Val/Val genotype (Chang *et al.*, 2016), and the structural integrity of corticospinal motor fibres and intracortical connections (Lindenberg *et al.*, 2010; Schulz *et al.*, 2015). Together with the measure of finger extension and shoulder abduction within 72 h after stroke (Nijland *et al.*, 2010) and the integrity of muscle synergy patterns (Cheung *et al.*, 2012; García-Cossio *et al.*, 2014), these features might be more or less relevant for the stratification of stroke patients and for the prediction of motor recovery (Kwakkel *et al.*, 2006; Prabhakaran *et al.*, 2008; Winters *et al.*, 2016*b*; Wolf *et al.*, 2016; Koch and Hummel, 2017) for each intervention. In addition, double blinding of patients and therapists is not always possible. Placebo effects cannot be completely controlled, but should be attended and carefully measured. A control group where only one critical variable is isolated is almost impossible and heterogeneous groups might cancel individual benefits in both intervention and control groups. To test the effect of a single treatment variation, the effort of a whole research community should be coordinated to carry on clinical trials including hundreds of patients each (Winters *et al.*, 2016*a*). This implies costly multicentre and international trials that are difficult to control, harmonize and finance.

The personalization of the rehabilitative intervention has been suggested as a critical step to improve the outcome of rehabilitation (Fuhrer and Keith, 1998; Krakauer, 2006; Koch and Hummel, 2017; Raffin and Hummel, 2018). *A priori* selection and attribution to different groups of patients with particular characteristics (differential indication) could help guiding rehabilitation of individual treatment protocols to achieve larger effects (Klamroth-Marganska *et al.*, 2014; Winters *et al.*, 2016*a*; Morishita and Hummel, 2017; Raffin and Hummel, 2018). Precision stroke medicine requires the identification of cortical, spinal and muscular correlates of individual stroke recovery (Guggisberg *et al.*, 2019) and an alternative to randomized-controlled trials to move towards within-patient approaches.

A possible solution for patients with severe chronic stroke might be to move towards longitudinal personalized study designs. Such an approach in neurotechnology trials would indicate that each patient is his/her own control in a longitudinal fashion of one or many successive interventions until the patient reaches the individual functional maximum with this specific treatment. Even more interesting, one could consider that the patient starts with a first intervention and when a functional plateau is achieved, treatment moves to another intervention and again leverages it individually until also here the functional plateau is reached. The elegance of this design is that it allows patients to train with different approaches for an extended time, increasing their chance to maximally improve, because each treatment modality will be applied until the personal plateau of functional recovery is reached in the individual patient. This interventional study design also allows one to compare the impact of each therapy stage across that individual, and after completing several patients statistical comparisons between baselines, achieved levels of functioning are possible. Such a design is especially useful for severe chronic stroke patients in whom spontaneous remission is not possible anymore and placebo-expectancy effects are carefully controlled with questionnaires and systematic quantitative behavioural observations.

In conclusion, the available technological solutions have the potential to provide an effective treatment for patients with chronic severe stroke to improve their quality of life and social functioning. It is crucial to provide a prolonged personalized combination of different treatments to maximize individual treatment effects. For this reason, it is necessary to move from classical single case or randomized-controlled trials and towards adopting the concept of individualized precision longitudinal designs. The choice of a trial aiming primarily to improve single patient outcome and only secondarily to allow the comparison of different interventions might significantly increase the present status of therapeutic stroke recovery and maximizes its effects. Finally, innovations towards portable and/or implantable systems to assist, support, control and promote paretic limb use outside the lab or clinic would move upper limb motor training to patients' life extending high-frequency training duration to life-time.

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Competing interests

The authors declare that they do not have any competing interest.

Supplementary material

Supplementary material is available at *Brain* online.

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